THE UNIVERSITY OF GLASGOW

FACULTY OF MEDICINE

MD THESIS

OCTOBER 2003

STUDIES OF ACCESS FOR MINIMALLY INVASIVE SURGERY

WILLIAM GEORGE AINSLIE

MBChB, FRCS(Glasg)

UNIVERSITY OF GLASGOW

ABSTRACT

THESIS SUBMITTED FOR THE DEGREE OF MD

STUDIES OF ACCESS FOR MINIMALLY INVASIVE SURGERY

By William George Ainslie

Introduction

The advantages of laparoscopic cholecystectomy over open cholecystectomy are now well established. Nevertheless, small changes in technique and careful attention to detail can result in further improvements in clinical outcome. The aim of this thesis was to apply this concept to studies of the trocar and cannula system used to gain access to the peritoneum.

Although trocars and cannulae are central to laparoscopic surgery and numerous theories abound over their use, there is relatively little prospective data on the impact of diameter on clinical outcome or the profile of the trocar tip on patterns of visceral and vascular injury.

Smaller wounds may result in less pain, a faster recovery and virtually invisible wounds but there are concerns over reductions in image quality, the flexibility and resilience of the instruments and a possible learning curve, even for experienced laparoscopic surgeons.

Conical trocars require a higher force of entry than pyramidal trocars but create smaller wounds and are less likely to injure small vessels in the abdominal wall. From these facts, it has been surmised that the higher force for entry results in less control, deeper incursion into the abdomen and higher rates of visceral or vascular injury. Other authors have contended that conical trocars deflect viscera and major vessels but neither faction has produced data that supports their assumptions.

Methods and Results

Patients were randomised to conventional laparoscopic cholecystectomy (CLC) or micropuncture laparoscopic cholecystectomy (MPLC, three 3.3mm, one 10mm cannulae). The duration of each operative stage and the procedure were recorded. Interleukin-6, adrenocorticotropic hormone (ACTH) and vasopressin were sampled for 24 hours. Pain scores and analgesic consumption were recorded for one week. Pulmonary function and quality of life (EQ-5D) were monitored for four weeks.

Forty patients participated. Groups were comparable for age, duration of symptoms and indications for surgery. Total operative time was similar but the time to clip the cystic duct after cholangiography was significantly longer for MPLC. Significantly fewer patients required postoperative parenteral opiates in the MPLC group but oral analgesic consumption was similar in both groups. Median pain scores were lower at all time points for MPLC but this was not statistically significant. There were no significant differences in interleukin-6, ACTH or vasopressin responses, pulmonary function or EQ-5D scores.

The purpose of the second study was to compare the maximum depth of penetration of the peritoneal cavity by the tips of pyramidal, sharp conical and blunt conical trocars. Sections of abdominal wall from pigs were stretched across a jig so that the skin and peritoneal surfaces could be visualised. Each trocar was inserted ten times by hand and then with a mechanical device. Using video footage, the depth of the tip of the trocar was measured as the tip penetrated the peritoneum, when the leading edge of the cannula breached the peritoneum and when the cannula had been completely inserted.

The depth of the tip of the pyramidal trocar was significantly less than for the sharp and blunt conical trocars at all stages. The sharp conical trocar breached the peritoneum earlier than the blunt conical trocar but upon complete insertion of the cannula, there was no statistically significant difference in depth of the tip. The findings were similar for trocars inserted by hand or the mechanical device.

In the third study, the incidence and characteristics of injury sustained by the bowel, when impinged by pyramidal, sharp conical and blunt conical trocars were compared. Rates of deflection were also recorded.

Pyramidal trocars caused stellate penetrating injuries and the sharp conical trocars, small round puncture wounds. The bowel did not deflect upon contact with either the pyramidal or the sharp conical trocar. The blunt conical trocar however, was more likely to cause deflection, never breached the serosa and only created a small round "dimple." These differences were all statistically significant.

The patterns of injury inflicted on the abdominal aorta by pyramidal, sharp conical, blunt conical and Hasson trocars were examined in the final study. Aortas from pigs were inflated with normal saline to a pressure of 120mmHg and were targeted with trocars. Each trocar was inserted ten times.

Deflection only occurred with the blunt trocars. Injuries were significantly less likely to occur with blunt trocars than sharp trocars but when the blunt trocars did cause an injury, the intimal wound was similar in size to wounds created by the sharp trocars.

Conclusions

Diameter of trocar

Cholecystectomy using smaller trocars, cannulae and instruments is widely applicable to elective cholecystectomy in a westernised population. Although the change from a 10mm to a 3mm laparoscope increased the time to clip and divide the cystic duct and artery, this had no impact on the overall time of the procedure. Despite a reduction in the consumption of parenteral analgesia among the patients in the micropuncture group, there was no corresponding reduction in pain scores. Overall, this study found no evidence that fine calibre instruments conferred any obvious major clinical benefits to the patients.

Profile of the trocar

Pyramidal trocars encroach less into the abdominal cavity during the process of insertion, but will injure bowel or aorta upon contact. Sharp conical trocars depress the abdominal wall to a greater extent before they facilitate entry of the cannula and will injure bowel or aorta upon contact. Blunt conical trocars require to be inserted to the same depth as sharp conical trocars but are unlikely to traumatise bowel. They can deflect aorta and are less likely to cause injury than trocars with a sharp tip.

It is not clear whether the risk of injury from a pyramidal trocar that facilitates entry of the cannula with less depression of the abdominal wall is safer than a blunt conical trocar that encroaches further into the abdomen but is less likely to cause injury should it contact bowel or aorta. However, it can be deduced that blunt conical trocars are unlikely to cause injury if bowel is inadvertently contacted during open or closed access. Trocars with a sharp tip should probably be avoided.

LIST OF CONTENTS

CHAPTER 2

THE IMPACT ON POSTOPERATIVE OUTCOME AND THE SURGICAL STRESS RESPONSE OF A REDUCTION IN THE DIAMETER OF THE TROCARS, CANNULAE AND INSTRUMENTS.

A RANDOMISED COMPARISON OF CONVENTIONAL LAPAROSCOPIC AND MICROPUNCTURE LAPAROSCOPIC CHOLECYSTECTOMY.

LIST OF FIGURES

CHAPTER 1

Introduction to the thesis

CHAPTER 2

A randomised comparison of conventional laparoscopic and micropuncture laparoscopic cholecystectomy

CHAPTER 3

The effect of trocar tip profile on abdominal wall penetration

CHAPTER 4

The effect of trocar tip profile on bowel injury

CHAPTER 5

The effect of the profile of the trocar tip on the pattern of vascular injuries

LIST OF TABLES

CHAPTER 1

Introduction to the thesis

CHAPTER 2

A randomised comparison of conventional laparoscopic and micropuncture laparoscopic cholecystectomy

DEDICATION

To my wife, Michelle who has spent the first two years of our marriage watching me work on this thesis and without whose support I could not have hoped to complete it. Also to my parents, who would have seen a lot more of me if I had not undertaken this work.

ACKNOWLEDGEMENTS

Supervisors

Professor MJ McMahon, Professor of Surgery, University of Leeds

Professor PJ O'Dwyer, Professor of Surgery, University of Glasgow

With Special Thanks to:-

Professor ML Larvin, Professor of Surgery, University of Nottingham (formerly Senior Lecturer in Surgery, The General Infirmary at Leeds)

Professor MJ McMahon, Professor of Surgery, University of Leeds

Also to (in alphabetical order):-

Mrs ML Ainslie, Personal Assistant to Professor McMahon, The General Infirmary at Leeds

Mr A Campbell and Laboratory Staff, Wharfedale General Hospital, Otley

Mr J Catton, Clinical Research Fellow in Surgery, The General Infirmary at Leeds

Dr R Chatrath, Consultant Anaesthetist, The General Infirmary at Leeds

Professor C Cooke, Professor of Sports Science, Leeds Metropolitan University

Sister C Denman and the Nursing Staff of Ward 7, Wharfedale General Hospital, Otley

Mr S Dexter, Consultant Surgeon, The General Infirmary at Leeds

Dr J Gibson, Consultant Anaesthetist, The General Infirmary at Leeds

Mr J Holmfield, Laboratory Technician, University of Leeds

Mrs K Ibrahim, Laboratory Technician, University of Leeds

Mr P Kind, Principal Statistician at EuroQoL, University of York

Dr R King, Consultant Biochemist, University of Leeds

Dr M Moore, Consultant Anaesthetist, The General Infirmary at Leeds

Mr C Osbourn, Technician, LIMIT, The General Infirmary at Leeds

Miss W Parsons, Medical Statistician, The General Infirmary at Leeds

Dr M Penney, Consultant Biochemist, Royal Gwent Hospital, Newport

Miss G Salter, Chief Laboratory Technician, University of Leeds

Dr S Smith, Consultant Anaesthetist, The General Infirmary at Leeds

Mr T Smith, Surgical Innovations, Leeds

Miss B Treder, Medical Student, Hamburg, Germany

Sister G Turnbull and the Theatre Staff, The General Infirmary at Leeds

Mr M Webster, Technician, LIMIT, The General Infirmary at Leeds

Sister G Welch and the Theatre Staff, Wharfedale General Hospital, Otley

Mrs P Wilkinson, Secretary to Professor McMahon, Wharfedale General Hospital, Otley

And last but by no means least, the patients who trusted me enough to enrol them in a clinical trial and study their recovery despite the inconvenience it must have caused.

DECLARATION

This thesis is the result of my own work emanating from my employment as a Clinical Research Fellow in Surgery at the Leeds NHS Teaching Hospitals. The material contained herein has not and will not be presented either in part or in whole for any other degree or qualification.

Patients for the clinical studies were under the care of the Consultant Surgeons in the Academic Unit of Surgery and were treated within the General Infirmary at Leeds or Wharfedale General Hospital, Otley. Approval was obtained from the local Ethics Committee for the randomised trial of conventional laparoscopic and micropuncture laparoscopic cholecystectomy and all patients who participated gave written informed consent.

Data collection was performed by myself with three exception. Due to clinical commitments and annual leave (my wedding), a colleague, Mr James Catton, collected blood samples and performed pulmonary function tests as part of the follow up of patients who I had enrolled in the micropuncture trial.

The assays performed in chapter 2 for interleukin-6 and adrenocorticotropic hormone were performed by myself under the supervision of the laboratory technicians in the Academic Unit of Surgery at the General Infirmary at Leeds. The samples for the assays for vasopressin were collected and prepared by myself but were performed in the Department of Biochemistry, Royal Gwent Hospital, Newport, UK for technical reasons.

No live animals were involved in this research. All sections of abdominal wall, bowel and aortas were obtained from the local abattoir. The apparatus for the in-vitro studies was developed by myself, although technical advice and assistance were obtained from Professor Michael J McMahon and the LIMIT technicians, Mr Martin Webster and Mr Colin Osbourn.

Where other work has been cited, appropriate acknowledgement has been given. References published in German were kindly translated for me by Miss Britta Treder, a Medical Student from Hamburg, who was on a clinical attachment at York District Hospital.

Conflict of interests: None.

ABBREVIATIONS

ACTH	-	adrenocorticotropic hormone
ASA	-	American Society of Anaesthesiologists Score (cf. appendix 1)
AUC	-	areas under the curves
AVP	-	arginine vasopressin
χ^2	-	Chi-square test
CLC	-	conventional laparoscopic cholecystectomy
cm	-	centimetres
cmH_2O	-	centimetres of water
CO_2	-	carbon dioxide
CRH	-	corticotropin releasing hormone
CRP	-	C-reactive protein
CSF	-	colony-stimulating factors
CVP	-	central venous pressure
dl	-	decilitre
EDTA	-	ethylene diamine tetra-acetic acid
ELISA	-	enzyme-linked immunosorbent assay kits
EQ-5D	-	EuroQoL quality of life questionnaire
ESWL	-	extra-corporeal shock-wave lithotripsy
$EtCO_2$	-	end-tidal carbon dioxide
FEV_1	-	forced expiratory volume in 1 second
FRC	-	functional residual capacity
FVC	-	forced vital capacity
G-CSF	-	granulocyte colony stimulating factor
GGSQLI	-	German Gastro-intestinal Surgery Quality of Life Index
IFN-γ	-	interferon-γ
IL-x	-	interleukin-x

IL-1R	-	interleukin-1 receptor
IL-1Ra	-	interleukin-1 receptor antagonist
kg	-	kilograms
kPa	-	kilopascals
l	-	litres
lb	-	pounds
LC	-	laparoscopic cholecystectomy
LIMIT	-	Leeds Institute for Minimally Invasive Therapy
MC	-	minicholecystectomy
M-CSF	-	macrophage colony stimulating factor
mg	-	milligrams
min	-	minute
ml	-	millilitres
mm	-	millimetres
mmHg	-	millimetres of mercury
mmol	-	millimoles
MPLC	-	micropuncture laparoscopic cholecystectomy
MRCS	-	Membership of the Royal College of Surgeons
mRNA	-	messenger ribonucleic acid
MTBE	-	methyl tert-butyl ether
µg	-	micrograms
µL	-	microlitres
NAG	-	N-acetyl-beta-D-glucosamine
NHPQ	-	Nottingham Health Profile Questionnaire
nmol	-	nanomoles
N/V	-	nausea and vomiting
OC	-	open cholecystectomy
°C	-	degrees centigrade

$PaCO_2$	-	arterial pressure of carbon dioxide
PAWP	-	pulmonary arterial wedge pressure
PEFR	-	peak expiratory flow rate
pg	-	picograms
pH	-	negative log of the hydrogen ion concentration
pmol/l	-	picomoles per litre
SD	-	standard deviation
SPSS	-	Statistical Package for Social Sciences v 9.0
Th cells	-	T-helper lymphocytes
™	-	trade mark
TNF-α	-	tumour necrosis factor α
UK	-	United Kingdom
USA	-	United States of America
VAPS	-	visual analogue pain score
VAS	-	visual analgue score
W	-	watt
WCC	-	white cell count

CHAPTER 1

INTRODUCTION TO THE THESIS

1.1 Introduction

Minimally invasive surgery swept around the world during the last decade of the 20th century. This revolution was led both by patients and surgeons, spurred on by the perceived benefits of shorter hospitalisation, more rapid recovery and improved cosmetic results. Although initially applied to cholecystectomy, surgeons, realising the potential, were quick to adopt and adapt the new technology to other more complex procedures.

The key to this "new" form of surgery is the method of access to the operative field. In traditional surgery, the incision allows the surgeon to see and feel both instruments and tissues. Good exposure is mandatory for safe surgery, but this may require a large incision. In laparoscopic surgery, the incision is replaced by several, much smaller incisions, through which cannulae of 5 - 12mm diameter are inserted. A metal trocar is inserted into the cannula to enable it to be introduced into the abdominal cavity and is removed once the cannula is within the operating space. This facilitates access for the surgical instruments and the view is supplied through a video camera, coupled to the laparoscope.

The concept of minimal access is not new, however and it was only the development of improved optics followed by the solid-state charge coupled device in the mid 1980's that sparked the recent explosion in laparoscopic surgery. This provided a sufficiently good picture for the procedure to be carried out while looking at a monitor.

Although the trocar and cannula system is central to laparoscopic surgery, it has received relatively little attention over the years compared to other aspects of laparoscopy such as the physiological effects of the pneumoperitoneum. In this thesis, the rise of laparoscopic surgery will be explored and, using cholecystectomy as a model, it will be contended that further improvements in the benefits for the patients can be achieved by small changes in technique

and attention to detail. The medical literature in relation to trocar design, up to the conception of this thesis, will be reviewed and the gaps in knowledge pertaining to the influence of size and profile of the trocar and cannula system on clinical outcome will be exposed. These will then be studied in the clinical and laboratory settings.

1.2 Early developments in laparoscopy

1.2.1 Early historical aspects

The quest for less invasive treatment stretches back through the millennia. The Greek physician, teacher and scientist, Hippocrates of Kos wrote of his frustration at not being able to visualise the internal organs, leading to difficulties and delays in diagnosis and treatment. This curiosity with the internal organs led him to experiment with the use of natural sunlight to illuminate and visualise the rectum. A similar approach was employed by the Romans to examine the cervix (Semm, 1995).

1.2.2 The 19th Century

Phillipp Bozzini pioneered the concept of modern endoscopy. He produced the "Lichtleiter" in 1805, which was a lantern that reflected and channelled light from a candle and enabled body cavities to be visualised. The device was made of tin and as it could become quite warm, was clad in leather to reduce heat transfer to the user. A variety of interchangeable speculae could be attached which were designed specifically for examination of the mouth, nose, ear, vagina, cervix, rectum and female bladder (Bozzini, 1806). The device did not receive widespread acceptance and Bozzini died shortly thereafter in 1809 from typhoid fever. Recently, in the early 1970's, old documents were discovered which revealed that the "lichtleiter" had actually been highly acclaimed by the Josephs Medical Academy (the military medical academy in Vienna) as an "ingenious invention." However, as a result of medical politics and jealousy from the rival and more powerful Vienna Medical Faculty, the device was ultimately ridiculed and dismissed as a "mere toy" (Rathert *et al*, 1974).

In 1826, Pierre Segalas described a "speculum urethro-cystique" that consisted of a polished cylindrical tube that was placed within the urethra with the aid of a gum trocar. Once the trocar was removed, light from two tapers was directed through the speculum to illuminate the lumen of the urethra and bladder. Different sizes of speculum could also be used to examine the rectum, vagina, ear, nose and pharynx (Segalas, 1826).

Antonin Desormeaux designed an endoscope in the autumn of 1852 and presented his device to the l'Académie Impériale de Médecine in 1853. Light was supplied by the combustion of "gazogène" (a mixture of turpentine and alcohol that produced a bright light from a small flame) within a combustion chamber and the rays were reflected through to the endoscopic section of the instrument by a series of silver mirrors and lenses. A swivelling connection between these two components allowed the operator to keep the light source upright but at the same time, angle the endoscope to obtain an optimal view of the urethra and bladder. Additional lenses were available for the magnification of small lesions and also for the correction of myopia and presbyopia. In 1855, Desormeaux presented his initial clinical results and observations to the l'Académie Impériale de Médecine and won the Society's prestigious Argenteuil Prize. He went on to use the device in clinical practice to perform urethroscopy, cystoscopy, proctoscopy, colposcopy and hysteroscopy and also found that he was also able to insert catheters and dilate strictures under direct visual control, perform internal urethrotomy and undertake the destruction and retrieval of bladder calculi. In 1865, he published the first textbook of endoscopy and its applications in the diagnosis and treatment of diseases of the urethra and bladder (Desormeaux, 1865).

Maximillian Nitze produced a cystoscope in 1877. The light was supplied by an electrically heated platinum wire, sheathed by a quill and cooled by a continuous stream of water. The image was relayed and magnified by lenses to further improve the angle of vision and image quality (Nitze, 1879). Following the invention of the electric light bulb by Thomas Edison in 1879, David Newman of Glasgow Royal Infirmary placed a miniature incandescent bulb at

the end of a rod that could be placed into the bladder via the urethra. Using a separate speculum, the illuminated lumen of the bladder could then be inspected for any abnormalities. The technique was described within the text of his thesis, submitted to the University of Glasgow for the degree of MD and was published in the Glasgow Medical Journal in 1883. Newman used this device in clinical practice and was able to visualise the female bladder and to selectively cannulate the ureters (Newman, 1883). Likewise, Nitze incorporated an incandescent bulb into his cystoscope but also included a prism for angled viewing. He became a strong proponent of the advantages of the new cystoscopic technique, particularly for the localisation of the source of haematuria and pyuria. He did accede however, that the technique not only required a high quality instrument and practice but that it could not be used to localise renal sources of haematuria in an inflamed bladder, to visualise the ureter nor to retrieve calculi that were above the level of the vesico-ureteric junction. Preoperatively, Nitze was able to correctly identify the pathological kidney in patients with impalpable renal tumours by selective occlusion and observation of the ureteric orifices for blood. On one occasion, when the tumour was not palpable at laparotomy, a sceptical Professor who performed the operation ignored Nitze's localisation of the source of the haematuria and did not resect the kidney, only for the patient to represent with an advanced lesion three months later (Nitze, 1895).

1.2.3 Early 20th Century

In 1901, George Kelling from Dresden, gave a speech to the 73rd Assembly of German Scientists and Physicians in Hamburg on oesophagoscopy, gastroscopy and coelioscopy. He described 134 cases in which the diagnosis could not have been made without oesophagoscopy and also discussed the use of gastroscopy in preference to laparotomy for the diagnosis of gastric carcinoma. He concluded with a description of an endoscopic laparotomy which he called "coelioscopy" and performed a demonstration on a dog. The procedure involved insufflation of the abdomen with filtered air followed by the insertion of a cannula, through which the cystoscope could be introduced (Kelling, 1902).

Subsequently, Hans Christian Jacobaeus from Stockholm, Sweden, published an article "on the possibility of the examination of the serous cavities with zystoscopy." He described a trocar and cannula system that he had developed to facilitate entry to the abdominal or thoracic cavities and had tested on 50 cadavers. Once he was satisfied that the risk of injury to the bowel was minimal, he went on to perform three laparoscopies and two thoracoscopies on patients without complication (Jacobaeus, 1910).

Somewhat riled, Kelling promptly responded with an article in which he once again described his version of coelioscopy, stated that he too had performed it on patients and laid claim to his "priority on the subject." His reason for silence over the intervening years was that he had developed an interest in another field and had not studied the technique any further (Kelling, 1910).

Although it was realised from the outset that pneumoperitoneum was necessary to enable clear visualisation of the viscera, no consensus was reached on the optimal gaseous agent for the creation and maintenance of the pneumoperitoneum. In 1924, Richard Zollikofer from Switzerland recommended carbon dioxide as the preferred gaseous agent, instead of filtered air or oxygen, due to its rapid absorption and inability to support combustion (Zollikofer, 1924). Various needles were produced to facilitate insufflation but it was one with a spring-loaded obturator, designed by Janos Veress of Hungary, which became popular (Figure 1.1). This device, originally called a "Mandarin Needle" and produced by Aesculap in Tuttlingen, Germany, was described as a "new instrument for pleural and abdominal punctures and for the treatment of pneumothorax" (Veress, 1938). Veress described its use in almost 2000 patients among whom there was a striking reduction in the complication of "pyrexial pleural exudates" but interestingly, did not suggest that it be used for insufflation of the abdomen prior to laparoscopy! Despite controversy over its use, is still widely used (McMahon *et al*, 1993(b); Semm, 1995; Wherry *et al*, 1996).

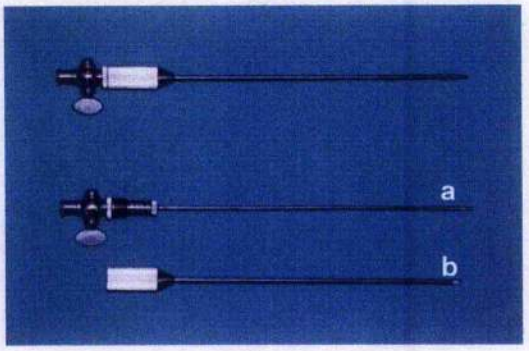


Figure 1.1 The Veress needle. The lower example has been dismantled to demonstrate the spring-loaded obturator (a) that sits within the needle (b).

1.2.4 Optics and cameras - the final frontiers

The two most significant developments that widened the application of laparoscopy, were the Hopkins rod lens laparoscope and the computer chip video camera.

The rod lens was a revolutionary idea. Early laparoscopes were manufactured as a series of glass lenses with air in between, which refracted light inefficiently. During the 1950's, Professor Sir Harold Hopkins, Professor of Optics of Reading University, UK, designed a laparoscope using glass rods and an antireflective coating, interspersed with air lenses that enhanced the efficiency and quality of light conduction. This improved the illumination of the target, the quality of the image and simplified construction. The idea was initially rejected, but later adopted by a then small, relatively unknown German company run by Karl Storz (Cheslyn-Curtis & Hopkins, 1995).

Routine cystoscopy and laparoscopy became feasible and the gynaecologists, in particular, Kurt Semm of Kiel, Germany, pioneered its early introduction to clinical practice. However, a major disadvantage of laparoscopy was that usually only the surgeon could view the procedure and had to personally hold the laparoscope. Beam splitting devices were available to allow an assistant to view the procedure, but they were unwieldly and reduced the brightness of the image. Even with this equipment, Semm performed tubal and ovarian surgery and completed the first laparoscopic appendicectomy on September 12th 1980 (Semm, 1995).

A solid-state charge coupled device, was first introduced by the Circon Company, USA in the mid-1980s, principally for use in lightweight outside broadcast cameras and personal camcorders. It converted photons to an electrical signal, which after processing, resulted in an image that could be viewed on a standard television monitor (Chang, 1995). For surgeons undertaking laparoscopy (and for endoscopists), the charge coupled device improved the ergonomics of posture, facilitated bimanual dissection and enabled trainees and theatre staff to visualise and participate in operations (Chang, 1995).

1.3 The conversion from open to laparoscopic cholecystectomy

1.3.1 Open cholecystectomy

Cholecystectomy is a common elective operation in the Western hemisphere with an estimated rate in the USA of 500,000 to 700,000 procedures per year and approximately 50,000 procedures per year in the United Kingdom (Nair *et al,* 1997; Roslyn *et al,* 1993; Tait & Little, 1995).

Carl von Langenbuch first performed open cholecystectomy in 1882 (Trede *et al,* 1995). Initially, it was only performed for complications of gallstones but the indications soon expanded to include patients with biliary pain (Tait & Little, 1995). A review of 21 reports containing 36,623 cases identified in the American and European literature between 1923 and 1933, revealed a mortality rate of 6.6%, with rates among individual centres ranging from 2.6% to 10.4%. Mortality increased in the presence of acute cholecystitis to 8% (range 4.7% - 22.5%) and in the presence of perforation, to 46% (range 15% - 65%). Death occurred principally in older patients and was due to inflammation and fibrosis of the gallbladder, technical error, pulmonary complications or cardiac, renal and liver failure (Heuer, 1934). Longitudinal studies from a hospital in New York, the Cornell Medical Center, showed that with the passage of time, the mortality rate dropped from 2.5% (Heuer's personal series of 200 cases between 1932 and 1934) to 1.3% by 1984 (Heuer, 1934; McSherry, 1989). This reduction in mortality occurred even though the proportion of patients with acute

cholecystitis who were over 65 years old, rose from 5.3% to 39.8% during the study period.

More recently, the mortality has been further reduced (Dunn *et al*, 1994; Girard & Morin, 1993; Nair *et al*, 1997; Roslyn *et al*, 1993). One report retrospectively identified all cholecystectomies (42,474) performed in California and Maryland in 1989 from the hospitals' Uniformed Billing Discharge Analysis information. The authors recorded an in-patient morbidity rate of 14.7% but a mortality rate of only 0.17% and a bile duct injury rate of 0.2%. The mortality and morbidity rates were related to age (mortality 0.03% among patients <65 years and 0.5% among patients >65 years, morbidity 10.1% vs 25.7% respectively), severity of disease (up to 6 fold increase in mortality for acute complicated disease) and comorbidity (heart failure, hypertension and diabetes) (Roslyn *et al*, 1994).

A retrospective review from one institution in Montreal, Canada, evaluated 10,471 patients who underwent open cholecystectomy between 1971 and 1990 (Girard & Morin, 1993). The overall mortality rate was 0.4% but this varied with age and was higher among patients over 50 years of age (0.07% for patients <50 years, 0.6% if 50 – 70 years and 2.5% if older than 70 years). For cholecystectomy alone, the mortality was 0.3% but for patients who underwent common bile duct exploration, it was 1.6%. Fifty-nine percent of deaths among patients undergoing cholecystectomy alone were due to cardiac complications compared with only 33% after bile duct exploration, where sepsis from the intra-abdominal pathology was the predominant factor. The overall rate of morbidity was 5.1% but increased with age, from 3.0% for patients less than 50 years to 13.8% for those over 70 years. Wound and pulmonary complications accounted for 28% and 23% of the morbidity respectively. The bile duct injury rate was 0.3%. As with mortality, common bile duct exploration increased the rate of complications (from 3.6% to 17.5%).

The Comparative Audit Service of the Royal College of Surgeons of England reported morbidity and mortality rates of 13% and 0.76% respectively for 8,035 open

cholecystectomies performed within the United Kingdom between 1990-1991. A subsequent study recorded similar rates in 1994 (Dunn *et al,* 1994; Nair *et al,* 1997). The data were retrospective, self-reported and were not checked for accuracy. However, this audit represents the best available recent data relating to outcome of open cholecystectomy in England and Wales.

Despite the low mortality rate and overall safety of open cholecystectomy, alternative strategies for gallstone treatment were already under evaluation in the 1980's. Proponents aimed to minimise the trauma of intervention, particularly for patients considered to have a high operative risk.

1.3.2 Oral dissolution therapy

Cholesterol gallstones are believed to form as a result of supersaturation of bile with cholesterol, often in combination with poor gallbladder motility and a reduction in bile acid formation. Dieting with rapid weight loss and pregnancy are also implicated. Higher prevalences of gallstones within certain ethnic groups have been well documented and can be accounted for by differences in gallbladder motor function, genetic and dietary factors (Basso *et al,* 1992; Davion *et al,* 1989; Sampliner & O'Connell, 1968; Tait & Little, 1995)

Oral dissolution therapy aims to dissolve cholesterol gallstones through the ingestion of the bile acids, urso- or chenodeoxycholic acid, which are secreted in bile (Erlinger *et al,* 1984). Dissolution can be enhanced by the inclusion of a terpene compound that conveniently also has antispasmodic properties (Darzi *et al,* 1989; Somerville *et al,* 1985).

However, only 30% of patients with calculi are suitable for this treatment. Oral dissolution therapy is not effective if the gallstones are over 1cm in diameter or occupy greater than 40% of the gallbladder. It is also ineffective in the presence of a poorly functioning gallbladder (<50% contractility) and calcified or mixed calculi. Biliary symptoms persist during

treatment in up to 23% of patients and can precipitate emergency admission. Complete dissolution only occurs in 23% and recurrence rates of calculi are between 25 – 50% (Erlinger *et al,* 1984; Tait & Little, 1995). One study that combined Rowachol with bile salts reported a success rate of 73% for this combination, but it only included 15 patients (Somerville *et al,* 1985).

In one study, bile salt induced diarrhoea occurred in 6% of patients on ursodeoxycholic acid and 57% on chenodeoxycholic acid, resulting in cessation of therapy in 5% and 23% of patients respectively (Erlinger *et al,* 1984). Other reported complications include transient elevation of transaminases and fatal pancreatitis (Erlinger *et al,* 1984; Somerville *et al,* 1985).

1.3.3 Extracorporeal shock wave lithotripsy (ESWL)

In combination with oral dissolution therapy, ESWL has a complete clearance rate for gallbladder calculi of between 47 – 83% (Darzi *et al,* 1989; Sackman *et al,* 1991). It has the advantage that it can fragment larger stones, making them more amenable to oral dissolution therapy but the above restrictions to therapy still apply (cf. section 1.3.2). In addition, it is not recommended for ductal calculi or in the presence of pancreatic or biliary inflammation, pregnancy, peptic ulceration or coagulopathy. Sackman and colleagues found that only 19% of patients were suitable for this treatment (Sackman *et al,* 1991).

Results are best for patients with single stones up to 20mm diameter, with fragments of 3mm or less after ESWL (83% clearance rate) (Sackman *et al,* 1991). Non-compliance with oral dissolution therapy (19% of patients) led to a poor outcome with a stone clearance rate of only 7% after 5 to 8 months of treatment. Side effects include episodes of biliary colic in 16-36% of patients, cutaneous petechiae (8%), pancreatitis (1.8%) and cholestasis (1-2%) (Darzi *et al,* 1989; Sackman *et al,* 1991). Cholecystectomy was performed in 2.3% of patients in one study due to pain, treatment failure or patient dissatisfaction (Sackman *et al,* 1991).

Recurrence rates of 9% at one year and 11% at 3 years were due to the persistence of a diseased gallbladder and cessation of oral dissolution therapy, which allowed biliary stasis and an increase in lithogenicity of bile (McSherry, 1989; Sackmann *et al*, 1990; Sackmann *et al*, 1991).

Even without considering recurrence rates, a course of lithotripsy is more expensive than surgery. In one study, the cost of lithotripsy and oral dissolution therapy was calculated at $15,087 for each successful treatment compared with $3,685 for cholecystectomy. These figures included, screening for eligibility with ultrasound, oral cholecystograms and if necessary (for non-visualised gallbladders on cholecystography), HIDA scans, lithotripsy treatment sessions, theatre time, plus an average of 1 year of dissolution therapy and follow-up visits. Expenditure for treatment failures (at a modest rate of 10%) and screening of non-suitable individuals were also factored into the cost (Nealon *et al*, 1991).

In addition to the low success rates, side effects and costs, the exclusion criteria drastically reduce the role of oral dissolution therapy and lithotripsy among patients at high operative risk. For example, of the 30 patients who died after cholecystectomy, in the most recent series reported from the Cornell Medical Center in 1989, only one potentially met the criteria for ESWL and oral dissolution therapy (McSherry, 1989).

1.3.4 Contact Dissolution – Methyl tert-butyl ether (MTBE)

A group from the Mayo clinic reported their initial experience with insertion and instillation of MTBE through either a percutaneous catheter or a nasobiliary tube. While most of the calculi were dissolved within 4 to 12 hours, three of the four patients had residual calculi after treatment or at follow-up, three months later. One patient experienced vomiting and ether could be detected on her breath. However, there are potentially serious complications as MTBE can cause haemolysis (MTBE is a powerful lipid solvent) and can be metabolised to methanol and formalin. Catheter placement can result in haemorrhage or bile leak, while

contamination of the peritoneal cavity by MTBE can occur due to leakage, catheter dislodgement or misplacement (Allen *et al,* 1985).

1.3.5 Mini-laparotomy cholecystectomy

Prior to initial developments in laparoscopic cholecystectomy, several authors had evaluated "mini-cholecystectomy." This is essentially open cholecystectomy performed through a 4 to 6cm transverse incision (Goco & Chambers, 1988; O'Dwyer *et al,* 1990).

Initial results were encouraging. It was applicable to approximately 80% of cases and the average postoperative stay for patients who did not require extension of the wound, was between 1 to 3.5 days. Complication rates were 3% to 9% and mortality was 0.2% (Goco & Chambers, 1988; O'Dwyer *et al,* 1990). It was estimated that if the technique could be applied to 50% of patients undergoing cholecystectomy in the USA, it would save $50 million in hospital costs every year (Goco & Chambers, 1988). A randomised trial in Glasgow, Scotland, one group compared cholecystectomy through 6 and 15cm incisions and recruited 30 patients. They demonstrated a significantly reduced postoperative stay for the small incision group (3 vs 5 days) and a trend for improved pulmonary function and lower analgesic requirements (O'Dwyer *et al,* 1992).

However, neither medical treatment, lithotripsy nor small incision cholecystectomy, were able to match the explosive popularity of the new surgical technique of laparoscopic cholecystectomy, which was introduced in the late 1980's.

1.3.6 Laparoscopic cholecystectomy

Credit for the first laparoscopic cholecystectomy undertaken in a human is ascribed to Phillipe Mouret, from Lyon, France although surgeons from Germany are quick to disagree and credit it to Mühe in 1985 (Deuss *et al,* 1994; Mühe, 1992). European proponents of the operation included Perissat, Dubois and Cuschieri, all of whom pioneered the procedure

using what is now commonly known as the French technique. For this, the patient is placed in the Lloyd-Davis position, an epigastric operating cannula is placed to the left of the midline and a rod retractor or suction tube is used to elevate the liver (Dubois *et al,* 1990).

The dissemination of the laparoscopic approach however, was chiefly due to the efforts of two American surgeons from Tennessee, Doug Olsen and Eddie-Joe Reddick, who pioneered formal training courses, thereby ensuring that their technique prevailed internationally. The main differences are that the surgeon operates from the patient's left side, the epigastric cannula is placed in the midline and the gallbladder is retracted over the liver by a grasper attached to the fundus (Reddick & Olsen, 1989). Initially a laser was employed but it soon became obvious that with the advent of appropriate instruments, electrocautery was superior and made the use of the laser superfluous in terms of time and cost, with no advantage in efficacy or safety (Graves *et al,* 1991; Soper *et al,* 1992; The Southern Surgeons Club, 1991; Voyles *et al,* 1991).

1.3.7 Initial results of laparoscopic cholecystectomy

Initial results were from small, but expanding personal series and fuelled the concept that the new procedure was superior to open cholecystectomy (Dubois *et al,* 1990; Grace *et al,* 1991; Nathanson *et al,* 1991; Perissat *et al,* 1990).

In a series of 39 procedures, there was a conversion rate of 10% for "pyocholecystitis" or bleeding and one postoperative bile leak (Dubois *et al,* 1990). Perissat's series of 25 procedures contained no conversions and the only complications were self-limiting pyrexia in two patients and a cannula site haematoma in another (Perissat *et al,* 1990). The patients were discharged by day four and returned to work within 5 to 8 days. Reddick and Olsen reported no complications in their initial 25 patients but did have two conversions for adhesions and gallbladder perforation that were not included in the series (Reddick & Olsen, 1989). On comparison with a concurrent but not randomly allocated group of mini-

laparotomy cholecystectomy patients, they noted a shorter hospital stay of 1.96 versus 2.8 days respectively and a faster return to work (6.5 vs 34 days).

The Dundee group, headed by Professor Sir Alfred Cuschieri, reported 61 procedures with a 2% conversion rate (for ductal calculi) and a 7% morbidity rate. Intraoperative complications included a Veress needle injury to the transverse mesocolon and two episodes of cystic artery bleeding (controlled laparoscopically). Postoperatively, an iatrogenic subcapsular liver haematoma was drained at laparotomy and one patient required blood transfusion. Diet was resumed by a mean of 24 hours and patients were discharged after a mean of 2.9 days. Normal work or activities were resumed by a median of 11 days (Nathanson *et al,* 1991).

A team led by Bouchier-Hayes in Dublin performed 50 laparoscopic cholecystectomies. They had a higher conversion rate of 12% but attributed this to the inclusion of patients with acute cholecystitis. Morbidity was 8%, due to a Veress needle injury of the jejunum, prolonged bile leak and postoperative jaundice from retained common duct calculi (Grace *et al,* 1991). Overall though, patients required minimal analgesia and were discharged between 2 to 4 days postoperatively.

1.3.8 Difficulties encountered during attempts to compare laparoscopic and open cholecystectomy

Initial comparisons were made between cohorts of laparoscopic patients and historical or concurrent open controls. Inherent difficulties of this approach were that the data for the control group were sometimes collected retrospectively or the indications for surgery in the two groups were different and changed over time (Dunn *et al,* 1994; Cohen *et al,* 1996; Nair *et al,* 1997).

For example, a comparison of the patterns of practice, relating to cholecystectomy, in Toronto for the years 1989 to 1994 noted that the proportion of laparoscopic

cholecystectomies rose from 1.0% to 85.6%. Analysis of the number of procedures and the case-mix demonstrated that the total number of cholecystectomies rose by 30.4% while the number of emergency procedures only rose by 8.8%. The proportion of elective cases increased by 48.3% while emergency cases fell by 15.1%. By 1994, the proportion of patients who underwent open cholecystectomy, who were over 65 years old or had coexisting morbidity, rose from 20.5% to 37.7% and 8.1% to 16% respectively. The authors concluded that the increase in the number of procedures by 1994 was due to a reduction in the threshold for cholecystectomy and that patients, who underwent open cholecystectomy, were older or had more comorbidity (Cohen *et al,* 1996). A similar review in Maryland, USA found an increase in cholecystectomy rates of 28% over a similar time period, with laparoscopic cholecystectomy accounting for 76% of procedures (Steiner *et al,* 1994).

Further evidence of a change in practice with the introduction of laparoscopic cholecystectomy, was presented in the study by the Comparative Audit Service of the Royal College of Surgeons of England (Dunn *et al,* 1994; Nair *et al,* 1997). The study was criticised because it was retrospective, compared two unmatched groups and depended entirely on the accuracy of data submitted by participating surgeons with no recourse to confirmation of its accuracy (Edmondson & Hale, 1995). Despite this, it was noted that only 0.73% of patients in the laparoscopic cholecystectomy group underwent bile duct explorations compared with 13.4% in the open cholecystectomy group, indicating perhaps that patients in the open cholecystectomy group had more severe disease and that surgeons were employing selection criteria for the new procedure (Dunn *et al,* 1994). In the later report, a much smaller proportion of procedures were performed by the open technique (21.1% vs 78.9%), demonstrating that surgical practice had already irrevocably altered (Nair *et al,* 1997).

The perceived differences in complications and recovery of patients undergoing laparoscopic cholecystectomy (LC) compared with open cholecystectomy (OC) caused considerable debate and difficulty in the organisation of randomised controlled trials.

Many surgeons who advocated the merits of LC were convinced that randomisation was unethical because OC was inferior treatment (Aktan *et al,* 1994; Neugebauer *et al,* 1991; Mealy *et al,* 1992). It was further argued that a trial could not occur until sufficient experience was attained with the new procedure to clear the "learning curve" and allow a fair comparison (Neugebauer *et al,* 1991). In addition, when attempts were made to perform a randomised controlled trial, many patients informed by media coverage, refused randomisation to the conventional arm (Barkun *et al,* 1992; Deuss *et al,* 1994; Karayiannakis *et al,* 1997; Majeed *et al,* 1996; McMahon *et al,* 1994 (b)).

There were also differences between groups in the methodology employed. Some surgeons had experience of as few as 10 previous LCs and were still in their "learning curve" (McGinn *et al,* 1995; Southern Surgeons' Club *et al,* 1995). Some centres adopted an "all-comers" policy (McMahon *et al,* 1994(b)) while others were highly selective, excluding over 20% of patients as unsuitable (Majeed *et al,* 1996; McGinn *et al,* 1995). Most studies compared LC with OC but some compared it to mini-cholecystectomy (Majeed *et al,* 1996; McGinn *et al,* 1995; McMahon *et al,* 1994(b)).

The literature now contains a mixture of randomised trials and cohort studies, the results of which can be broadly categorised into clinical and biochemical measures of outcome. These will now be reviewed.

1.4 Clinical outcome measures from randomised controlled trials and cohort studies

1.4.1 Operative time

Initial experience was that LC took longer to perform than OC. However, many compared the authors' recent conventional experience with their initial series of LC. Groups were not controlled and the LC group included a clear "learning curve." One such report clearly acknowledged this fact (Soper *et al,* 1992).

Within randomised and cohort studies, the median and mean operating times ranged from 43 to 122 minutes for LC. This compares with 40 to 112 minutes for OC. Direct comparison is difficult however as factors such as operator experience and cholangiography were inconsistent. Not only were there differences in policy with respect to intraoperative cholangiography, ranging from none (McGinn *et al,* 1995) to routine cholangiography (Majeed *et al,* 1996), but differences within trials, based on individual surgeon preference, also existed (McMahon *et al,* 1994(b)). One group used routine cholangiography for OC and a selective approach for LC (Berggren *et al,* 1994).

Four randomised trials with a total of 842 patients concluded that operating times were between 12 to 24 minutes longer for LC (Berggren *et al,* 1994; Majeed *et al,* 1996; McGinn *et al,* 1995; McMahon *et al,* 1994(b)). Seven other trials, with a total of 318 patients, found no difference in time (Barkun *et al,* 1992; Frazee *et al,* 1991; Karayiannakis *et al,* 1997; Ortega *et al,* 1996; Putensen-Himmer *et al,* 1992; Redmond *et al,* 1994; Schauer *et al,* 1993). One of these authors subsequently reported, in a published discussion from 102nd Annual Scientific Session of the Southern Surgical Association, that operative times for LC had since decreased by approximately 50% due to increased experience (Frazee *et al,* 1991, discussion). Only one trial with 50 patients found that LC was quicker than OC (mean 43.2mins vs 53.3mins, p=0.047) (Agnifili *et al,* 1993).

Prolonged conventional procedures are associated with an increased incidence of complications (Garibaldi *et al,* 1991; Scott, 1982). However, as demonstrated by experience in Leeds, this does not apply to laparoscopic cholecystectomy (Dexter *et al*, 1997). The clinical significance of increased operating time maybe important for the economics of health care but does not appear to have negative implications for outcome.

1.4.2 Postoperative pain

Pain is a subjective phenomenon and therefore difficult to quantify. In the literature

comparing OC and LC, pain scores and analgesic requirements have been used as outcome measures.

In five of the randomised trials, a form of visual analogue pain score was employed. In four of these studies, postoperative pain scores for 48 to 72 hours after surgery were lower in the laparoscopic group (Agnifili *et al,* 1993; Karayiannakis *et al,* 1997; McMahon *et al,* 1994(b); Ortega *et al,* 1996) but in a fifth study, the difference was only evident after 72 hours (Putensen-Himmer *et al,* 1992). The McGill group in Toronto used the McGill pain questionnaire and found lower, but non-significant values for LC on day 1 (Barkun *et al,* 1992). The three cohort studies, which employed visual analogue scores, produced conflicting results. One study demonstrated statistically lower scores for LC on the day of surgery but no differences on days one and two (Glasser *et al,* 1995). Another only found a statistical difference, in favour of LC, on day 2 (Joris *et al,* 1992), while a third study demonstrated statistically significant differences in favour of LC at 24, 36 and 48 hours (Mealy *et al,* 1992).

Analgesic consumption substantiated the impression of a reduction in pain after LC. With the exception of one study, in which analgesic consumption was not measured (Ortega *et al,* 1996), all of the above studies recorded significantly lower analgesic consumption among the patients receiving LC. Reductions in analgesic consumption were noted in three other randomised controlled trials in which pain scores were not recorded (Berggren *et al,* 1994; McGinn *et al,* 1995; Schauer *et al,* 1993).

1.4.3 Postoperative pulmonary function

After conventional surgery, postoperative lung function is restricted with a shallow, rapid breathing pattern, believed to result from pain and inhibition of diaphragmatic function. This can be objectively quantified by measurements of functional residual capacity (FRC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and peak

expiratory flow rate (PEFR). In addition, mucociliary flow is reversed and secretions are retained (Wahba *et al,* 1995).

Five randomised trials and four cohort studies examined the outcome of pulmonary function using FVC, FEV_1 and PEFR. The uniform finding was a less pronounced reduction in pulmonary function among the patients who underwent LC (Figure 1.2). In two studies, respiratory function among LC patients returned to normal on days 2 and 5, compared with days 5 and 12 in the respective conventional groups (Agnifili *et al,* 1993; Schauer *et al,* 1993).

A group from Innsbruck, Austria, measured FRC in LC and OC. Functional residual capacity expressed as a percentage of preoperative values, was significantly ($p<0.05$) greater in patients who underwent LC (24 hours, 85 ± 15%, 72 hours, 105 ± 16%) compared to those who had OC (24 hours, 64 ± 19%, 72 hours, 67 ± 17%) (Putensen-Himmer *et al,* 1992). Comparison of oxygen saturation in three studies revealed that PaO_2 was higher in the immediate postoperative period among LC patients than those who underwent an open procedure (McMahon *et al,* 1994(b), Putensen-Himmer *et al,* 1992; Schauer *et al,* 1993).

Another group from Dublin examined respiratory function using maximal inspiratory strength in non-randomised cohorts of OC and LC patients (Da Costa *et al,* 1995). Values in the LC group dropped to 83% of the preoperative baseline measurements but returned to normal within 48 hours. The drop was more significant in the OC group (73% of baseline) and took five days to resolve. While this study was not randomised, the patients were matched for age, sex and operative time.

Surprisingly, despite these results, in only three studies has a reduction in respiratory infection or atelectasis been demonstrated in patients undergoing LC (Da Costa *et al,* 1995; Redmond *et al,* 1994; Schauer *et al,* 1993).

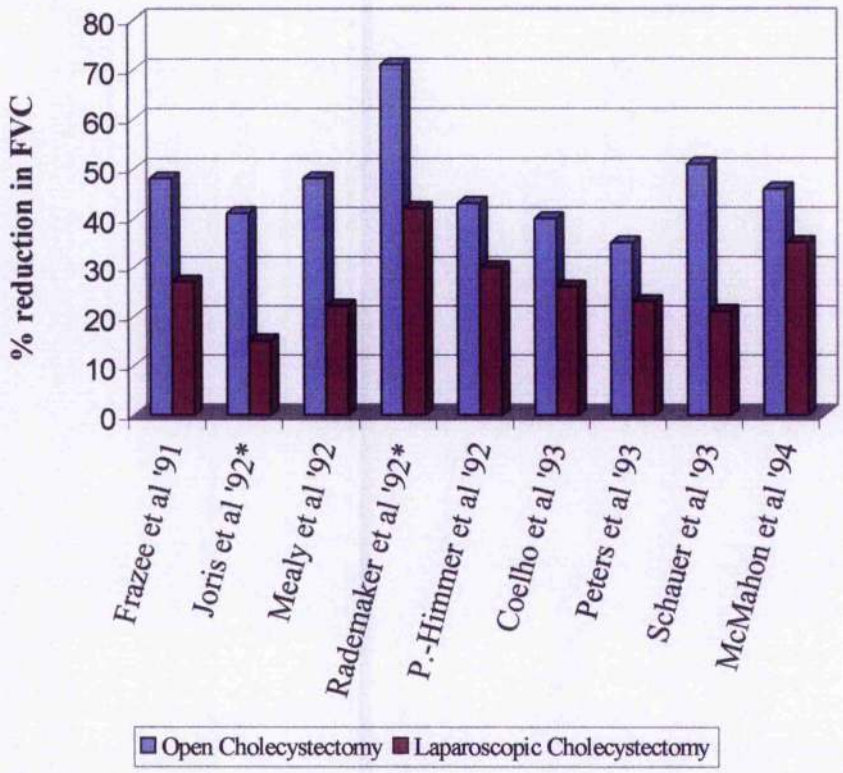


Figure 1.2 Comparison of percentage reduction in forced vital capacity (FVC) between open and laparoscopic groups compared to pre-operative values. Readings were taken at 24 hours, unless otherwise indicated (*). All differences were statistically significant. When measured, similar differences were obtained for FEV_1 and PEFR (not shown). Actual values are recorded in appendix 1.

*Joris *et al,* 1992 (48 hours) and Rademaker *et al,* 1992 (2 hours)

1.4.4 Cardiorespiratory response to exercise and fatigue

In a study of the cardiorespiratory response to exercise after LC, a group from Crétiel, France recruited nine patients who were listed for laparoscopic cholecystectomy (Delauney *et al*, 1995). Preoperatively, fatigue scores were collected and exercise tests were performed on a treadmill. During the exercise protocol, the maximum oxygen uptake and carbon dioxide production, blood pressure, heart rate and lactate levels were measured. All tests were repeated on days 3 and 10 postoperatively but there were no differences in any of the parameters when compared to the baseline values that had been collected preoperatively. In a

review of the literature, the authors highlighted that conventional upper abdominal surgery was associated with a 25% reduction in maximal oxygen consumption and a 10 to 30% reduction in muscle force. They therefore concluded that LC did not cause significant impairment in the cardiorespiratory response to exercise and was superior to OC. However, by their own admission, the investigators did not assess the patients on the evening after surgery or on days 1 and 2 and the study was restricted to patients who were Grade 1 on the American Society of Anaesthesiologists Physical Status Scale (ASA cf. appendix 1).

Fatigue scores were measured in a cohort study of patients who underwent LC (n=15) and OC (n=16). Fatigue scores were highest on the first postoperative day in both groups but there was no statistical difference between the two groups until day 7, when the scores for the LC group were lower than those for the OC group (p=0.02). The scores in the LC group returned to preoperative baseline values by day 14 but took until day 28 to return to normal in the OC group (Hill *et al*, 1993).

1.4.5 Discharge, return to normal activities and quality of life

Comparison of duration of hospitalisation and time to return to normal activities is notoriously difficult in view of cultural variations and different protocols of care. For example financial incentives for hospitals and patients play a role. In the USA, patient stay is short due to the pressure of insurance companies. In Germany however, hospital revenue depends on patient stay and this reduces incentive for early discharge.

Postoperative hospital stay ranged from 1.2 to 4 days for LC, compared with 3 to 4 days for mini-cholecystectomy and up to 7.7 days for conventional cholecystectomy. In eight randomised trials, time to discharge was shorter for LC than OC (Agnifili *et al*, 1993; Barkun *et al*, 1992; Bellón *et al*, 1997; Berggren *et al*, 1994; Karayiannakis *et al*, 1997; McGinn *et al*, 1995; McMahon *et al*, 1994 (b); Schauer *et al*, 1993), although in one study, inclusion of patients who were converted to an open procedure eliminated the advantage (McGinn *et al*,

1995). In two studies however time to discharge was similar in both groups. One of these trials attempted to remove carer bias by allowing the patients to leave when they wanted (Majeed *et al,* 1996), but by doing so, has been criticised for incorporating bias from the patients' perceptions (McClure *et al,* 1996; Wellwood, 1996). The second study from USA involved small numbers (n=20) and patients were sent home a mean of one day after surgery, even if they had a conventional cholecystectomy through the standardised 9cm incision (Ortega *et al,* 1996).

Return to normal activities, ranged from 1 to 3 weeks after LC and 2 to 6 weeks after OC (Barkun *et al,* 1992; Berggren *et al,* 1994; Majeed *et al,* 1996; McGinn *et al,* 1995; McMahon *et al,* 1994(b)). However, the definition of normal activities was nebulous and was influenced by the inclusion/exclusion of employment and whether or not the patient was self-employed. Self-employment was a strong motivation for early return to work (McLaughlan & MacIntyre, 1995; McMahon *et al,* 1994(b); Majeed *et al,* 1996). Cultural factors were also involved. One study that compared American and French cohorts of patients found that 63% and 25% returned to work at two weeks and 86% and 70% by four weeks respectively (Vitale *et al,* 1991). This was despite 93% and 73% stating that all discomfort had resolved by two weeks. Among older patients who have retired, it was noted that a higher proportion of "elderly" patients (>60 years) managed to return to normal activities by six months after LC (97%) than after OC (86%) (Vander Velpen *et al,* 1993).

With the introduction of LC, both the public and the general medical profession required guidelines for advice on postoperative recovery if the advantages of the new procedure were to be realised. One study from Scotland examined this area (McLaughlan & MacIntyre, 1995). The authors suggested that it was possible to return to manual labour after two weeks but a postal survey of general practitioners demonstrated that recommendations varied widely. These ranged from a return to normal activities when the patient felt ready, to eight weeks convalescence. Two-thirds advocated a return to normality within two to four weeks.

However, only 11% of patients (26 of 532) in this study were able to recall being given any advice by hospital staff or their general practitioner. Interestingly, there were no records of what advice *had* been given (if any), so the patients' recollection may have been correct. As a direct result of these findings, the unit now supplies leaflets with appropriate guidelines.

Only two randomised studies addressed the issue of quality of life (Barkun *et al,* 1992; McMahon *et al,* 1994(b)). The Toronto based McGill Gallstone Group utilised the Nottingham Health Profile Questionnaire (NHPQ), the German Gastro-intestinal Surgery Quality of Life Index (GGSQLI) and a Visual Analogue Scale (VAS). They noticed an improvement in the VAS scores among the LC patients at 10 days and the GGSQLI and NHPQ at one month. The mini-cholecystectomy group did not register a postoperative improvement in VAS and GGSQLI until 1 month and the NHPQ at 3 months. There were no statistical differences between groups three months after the procedures (Barkun *et al,* 1992).

McMahon and colleagues from Glasgow employed the SF-36 and Hospital Anxiety and Depression Scale. Patients in the laparoscopic cholecystectomy group had better physical and social functioning, less pain and depression than mini-cholecystectomy patients at the end of one week. They also enjoyed a faster return to leisure (7 vs 12 days), domestic (10 vs 15 days) and social activities (14 vs 21 days) but took just as long to return to sexual activity (21 days) and employment (5-6 weeks).

1.4.6 Long-term follow-up

Four studies have attempted to evaluate patient outcome one year after surgery (McMahon *et al,* 1995(b); Stiff *et al,* 1994; Vander Velpen *et al,* 1993; Wilson & Macintyre, 1993).

The Glasgow group sent questionnaires to patients who had participated in the earlier randomised trial (McMahon *et al,* 1994(c)) and had an 86% response rate. The only difference between the two groups was that there was a higher incidence of "heartburn"

reported by patients in the mini-cholecystectomy group (35% vs 19%, p=0.005) (McMahon *et al,* 1995(b)). The second study with positive findings involved a postal survey of patients treated between January 1988 and December 1991, and embraced two cohorts of patients undergoing either LC or OC. Patients who underwent LC, experienced less right upper quadrant pain than those who had OC (3.4% vs 9.7%) and had a lower incidence of persistent symptoms (4.9% vs 10.3%). There was no difference in the rate of dyspeptic symptoms (39% and 32%) (Stiff *et al*, 1994).

Two other studies detected no statistically significant difference in outcome between the groups, with 93-95% registering satisfaction with the outcome of their operation, regardless of the method of access (Vander Velpen *et al,* 1993; Wilson & Macintyre, 1993).

1.4.7 Cost

Due to the acquisition of equipment to facilitate the new surgery, it was perceived that cost was increased. One study that evaluated LC in three institutions in the USA, found that even with equipment costs included, LC charges ranged from the same to $1500 cheaper than OC (Graves *et al,* 1991). In one Scottish based study, the costs in 1994 for mini-cholecystectomy and LC, were £1090 and £1486 respectively. If reusable instruments had been used, the LC cost would have dropped to £1183, still an increase of £93 (McMahon *et al,* 1994 (b)). A study from Ireland, published in the British Journal of Surgery, calculated the cost of a laparoscopic procedure at £895, compared to £2210 for an open procedure. These figures however, appeared to only include bed costs and did not incorporate costs for equipment or theatre time (Grace *et al,* 1991). In France, one team calculated the cost of OC as 44,204 Francs and LC as 23,412 Francs with the difference entirely attributable to hospital stay (Dubois *et al,* 1995).

1.4.8 Complications

Only three randomised trials have recorded a difference in complications and the findings

were not similar (McGinn *et al,* 1995; Redmond *et al,* 1994; Schauer *et al,* 1993). Redmond and colleagues recorded only one complication (a self-limiting pyrexia, rate 4.5%) in the LC group (n=22), while the open group (n=22) had six chest infections, a gallbladder bed collection and two urinary tract infections (41%). Numbers however were small and the complications in the open group, high. Schauer and colleagues compared the number of patients who had radiological evidence of atelectasis on postoperative chest X-rays as reported by radiologists, blinded to the procedures. Atelectasis was significantly more common in patients after OC than LC (90% vs 40% respectively, $p<0.05$), although only one chest infection occurred in the OC group. Ileus (criteria not defined) was more frequent in the OC group (35% vs 5%).

McGinn and colleagues recorded a 10% complication rate in the LC group (including one death) and only a 3% rate in the mini-cholecystectomy group. However, the mini-cholecystectomy cohort had a commendably low complication rate, in keeping with the unit's expertise with this procedure. The surgeons though were still on their "learning curve" and relatively inexperienced with LC (see below, The Southern Surgeons Club *et al,* 1995). Peritoneal insufflation was performed with 4 litres of carbon dioxide and this may have resulted in high abdominal pressure in some patients and contributed to the fatal myocardial infarction and two deep venous thromboses in the LC group. Eight of the fourteen complications recorded for LC (57%) were potentially technical errors (six postoperative haemorrhages, a Richter's hernia and a clip dislodgement) and the conversion rate for trainees was much higher than the conversion rate for consultants (22% vs 10%). Although the authors advocated a high conversion rate of 10-15% as necessary for safety, the data they used to support this view only highlighted the inexperience with the procedure and the inadequate supervision of trainees on the unit.

Due to the inconclusive nature of these trials, evidence of differences in complication rates were sought from large cohort studies of LC or case series that were compared to historical

series of conventional cholecystectomies.

An early combined European experience of 1,236 cases reported in the American Journal of Surgery, recorded a conversion rate of 3.6%, a complication rate of 1.6% and no mortality (Cuschieri *et al,* 1991). The procedure took a median of 50 (range 30 – 90) minutes and cholangiography only incurred a further 20 minutes delay. Patients were discharged at a median of 3 days postoperatively and returned to normal activities by a median of 11 days. This represented an improvement when compared to historical, conventional cholecystectomy (Chapter 1.3.1). However, bile duct injuries occurred in 0.33% of procedures, which was a higher rate than experienced during OC (cf. section 1.3.1).

A similar report from the Southern Surgeons' Club, USA of 1,518 procedures revealed a conversion rate of 4.7%, a complication rate of 5.1% and a mortality of 0.07%. Complications were mostly minor (approximately 20% were superficial wound infections) but the bile duct injury rate was again high, at 0.5%. The injuries occurred in the presence of normal anatomy and the risk of injury was highest during a surgeon's first 13 procedures (2.2%). The risk for injury during subsequent procedures fell to 0.1% (The Southern Surgeons Club, 1991). In a subsequent analysis of 8,839 patients, the same group calculated that there was a steep learning curve for the first 15 to 20 cases of LC, that 90% of bile duct injuries occurred within a surgeon's first thirty cases and that the incidence of bile duct injury reached a plateau at 0.17% after 50 cases (The Southern Surgeons Club *et al,* 1995).

A large, multicentre but retrospective review of 77,604 procedures, reported a complication rate of 2%, mortality of 0.04% but a bile duct injury rate of 0.61%. Further analysis revealed that the bile duct injury rate for surgeons with experience of less than 100 cases was 0.65% compared with 0.42% at centres where the surgeons had experience of over 100 cases (Deziel *et al,* 1993).

A study from the United States Department of Defence and the Military Health Services System, reviewed 9,130 patients who had undergone LC between January 1993 and May 1994. The authors reported a complication rate of 6%, mortality of 0.13% and a bile duct injury rate of 0.41%. They also identified independent risk factors for sustaining a bile duct injury which were being female, the presence of aberrant anatomy and acute cholecystitis (Wherry *et al,* 1996).

The Comparative Audit Service of the Royal College of Surgeons of England reviewed the introduction of laparoscopic cholecystectomy in 1990-1991 and then again in 1994 (Dunn *et al,* 1994; Nair *et al,* 1997). It reported that general complications and mortality were higher for OC than LC (complications 13% vs 7.95%, mortality 0.76% vs 0.15% respectively), although this apparent difference has to be viewed in the context that, as discussed earlier (cf. section 1.3.8), only 0.73% of bile duct explorations were performed in the LC group versus 13.4% in the OC group. However, it detected a higher incidence of bile duct injuries from laparoscopic cholecystectomy than open cholecystectomy (0.33% vs 0.06%) and a subsequent fall in incidence with increasing experience of LC to 0.07% by 1994 (Dunn *et al,* 1994; Nair *et al,* 1997).

Further evidence from a 5-year audit in the West of Scotland that involved 5,913 cases corroborated this observed reduction in bile duct injury. The rate reduced during the study from 0.75% to 0.4% (all bile duct injuries) and latterly, the major bile duct injury rate was 0.1% (Richardson *et al,* 1996). Likewise, with experience, the rate of common bile duct injuries in France fell to 0.07% (Collet, 1997).

Several patterns of injury emerged. The "classical" injury involved the application of clips to the common bile duct and common hepatic duct and resection of a portion of the bile duct. Alternatively, clips were applied across the common bile duct and the cystic duct, with inadvertent transection of the common hepatic duct during dissection. Another variant was

the application of clips on the distal cystic duct so close to its junction with the common bile duct that the common duct was narrowed or occluded. The right hepatic duct also proved susceptible to injury, as it was mistaken for the cystic duct in some patients (McMahon *et al,* 1995(a); Ress *et al,* 1993; Richardson *et al,* 1996).

During open cholecystectomy, the liver is retracted cephalad and the gallbladder laterally and inferiorly. This opens the angle between the cystic and hepatic ducts. A study of the relative positions of the ducts during laparoscopic cholecystectomy, using intraoperative cholangiography, detected a difference in the angle between the cystic duct and common bile duct that depended on the direction of the traction applied to the gallbladder. In the normal anatomical position (with no traction applied), the angle between the cystic and common ducts was a mean of 59° ± 22°. Cephalad traction on the fundus of the gallbladder (as employed routinely in the Reddick-Olsen technique) reduced the angle between the cystic and common ducts to a mean of 30° ± 19° ($p<0.001$) and rotated the cystic duct anteriorly to the common hepatic duct (McIntyre *et al,* 1996). Failure to realise the distortion of the biliary anatomy, along with "tenting" the cystic duct/bile duct junction, was considered to be the principle cause of the increased rate of bile duct injuries seen during the introduction of LC (McIntyre *et al,* 1996; Ress *et al,* 1993; McMahon *et al,* 1995(a); Richardson *et al,* 1996). In view of the "learning curve" phenomenon and the fact that bile duct injury rates could be reduced by experience and attention to the orientation of the anatomy, the promotion of training courses and close supervision of trainees, particularly during initial cases, were deemed mandatory (Fullarton *et al,* 1994; McMahon *et al,* 1995(a); Southern Surgeons Club *et al,* 1995). Training in basic laparoscopic techniques and cholecystectomy is now compulsory for Basic Surgical Trainees in the UK, who are candidates for their first professional diploma (MRCS) and forms a third of the new Intercollegiate Skills Course. Attendance at a dedicated laparoscopic training course is also strongly advised.

1.5 Laparoscopic cholecystectomy and the surgical stress response

In an attempt to confirm the "minimal invasiveness" of the new laparoscopic technique, several authors examined the effects on the cytokine, acute phase, neuro-endocrine and immune responses. Before these are considered though, it is necessary to briefly review their role in the stress response to surgery to establish why they were measured.

1.5.1 The stress response to conventional surgery

The combination of surgical trauma and anaesthesia induces a number of changes in the physiology and metabolism of the body. Overall, the stress response assists the host with survival from the initial trauma, reprioritises the metabolic processes, directs substrates and inflammatory cells to the site of injury, breaks down injured tissue, repels infection and initiates repair of injured tissue (Hill & Hill, 1998; Stahl, 1987; Tan, 1997). While individual components such as the cytokine, inflammatory and neuroendocrine mediators or the metabolic, acute phase and immune responses can be considered individually, in reality they are inextricably linked and are controlled by complex feedback mechanisms.

1.5.2 Mediators of the stress response to surgery

1.5.2.1 Cytokines

Cytokines are a family of low molecular weight peptides, which are involved in the initiation of the inflammatory host response to injury or sepsis. They are predominantly released by reticulo-endothelial cells and mediate an incredibly complex series of local and global responses, which are as yet, incompletely understood. Due to a short half-life measured in minutes (Castell *et al*, 1990), they are virtually undetectable under conditions of normal homeostasis and are believed to principally exert their effects locally, where concentrations are maximal. In the presence of injury or sepsis, larger quantities enter the circulation and act systemically (Badia *et al*, 1996; Molloy *et al*, 1993; Sheeran & Hall, 1997). Cytokines interact with membrane bound receptors, which are internalised and translocated to the nucleus and these induce mRNA and protein synthesis in the target cell (Moshage, 1997;

Sheeran & Hall, 1997).

Cytokines can be divided into four broad categories based on their biological effects but individual cytokines may possess more than one of these functions (Sheeran & Hall, 1997). These functions are:-

a) **Regulation of natural immunity** – These cytokines are responsible for the protective inflammatory response against viruses and bacteria. They include tumour necrosis factor-α (TNF-α), interleukin-1 (Il-1), Il-5, Il-6 and Il-8.

b) **Control of lymphocyte activation, growth and differentiation** – In response to antigens on the surface of antigen presenting cells, T-helper lymphocytes (Th cells) are activated. There are two subsets, namely Th1 cells (that promote cell-mediated immunity) and Th 2 cells (that promote allergic and humoral immunity). Maturation of these cells is cytokine dependent and Il-2 favours the Th1 response and Il-4 the Th2 response. Other cytokines in this group include TNF-α, Il-1, Il-6, Il-7, Il-9 and Il-12.

c) **Activation of the non-specific inflammatory response** – Interferon-γ (IFN- γ), IL-1 and TNF-α stimulate macrophages to phagocytose bacteria and kill tumour cells. Natural killer cell function is also promoted.

d) **Stimulation of immature leucocyte growth and differentiation** – These cytokines stimulate the production of new leucocytes to replace those consumed in immune and inflammatory reactions. They act as colony-stimulating factors (CSF) for granulocytes (G-CSF) and macrophages (M-CSF).

Due to the potency of these messengers, mechanisms exist for control and regulation of cytokine release and function. Some of these are:-

a) **Feedback loops** - Cytokines and hormones, for example corticotropic releasing hormone, adreno-corticotropic hormone, steroids and catecholamines, influence further cytokine production by modulation of receptor expression or inhibition of gene transcription (Monick *et al*, 1994; van der Poll *et al*, 1995; Webster *et al*, 1998).

b) **Soluble cytokine receptors** - These have been described for Il-1, Il-2, Il-4, Il-7, Il-11 and TNF-α and are shed from cell membranes into body fluids. Soluble Il-1 and TNF- α receptors bind to their respective cytokine and inactive it, effectively functioning as antagonists. In contrast though, soluble Il-6 receptors on binding to Il-6, act as agonists and induce acute phase protein synthesis. (Dinarello, 1997; Moshage, 1997)

c) **Competitive antagonists** – The Il-1 receptor antagonist (Il-1Ra), which is produced by macrophages, competitively binds to the type 1 Il-1 receptor (IL-1R). In primates and human volunteers, it was found to inhibit the systemic effects of Il-1 and Il-6 production. However, clinical trials have failed to demonstrate a clinical attenuation of sepsis by Il-1Ra among patients on an Intensive Care Unit (Dinarello, 1997; Fischer *et al*, 1992).

d) **Anti-inflammatory cytokines** - Several cytokines have been noted to have anti-inflammatory properties, which modulate the inflammatory response. Interleukin-4, Il-10 and Il-13 inhibit gene expression and synthesis of Il-1, Il-6 and TNF-α and promote Il-1Ra release (Chernoff *et al*, 1995; Dinarello, 1997; Sheeran & Hall, 1997). Higher levels have been noted in women in conjunction with a reduction in septic mortality and a protective role has been postulated (Schröder *et al*, 1998).

Interleukin-1α (Il-1 α), Il-1β, Il-6 and TNF-α are cytokines with predominantly pro-inflammatory properties that have been extensively studied. Tumour Necrosis Factor-α, Il-1 and Il-6 appear in the plasma in consecutive order in response to sepsis and trauma and are thought to represent a signalling cascade (Baigrie *et* al, 1992; Di Padova *et* al, 1991; Molloy *et al*, 1993).

Interleukin-1 and TNF-α have similar biological effects and when combined, act synergistically. Interleukin-1 stimulates the immune response and causes a lymphocytosis through the induction of colony stimulating factors, stimulates T-lymphocytes to produce Il-2 (which up-regulates cell mediated immunity) and induces Il-8 production, a potent chemotactic cytokine for neutrophils. TNF-α serves to enhance neutrophil function and

cytotoxicity (Yee & Christou, 1994). Interleukin-1 and TNF-α can activate the acute phase response either independently or through the induction of Il-6 synthesis in hepatocytes and fibroblasts. Endocrine effects of Il-1 include the release of corticotrophin releasing factor from the hypothalamus and stimulation of insulin and glucagon secretion. The metabolic consequence of these cytokines is a hypercatabolic state that mobilises protein and energy stores in response to injury (Dinarello, 1997; Hill *et al*, 1997; Molloy *et al*, 1993; Sheeran & Hall, 1997; Tan, 1997; Webster *et al*, 1998).

Interleukin-6 stimulates the immune response through a direct effect on B and T cell differentiation. It induces haemopoeisis, causes neutrophilia and thrombocytosis and delays neutrophil apoptosis. Interleukin-6 also activates the acute phase response either alone or in combination with Il-1 and TNF- α (Kishimoto *et al*, 1995; Kobayashi & Yamauchi, 1997; Moshage, 1997; Sheeran & Hall, 1997; van Snick, 1990). Hormonal effects include increases in plasma cortisol and glucagon levels and a transient, but marked elevation of noradrenaline. Resting energy expenditure, temperature, glucose and free fatty acid metabolism are increased (Stouthard *et al*, 1995; Tan, 1997).

There is a recognised correlation between the Il-6 response and the magnitude of tissue trauma, with peak levels occurring from 6 to 24 hours postoperatively (Baigrie *et al*, 1992; Cruikshank *et al*, 1990; Ohzato *et al*, 1992). The Il-1 and TNF-α responses do not always display this linear correlation, are often variable and sometimes not detectable (Baigrie *et al*, 1992; Di Padova *et al*, 1991; Wortel *et al*, 1993).

1.5.2.2 Neuroendocrine mediators

The neuroendocrine response, which is centred on the hypothalamus and pituitary, is induced, mediated and controlled by a complex combination of inter-dependant neural and humoral factors. The purpose of this group of hormones is to mediate rapid changes in host physiology that will facilitate survival and subsequent repair of injured tissue.

a) **Hypothalamic-pituitary-adrenal axis** - Afferent neural signals, noradrenaline, Il-1, Il-6 and TNF-α cause an increase in corticotropin releasing hormone (CRH) secretion from the hypothalamus. Corticotropin releasing hormone passes through the portal circulation to the anterior pituitary where it promotes adrenocorticotropic hormone (ACTH) release, which subsequently stimulates glucocorticoid steroidogenesis in the adrenal cortex. Vasopressin, oxytocin and Il-1 increase pituitary sensitivity to CRH and amplify ACTH production (Chrousos, 1995; Munck & Náray-Fejes-Tóth, 1994; Raff, 1993).

The classical pathway for stimulation of cortisol production is not exclusive, as Il-1 can stimulate the adrenal cortex directly (Roh *et al*, 1987). As a result of the multi-factorial control of this system, complete afferent neural blockade does not completely ameliorate the cortisol response (Gershenwald *et al*, 1990; Kehlet, 1989; Naito *et al*, 1992).

The hypothalamic-pituitary-adrenal axis is regulated by a negative feedback loop. Cortisol suppresses CRH and ACTH production and also abrogates the production of the pro-inflammatory cytokines, Il-1 and Il-6. Glucocorticoids have a wide number of systemic actions that control inflammation, immune function and metabolism. They reduce the production of local inflammatory mediators such as histamine, leukotrienes and prostaglandins and prevent leukocyte migration and recruitment at the site of injury. This immuno-modulatory role is considered crucial for protection of the host from the harmful effects of the stress response. Glucocorticoids also stimulate the acute phase response in conjunction with cytokines IL-1 and IL-6 and potentiate lipolysis, gluconeogenesis, insulin resistance and inhibition of insulin secretion (Chrousos, 1995; Munck & Náray-Fejes-Tóth, 1994; O'Riordain *et al*, 1995; Raff, 1993).

Under normal conditions of homeostasis, ACTH and cortisol release is diurnal with peak levels obtained in the morning. Following surgery, this diurnal control is lost and both hormone concentrations rise steeply. Adrenocorticotropic hormone reaches peak levels

(approximately 200pg/ml) around the time of extubation and remains elevated up to six hours postoperatively, returning to normal within 24 hours. Cortisol peaks at the same time (approximately 100 to 150 μg/dl) but remains elevated for up to a week postoperatively. The response of cortisol to ACTH after trauma is biphasic. Initially, cortisol release is precipitated by the increase in ACTH. As ACTH concentrations fall, the persistent elevation of cortisol is due to increased adrenal sensitivity to ACTH, probably mediated by prostaglandins or Il-1 (Furuya *et al*, 1993; Naito *et al*, 1991; Naito *et al*, 1992; Roh *et al*, 1987). The peak levels of cortisol are graded in proportion to the magnitude of the surgical insult (Chernow *et al*, 1987).

b) **Catecholamines** – Afferent neural stimuli from fear, pain, tissue injury or hypotension, converge on the hypothalamus and activate the sympathetic nervous system. Adrenaline is released from the adrenal medulla and noradrenaline from noradrenergic nerve terminals. While the principle stimulus for the induction of catecholamine release is afferent neural impulses, there is evidence of interaction with cytokines as Il-1 also stimulates adrenal catecholamine release (Gwosdow, 1995). The effects of catecholamines are mediated through α and β receptors and there are similarities and differences in their effects (Ganong, 1995(b)).

The cardiovascular effects differ. Adrenaline causes an increase in the heart rate and vasoconstriction. This is offset by β_2 receptor induced vasodilatation in the liver and skeletal muscle, with the result that the systemic vascular resistance actually falls. The pulse pressure widens and cardiac output increases. Noradrenaline however, causes an increase in systemic vascular resistance via α_2 receptors and results in hypertension. This stimulates the carotid and aortic baroreceptors and induces a reflex bradycardia, with a net reduction in cardiac output. Other catecholamine-induced effects include a reduction in renal blood flow with stimulation of the renin-angiotensin system, increased awareness, ciliary dilatation and potentiation of the acute phase response in combination

with Il-6 (Ganong, 1995(b); O'Riordain *et al*, 1995). The metabolic effects include the liberation of free fatty acids by lipolysis, an increase in blood glucose by stimulation of glycogenolysis, gluconeogenesis and promotion of increased peripheral insulin resistance (Ganong, 1995(b); Hill & Hill, 1998).

In a negative feedback loop, adrenaline inhibits systemic TNF-α production and increases release of the anti-inflammatory cytokine, Il-10 (van der Poll *et al*, 1995), while noradrenaline reduces monocyte production of IL-6 and TNF-α via stimulation of β_1-adrenergic receptors (Van der Poll *et al*, 1994; Webster *et al*, 1998).

The levels of adrenaline and noradrenaline rise during surgery and after tracheal extubation, reach peaks of around 400 pg/ml and 1000 pg/ml respectively (Chernow *et al*, 1987; Furuya *et al*, 1993). Thereafter, they fall rapidly, returning to normal within 24 hours (Douglas & Shaw, 1989). The peak levels correlate with the degree of surgical stress (Chernow *et al*, 1987; Douglas & Shaw, 1989).

c) **Vasopressin** – Vasopressin is produced by the magnocellular neurones of the supraoptic and para-ventricular nuclei and is transported in neuro-secretory granules to the axon terminals in the posterior pituitary. It is stored in the nerve endings until action potentials, generated in the body of the neurone, stimulate its release into the hypophyseal portal circulation (Wu & Zbuzek, 1982). Osmoreceptors in the hypothalamus detect increases in the osmolality of the plasma and cause vasopressin to be released. Reductions in blood volume generate afferent neural impulses from stretch receptors in the great veins, right atrium and the pulmonary vessels, that converge on the hypothalamus. Likewise, aortic and carotid baroreceptors detect reductions in blood pressure and transmit afferent impulses that act as a stimulus for vasopressin release (Cochrane *et al*, 1981; Wu & Zbuzek, 1982). Pain, nausea, bowel distension and traction also stimulate rapid releases of large amounts of vasopressin and are mediated by afferent nociceptive

and vagal impulses (Grant *et al*, 1986(a); Grant *et al*, 1986(b); Hampton *et al*, 1991; Haas & Glick, 1978; Wu & Zbuzek, 1982).

Vasopressin acts on V_{1A}, V_{1B} and V_2 receptors. The V_{1A} receptors are located in blood vessels and mediate the vasoconstrictive effects of vasopressin. In the anterior pituitary gland, there are V_{1B} receptors that stimulate ACTH secretion. The V_2 receptors principally mediate water reabsorption in the kidney by increasing the permeability of the collecting tubules but are also found in blood vessels. At high doses (>10 pg/ml), vasopressin induces a pressor effect on arteriolar smooth muscle via stimulation of the V_{1A} and V_2 receptors. This causes an increase in the systemic vascular resistance and the mean arterial blood pressure with a decrease in the cardiac index (Cowley & Liard, 1988). Other effects include activation of plasminogen activator activity at plasma levels in excess of 15pg/ml and Factor VIII activity above 20pg/ml (Grant *et al*, 1985), while Von Willebrand Factor is activated at concentrations between 10 and 25 pg/ml (Nussey *et al*, 1986).

During abdominal surgery, vasopressin concentrations increase from less than 3pg/ml to between 25 and 150 pg/ml and remain elevated for at least two hours after extubation (Cochrane *et al*, 1981; Furuya *et al*, 1993; Grant *et al*, 1986(b); Wu & Zbuzek, 1982) Plasma levels correlate with the magnitude of surgery (Haas & Glick, 1978; Wu & Zbuzek, 1982).

d) **Glucagon and insulin** – Glucagon secretion, from the pancreas and upper gastrointestinal tract, increases glycogenolysis, gluconeogenesis and lipolysis and is precipitated by hypoglycaemia, cortisol, catecholamines, elevations in amino acid concentrations and exercise. It is inhibited by insulin and hyperglycaemia (Ganong, 1995(a)). Glucagon levels increase after major abdominal surgery, peaking one day postoperatively, remain elevated for nearly a week and reflect the magnitude of the

trauma (Russell *et al*, 1975).

Insulin, secreted from the islet cells of the pancreas, inhibits gluconeogenesis, promotes the production of glycogen and increases the uptake of glucose into muscle and fat. It also stimulates protein synthesis, triglyceride deposition and transportation of potassium into cells. Its secretion is inhibited by hypoglycaemia and increased sympathetic activity (Douglas & Shaw, 1989; Ganong, 1995(a)).

In response to trauma, catecholamines, cortisol and glucagon concentrations rise and hyperglycaemia occurs. Despite this, insulin concentrations remain suppressed and there is peripheral insulin resistance (Douglas & Shaw, 1989; Russell *et al*, 1975; Tan, 1997). After about a week, the catecholamine, cortisol and glucagon levels return to normal and insulin levels become elevated. Despite these high insulin levels, plasma glucose concentrations remain elevated, probably due to the peripheral insulin resistance (Douglas & Shaw, 1989).

1.5.3 Systemic responses

1.5.3.1 The metabolic response

Initially there is a transitory "ebb" phase (~24-72 hours) but this is replaced by a hypermetabolic "flow" phase during which time, the basal metabolic rate increases by 20 to 40%. There are changes in the metabolism of protein, fat and carbohydrate that are necessary to provide energy and protein for the immune and acute phase responses, and ultimately the repair of injured tissue (Douglas & Shaw, 1989; Hill & Hill, 1998; Tan, 1997).

Protein metabolism - Protein catabolism releases amino acids from skeletal muscle into the bloodstream. These are subsequently utilised by the liver as substrates for the production of acute phase proteins or gluconeogenesis. Catabolism proceeds at a rate in excess of protein synthesis and the net result is a negative nitrogen balance (Douglas & Shaw, 1989; Hill &

Hill, 1998; Tan, 1997).

Fat metabolism – Activation of hormone sensitive lipase (that controls lipolysis) and a reduction in lipoprotein lipase activity (that regulates the uptake of free fatty acids (FFA) into adipose tissue) results in an increase in the production but not the plasma concentrations of FFAs. These can be used by peripheral tissues for energy, thus preserving glucose as the principle energy source for the immune response and protein synthesis (Douglas & Shaw, 1989; Hill & Hill, 1998; Tan, 1997).

Carbohydrate metabolism - Hyperglycaemia occurs as a result of the mobilisation of glycogen stores (glycogenolysis), and the production of glucose from lactate, glycerol and protein (gluconeogenesis), which are by-products of anaerobic metabolism, lipolysis and protein catabolism respectively. Insulin resistance reduces the uptake of glucose by peripheral tissues and further increases plasma concentrations of glucose for the inflammatory process and wound repair (Douglas & Shaw, 1989; Hill & Hill, 1998; Tan, 1997).

1.5.3.2 The acute phase response

This is a physiological phenomenon that causes rapid alterations in plasma proteins, known collectively as hepatic acute phase proteins. They are involved in haemostatic, antithrombotic, phagocytic, anti-proteolytic and transportation functions and are essential for the limitation of injury and restoration of homeostasis after a noxious insult. Proteins that are beneficial for these purposes, are up-regulated. These include fibrinogen, α_1-acid glycoprotein, type 1 plasminogen activator inhibitor, complement C_3, C-reactive protein (CRP), α_1-antitrypsin, α_1-antichymotrypsin, α_2-macroglobulin, serum amyloid A, caeruloplasmin and haptoglobin. Proteins that are exported during normal homeostasis and are less involved with survival in the acute situation, for example albumin, prealbumin and transferrin, are down-regulated (Stahl, 1987; Moshage, 1997).

Interleukin-1 and Il-6, through common signalling mechanisms and transcription factors, induce the synthesis of acute phase proteins, of which there are two broad categories. Type 1 proteins require Il-1 for induction but a combination of Il-1 and Il-6 for maximal expression and type 2 proteins only require Il-6 (Moshage, 1997).

Considerable interaction exists between cytokines and hormones to further modulate the acute phase response. A complex set of interactions has been demonstrated using hepatocytes taken from patients undergoing liver resection (O'Riordain *et al*, 1995). In the absence of Il-6, dexamethasone, glucagon, adrenaline and insulin only have minimal influence on the synthesis of acute phase proteins. However, in the presence of Il-6, dexamethasone increases the production of positive acute phase proteins in a dose dependant manner. Adrenaline and glucagon increase CRP synthesis but reduce α_1-anti-chymotrypsin, α_1-acid glycoprotein and haptoglobin, while insulin reduces CRP and haptoglobin expression with no effect on the other acute phase proteins. Combinations of dexamethasone, glucagon and adrenaline in association with Il-6 have a cumulative effect and when all combined, nullify the inhibitory effects of insulin on CRP synthesis. There is therefore potential for individual and global control of acute phase proteins.

The acute phase proteins that increase in response to surgical trauma peak at 48 to 72 hours after the insult and return to normal levels by one week. A correlation between peak levels of CRP and the degree of trauma has been reported (Baigrie *et al*, 1992; Cruikshank *et al*, 1990; Stahl, 1987) but other researchers have failed to observe such a relationship or any correlation with the incidence of postoperative complications (Ohzato *et al*, 1992).

1.5.3.3 The immune response

Surgery results in depressed immune function that correlates with the magnitude and duration of open surgery (Lazarou *et al*, 1989; Lennard *et al*, 1985; Meakins, 1988). This phenomenon is mediated by circulating factors released from the wound and through the actions of

glucocorticoids (Lazarou *et al*, 1989; Munck & Náray-Fejes-Tóth, 1994). The pro-inflammatory cytokine, Il-2, is suppressed which results in depressed macrophage, neutrophil and natural killer cell function, reduced numbers of circulating lymphocytes and a curtailment of T-cell proliferation. As natural and lymphocyte activated killer cells are important in tumour surveillance, this depression of the immune response not only increases the potential for infection but also the risk of metastasis of malignant cells (Horgan *et al*, 1988; Lennard *et al*, 1985; Pollock *et al*, 1991; Redmond *et al*, 1992; Shigemitsu *et al*, 1992; Stephan *et al*, 1987). However, it is believed that this suppression protects the host from the harmful effects of "overshoot" of the inflammatory mediators (Munck & Náray-Fejes-Tóth, 1994).

1.5.4 The effects of laparoscopic cholecystectomy on the stress response

1.5.4.1 The cytokine, acute phase and immune responses

a) The cytokine response

In eleven studies that compared the Il-6 responses to open cholecystectomy (OC) and laparoscopic cholecystectomy (LC) in a total of 333 patients (136 randomised, 221 non-randomised), the Il-6 levels were found to be lower in patients who underwent LC. (Bellón *et al*, 1997; Glasser *et* al, 1995; Jakeways *et al*, 1994; Joris *et al*, 1992; Karayiannakis *et al*, 1997; Kloosterman *et al*, 1994; Maruszynski & Pojda, 1995; Reith *et al*, 1997; Roumen *et al*, 1992; Targarona *et al*, 1996; Ueo *et al*, 1994). The findings are summarised in tables 1.1 and 1.2.

One group in Glasgow, Scotland who performed a randomised trial of mini-cholecystectomy and LC, failed to show a difference in the Il-6 response between the two groups (McMahon *et al*, 1993(c)). However, the sample size was relatively small (n=20), there was wide variation of the results within each group and the median Il-6 response was higher in both groups than was seen in another study that used the same assay (Jakeways *et al*, 1994; Joris, 1993). In another randomised study of OC versus LC,

conducted in Uppsala, Sweden, no difference was demonstrated in the Il-6 response (Berggren *et al*, 1994). However, it was not clearly stated in the paper, exactly when the Il-6 samples were collected (it may have been at the same time as the CRP, which was sampled preoperatively and at 24 hours), which makes interpretation of the results difficult. The third study in the literature in which the authors found no statistically significant difference between OC and LC was performed in Belgium. Twenty-four patients were recruited but they were not randomised. The peak Il-6 response was at 8 hours postoperatively and although it was lower in the laparoscopic cohort, there was no significant difference from the OC cohort (Vander Velpen *et al*, 1994).

b) The acute phase response

The acute phase response has been assessed most extensively by measurement of CRP. In eight studies that contained 251 patients (83 randomised, 168 non-randomised), the CRP response was lower after LC than OC (Jakeways *et al*, 1994; Joris *et al*, 1992; Karayiannakis *et al*, 1997; Mealy *et al*, 1992; Reith *et al*, 1997; Roumen *et al*, 1992; Targarona *et al*, 1996; Ueo *et al*, 1994). Only one study was randomised (Karayiannakis *et al*, 1997). The findings are summarised in tables 1.1 and 1.2.

As with the Il-6 response, the group from Uppsala, Sweden, failed to demonstrate a significant difference between the CRP responses to LC and OC, while McMahon and colleagues found no statistically significant difference in the CRP, albumin, fibrinogen or transferrin responses to LC or mini-cholecystectomy (Berggren *et al*, 1994; McMahon *et al*, 1993(c)). However, in the latter study, CRP levels up to 72 hours postoperatively and the median area under the curve, were less after LC than mini-cholecystectomy (48 versus 84 mg/l.h.10^2 respectively). Small numbers and wide variation in the results may have precluded statistical significance.

c) The immune response

Laparoscopic surgery appears to cause less suppression of cell-mediated immunity than conventional, open surgery. One group in Leeds measured T-cell proliferation to mitogen stimulation preoperatively then again at 24 hours in two cohorts of patients who underwent LC and OC. In the LC group, the T-cell response was unimpaired at 24 hours but was significantly reduced among patients in the conventional group. This occurred even though the operative times for LC were longer than for OC. However, no difference in natural killer cell function was found (Griffiths *et al*, 1995).

Another group demonstrated a reduction in skin phytohaemagglutanin reactivity and HLA-DR expression on monocytes (required for antigen presentation to T-helper cells) among patients treated by conventional cholecystectomy, but no postoperative reduction among patients who underwent LC (Kloosterman *et al*, 1994).

The results of other studies have demonstrated a less marked elevation of white cell count (Joris *et al*, 1992) with better preservation of neutrophil, lymphocyte and monocyte function after LC compared to OC (Carey *et al*, 1994; Horgan *et al*, 1992; Redmond *et al*, 1994). Despite the preservation of immune function after LC, only one study has recorded a lower incidence of septic complications after LC compared to OC (Redmond *et al*, 1994). There were two patients with unexplained pyrexias, six respiratory and two urinary tract infections and one gallbladder bed collection that required treatment in the OC group compared with one patient in the LC group who had a pyrexia ($p<0.05$).

1.5.4.2 The neuroendocrine response

a) Hypothalamic-pituitary-adrenal axis

The CRH response has not been shown to differ between LC and OC although there has only been one study and the numbers were small (n=12) (Donald *et al*, 1993).

Adreno-corticotropic hormone was found to rise within 20 minutes of the start of LC and OC, to peak at values of around 400 pg/ml and remain elevated for four to six hours after surgery (Deuss *et al*, 1994; Donald *et al*, 1993; Glaser *et al*, 1995; Ortega *et al*, 1996; Targarona *et al*, 1996). In two randomised studies and one cohort study, there was a tendency for ACTH levels to be lower in the laparoscopic group but this was not significant (Donald *et al*, 1993; Glaser *et al*, 1995; Ortega *et al*, 1996).

Fourteen studies that involved comparisons of the cortisol responses to open / minicholecystectomy and LC failed to reveal any significant differences between the groups. Levels rose within about thirty minutes of the start of surgery to reach between 30 to 50μg/dl by the time of extubation (Deuss *et al*, 1994; Donald *et al*, 1993; Jakeways *et al*, 1994; Ortega *et al*, 1996; Rademaker *et al*, 1992). Thereafter, cortisol concentrations decreased and reached preoperative baseline values by around 24 hours postoperatively (Aktan *et al*, 1994; Bellón *et al*, 1997; Deuss *et* al, 1994; Jakeways *et al*, 1994; Joris *et al*, 1992; McMahon *et al*, 1993(c); Ortega *et al*, 1996; Redmond *et al*, 1994; Targarona *et al*, 1996). Likewise, no difference was detected in 24-hour urinary cortisol measurements for patients who underwent LC or OC (Berggren *et al*, 1994; Mealy *et al*, 1992; Ortega *et al*, 1996).

However, in one study of 50 patients randomised to LC or OC, plasma concentrations of cortisol peaked intraoperatively in both groups at around 30μg/dl but returned to baseline levels over the next 24 hours in the LC group and remained elevated in the OC group (Agnifili *et al*, 1993). In another large randomised study (n=83), plasma cortisol levels increased during LC and OC to peak four hours after surgery at a mean of 36.3μg/dl and 34.1μg/dl respectively. Thereafter, they fell towards baseline values but were significantly lower in the LC group at 8 hours postoperatively ($p<0.05$) (Karayiannakis *et al*, 1997).

A group who performed a relatively small cohort study of LC and OC obtained similar statistically significant results. Plasma cortisol concentrations increased significantly during surgery in both groups to around 30μg/dl. Nine hours after surgery (the end of the study period), cortisol levels had returned to baseline in the LC group but were still elevated in the OC group (Schauer & Sirinek, 1995). Likewise, in a study in which a cohort of patients who underwent LC were compared with historical conventional controls, a statistically lower concentration of cortisol was detected six hours after surgery (Hill *et al*, 1993). The findings are summarised in tables 1.1 and 1.2.

b) Catecholamines

In one cohort study, the authors reported higher 24-hour urinary vanillyl-mandelic acid levels (metabolites of catecholamines) for LC than OC and this was corroborated by another cohort study in which the investigators also found higher urinary noradrenaline and dopamine levels in the LC group (Mealy *et al*, 1992; Hill *et al*, 1993). In yet another randomised study, a group reported that noradrenaline levels were significantly higher, both intra- and post-operatively, among patients who underwent LC rather than OC. Adrenaline levels increased in both groups but the responses were not significantly different (Donald *et al*, 1993).

In three papers published between 1992 and 1994, it was reported by the authors that no differences in urinary (Berggren *et* al, 1994; McMahon *et al*, 1993(c)) or plasma catecholamines (Joris *et al*, 1992) were detected between patients who underwent LC or OC. The latter study however, did not take samples until four hours after surgery by which time, levels could have subsided (Chernow *et al*, 1987; Furuya *et al*, 1993).

Study	N	Il-6	CRP	AVP	CRH	ACTH	Cortisol	Catechol	Glucose	Insulin
Agnifili *et al*, 1993	50						↓		↔	
Bellón *et al*, 1997	28	↓[a]					↔			
Berggren *et al*, 1994	30[b]	↔	↔				↔[c]	↔[c]	↔	↔
Donald *et al*, 1993	12			↓	↔	↔	↔	↔/↑[c]		
Karayiannakis *et al*, 1997	83	↓	↓				↓	↓	↓	
Maruszynski & Podja, 1995	25	↓								
McMahon *et al*, 1993(c)	20	↔	↔				↔	↔[c]		
Ortega *et al*, 1996	20			↑		↔	↔[d]	↑/↔/↓[f]	↑/↓[g]	↓
Redmond *et al*, 1994	44		↔				↔			

Table 1.1 Summary of results from published randomised trials that have compared the stress response to open and laparoscopic cholecystectomy.

Key

N - number of patients; **Il-6** – Interleukin-6; **CRP** – C-reactive protein; **AVP** – arginine vasopressin; **CRH** – corticotropic releasing hormone; **ACTH** – adreno-corticotropic hormone; **Catechol** – catecholamines

↔ - no difference, ↓ - lower levels in LC than OC, ↑ - higher levels in LC than OC

a - no difference between groups for Il-1β, Il-10, TNF-α,

b - data for only 27 patients – no reason stated for missing data/withdrawal, **c** - urine sample, **d** – urine and plasma

e - no difference in adrenaline between groups but higher noradrenaline levels in the LC group,

f - higher serum adrenaline measurements for LC but lower urinary catecholamines for LC, no difference in noradrenaline,

g - glucose measurements were significantly higher intraoperatively for LC than OC but were lower postoperatively in the LC group.

Study	N	Il-6	CRP	ACTH	Cortisol	Catechol	Glucose	Insulin
Aktan *et al*, 1994	40				↔			↔
Deuss *et al*, 1994	65			↔	↔			
Glaser *et al*, 1995	58	↓		↔	↔	↓	↓	
Hill *et al*, 1993	31				↓	↑[a]	↔	
Jakeways *et al*, 1994	24	↓	↓		↔		↓	
Joris *et al*, 1992	30	↓	↓		↔	↔	↓	
Kloosterman *et al*, 1994	16	↓						
Mealy *et al*, 1992	21		↓		↔[a]	↑[a]		
Rademaker *et al*, 1992	20				↔		↔	
Reith *et al*, 1997	23	↓[b]	↓					
Roumen *et al*, 1992	21	↓	↓					
Schauer & Sirinek, 1995	23				↓	↓	↓	
Targarona *et al*, 1996	25	↓	↓	↔	↔		↔	
Ueo *et al*, 1994	24	↓	↓					
Vander Velpen *et al*, 1994	24	↔						

Table 1.2 Summary of results from published, non-randomised cohort studies that have compared the stress response to open and laparoscopic cholecystectomy.

Key: N - number of patients; **Il-6** – Interleukin-6; **CRP** – C-reactive protein; **ACTH** – adreno-corticotropic hormone; **Catechol** – catecholamines.

↔ - no difference, ↓ - lower levels in LC than OC, ↑ - higher levels in LC than OC

a – urine sample, **b** – no difference between groups for TNF-α

In 1995, two cohort studies were reported that contradicted the initial studies. A small, study (n=23) noted similar intraoperative increases in catecholamines during LC and OC but lower levels of noradrenaline from 3 to 9 hours, adrenaline from 2 to 9 hours and dopamine from 1 to 9 hours after induction, in the LC group compared to the OC group. Although the patients were not randomised and were assigned to each arm of the trial by the attending surgeon, the demographics of the patients and the severity of biliary disease were well matched (Schauer & Sirinek, 1995). In the second study reported that year, there were no differences between groups during the operation but patients in the LC group had plasma concentrations of noradrenaline and adrenaline that were significantly lower than in the OC group at 24 hours postoperatively (Glaser *et al*, 1995).

To further confuse the issue, a group who performed a randomised trial in Los Angeles, USA, reported that they found plasma concentrations of adrenaline to be higher during LC than OC and that plasma noradrenaline was similar in both groups. Paradoxically however, combined *urinary* levels of catecholamines were higher in the OC group than the LC group. The authors suggested that the lower urinary levels in the LC group could be accounted for by differential plasma catecholamines clearance associated with reduced renal blood flow and urine output secondary to the pressure effects of pneumoperitoneum (Ortega *et al*, 1996).

In a large randomised controlled trial of LC and OC that contained 83 patients, it was found that plasma concentrations of noradrenaline at 8 and 24 hours and adrenaline at 4, 8 and 24 hours were significantly lower among patients who had LC than those who had OC (Karayiannakis *et al*, 1997).

Despite the differences in the results in the literature, it is clear that catecholamines increase in response to both LC and OC. It is not possible from the studies published to date to ascertain whether differences in technique, sampling times or assays are

responsible for the conflicting results or to state which approach (LC or OC) generates the least response. It is clear though that further evaluation of the catecholamine response is required.

c) Vasopressin

Only two groups have directly compared vasopressin responses to LC and OC and managed to obtain diametrically opposite results. A group from New Zealand noted that during LC and OC, vasopressin increased to reach peaks of 49.2pmol/l and 117pmol/l respectively, ten minutes after skin incision. Vasopressin remained elevated in the OC group until the end of the procedure but increased further to 140pmol/l just after extubation. In the patients who underwent LC however, vasopressin levels were lower throughout the procedure ($p<0.05$) and remained lower until sampling ceased at 40 minutes post-extubation ($p<0.01$) (Donald *et al*, 1993).

In another randomised study, the vasopressin response one hour after the start of surgery was over five times higher in patients who underwent LC than those who had an OC (281 pg/ml vs 54 pg/ml respectively, $p<0.01$) There was no difference postoperatively and vasopressin returned to baseline levels by 24 hours (Ortega *et al*, 1996).

It is not clear why the vasopressin response was lower for LC than OC in the first study but higher for LC than OC in the second study. This could be due to differences in sampling times, technique or the fact that both studies involved small numbers ($n=12$ and $n=20$ respectively).

d) Glucose and insulin – Four randomised and seven cohort studies have been performed in which the authors have addressed the response of glucose to LC and OC. (Agnifili *et al*, 1993; Berggren *et al*, 1994; Glaser *et al*, 1995; Hill *et al*, 1993; Jakeways *et al*, 1994; Joris *et al*, 1992; Karayiannakis *et al*, 1997; Ortega *et al*, 1996; Rademaker *et al*, 1992;

Schauer & Sirinek, 1995; Targarona *et al*, 1996).

During LC and OC, perioperative plasma glucose concentrations rose to a similar extent and there were no differences between the groups (Agnifili *et al*, 1993; Berggren *et al*, 1994; Glasser *et al*, 1995; Karayiannakis *et al*, 1997; Ortega *et al*, 1996; Rademaker *et al*, 1992; Schauer & Sirinek, 1995). In one study where glucose was sampled at the time of extubation, levels were significantly higher in the LC than the OC group (Ortega *et al*, 1996).

In the postoperative period, it was noted in several reports that glucose concentrations were lower in patients who underwent LC rather than OC, from 4 hours up to 2 days after surgery (Glasser *et* al, 1995; Jakeways *et al*, 1994; Joris *et al*, 1992; Karayiannakis *et al*, 1997; Ortega *et al*, 1996; Schauer & Sirinek, 1995). However, in five studies, no difference was detected. In three of these studies (of which only one was randomised), the glucose concentrations were sampled for a minimum of 24 hours after surgery (Agnifili *et al*, 1993; Hill *et al*, 1993; Targarona *et al*, 1996) but in two, glucose sampling ceased within 3 hours of surgery and could have potentially missed a later difference between the groups (Berggren *et al*, 1994; Rademaker *et al*, 1992).

Only three studies have examined the insulin response, of which two were randomised and one was non-randomised. Berggren and colleagues sampled insulin at the end of the operation and found that the levels were normal in all patients (n= 30) regardless of whether they had undergone LC or OC (Berggren *et al*, 1994). In another randomised study (n=20), insulin levels did not rise during the intraoperative period but did rise postoperatively in both LC and OC groups. The increase however was less pronounced and statistically significant after LC than OC at 4, 12 and 24 hours after extubation (Ortega *et al*, 1996). In a non-randomised study (n=40), insulin rose in both groups between 8 and 48 hours after surgery but there was no significant difference between the

groups (Aktan *et al*, 1994). However, both groups of patients had a dextrose infusion postoperatively, which could have affected insulin levels.

1.5.5 Overview of the stress responses to open and laparoscopic cholecystectomy with reference to the size of the wounds and the physiological sequelae of pneumoperitoneum

Examination of the available literature discussed above suggests that during laparoscopic cholecystectomy, there is a schism of the tissue mediated responses and the neurally mediated responses, which has not been seen during conventional surgery.

The cytokine and acute phase responses are activated to a lesser extent and postoperative immune function is better preserved after laparoscopic than open cholecystectomy. This is logical in view of the fact laparoscopic cholecystectomy creates smaller wounds than a conventional cholecystectomy and that the magnitude of the cytokine, acute phase and immune responses is proportional to the degree of tissue trauma (cf. sections 1.5.2 and 1.5.3).

However, the effect of LC on the neuroendocrine response is more ambiguous. Overall, it would appear that there are no significant differences in the hypothalamic-pituitary-adrenal axis, catecholamine or vasopressin responses. However, in the two largest randomised trials of LC versus OC in which the stress response has been measured, there was less activation of the cortisol response after LC compared to OC that cannot be easily explained away. The response of catecholamines remains to be clearly and unequivocally documented but all studies to date concurred in one respect; the levels of adrenaline and noradrenaline increased in response to LC and OC.

One of the major differences between open and laparoscopic surgery is insufflation of the peritoneal cavity. This may contribute to the neuroendocrine responses through a combination of the pressure effects and the physical properties of the gaseous agent employed. A closer examination of the technique of laparoscopy and its physiological

impact is therefore required while considering the neuroendocrine response.

Insufflation is followed by a rapid increase in systemic vascular resistance, mean arterial blood pressure and heart rate with a reduction in cardiac output of as much as 20-30% (Joris *et al*, 1993; Westerband *et al*, 1992). Direct pressure on the splanchnic bed and the major abdominal vessels reduces arterial blood flow and increases the afterload. This increases myocardial work-load and reduces cardiac output (Coventry, 1995; Shuto *et al*, 1995; Wahba *et al*, 1995).

Simultaneously, there is a two-phase pressure effect on the abdominal venous system. Initially as pneumoperitoneum is established, there is an increase in venous return due to pressure induced emptying of the portal venous system and the inferior vena cava. However, once the pneumoperitoneum has been established and these capacitance vessels have been compressed, there is a reduction in the venous return as the extrinsic pressure from the abdominal cavity impedes flow through the inferior vena cava, the iliac and portal venous systems (Wahba *et al*, 1995). This is manifest as a reduction in femoral vein flow velocity and increased femoral venous pressure (Goodale *et al*, 1993). During both phases however, there is an increase in central venous pressure (CVP) and pulmonary arterial wedge pressure (PAWP). The elevation in the first phase is as a direct consequence of the increased flow as blood is displaced from the capacitance vessels. The elevation in CVP and PAWP in the second phase though, is paradoxical due to transmission of the intra-abdominal pressure to the thorax via the diaphragm (Wahba *et al*, 1995). The resultant reduction in venous return reduces end-diastolic volume and therefore stroke volume and cardiac output in accordance with Starling's law of the heart (Ganong, 1995(c); Joris *et al*, 1993).

In addition to the physiological sequelae of the pressure of pneumoperitoneum, the chemical properties of the gas used to insufflate the abdomen have to be considered. The ideal gas for insufflation should be colourless, odourless, physiologically inert, not support combustion

and cost-effective (Eisenhauer *et al*, 1994; McMahon *et al*, 1994(a)). Currently, no gaseous agent fits all of these criteria and each gas has both advantages and disadvantages. Recently, abdominal wall retractors have been developed which obviate or reduce the requirement for "pneumoperitoneum"; the impact of these will be discussed later (cf. section 1.6.5).

Carbon dioxide (CO_2) is currently the gas of choice because it is colourless, odourless, does not support combustion and has a low cost. An additional advantage is its solubility in water, which contributes to rapid absorption from the peritoneum or fascial planes after surgery and is important in mitigating the clinical consequences of the rare event of gas embolism. However, the physiological effects of CO_2 are also a disadvantage. This gas, a normal waste product of respiration, is primarily excreted via the lungs. Insufflated CO_2 rapidly dissolves on the moist peritoneal surface to produce carbonic acid, which is absorbed systemically. Following the induction of anaesthesia and insufflation, there is a reduction in functional residual capacity due to reductions in chest wall and diaphragmatic muscle tone. Insufflation of the peritoneal cavity also splints the diaphragm, further reducing functional residual capacity and pulmonary compliance. Obesity, commonly present in patients undergoing cholecystectomy, augments these changes. As functional residual capacity diminishes, there is an increase in the ventilation to perfusion mismatch, with physiological right to left shunting of pulmonary blood flow. This results in an increase in the difference between alveolar and arterial oxygen tensions and favours carbon dioxide retention. Carbon dioxide absorbed from the peritoneum compounds the increase in arterial CO_2 ($PaCO_2$), expired end-tidal CO_2 ($EtCO_2$) and acidosis (Coventry, 1995; Wahba, 1995).

To counteract these changes and maintain the $PaCO_2$ and pH within normal limits while the abdomen is insufflated, ventilatory peak airway pressure has to increase by 6 cmH_2O and the minute volume by 7 to 35% (Baraka *et al*, 1994; Joris *et al*, 1993; Koivusalo *et al*, 1997; McMahon *et al*, 1993(a)). Even so there is still a small rise in the $PaCO_2$ and pH and this persists postoperatively. In the study by McMahon and colleagues, increases in $PaCO_2$ from

5.3kPa preoperatively to 6.0kPa postoperatively and of hydrogen ion concentration from 41nmol/l to 46nmol/l were recorded despite an increase in ventilation (McMahon *et al*, 1993(a)). These results correlate with another study of 14 patients who underwent diagnostic laparoscopy, during which it was found that $PaCO_2$ increased from 5.03kPa just before insufflation, reached a peak of 5.63kPa during laparoscopy and remained high after desufflation at 5.63kPa ($p<0.01$ compared to initial measurement) (Puri & Singh, 1992). Caution is required in patients with chronic obstructive pulmonary disease, as $EtCO_2$, which is normally used as an indirect measurement of $PaCO_2$, tends to underestimate $PaCO_2$. In addition, the increase in peak airway pressure is associated with a risk of pneumothorax (McMahon *et al*, 1993(a); Feig *et al*, 1994).

Hypercarbia and acidosis stimulate the sympathetic nervous system via the carotid and aortic chemoreceptors (Ortega *et al*, 1996; Wahba *et al*, 1995). As discussed above, the direct mechanical pressure effects of pneumoperitoneum stimulate the sympathetic nervous system through a reduction in cardiac output (Joris *et al*, 1993). Noradrenaline is known to increase the systemic vascular resistance and mean arterial blood pressure (Ganong, 1995(b)) and rapid increases in plasma levels that coincide with the process of insufflation have been reported (Aoki *et al*, 1994; Koivusalo *et al*, 1996(b); Mikami *et al*, 1996). However, while other authors have reported intraoperative increases in noradrenaline, they have found that the peak concentrations occurred at or after desufflation (Donald *et al*, 1993; O'Leary *et al*, 1996; Ortega *et al*, 1996; Schauer & Sirinek, 1993).

The response of vasopressin to peritoneal insufflation is also rapid and pronounced with plasma levels reaching between 5 and 70 times pre-insufflation values within three minutes. As the release of vasopressin is so rapid and it is known to have a pressor effect on arteriolar smooth muscle at high concentrations, it has been implicated in the increases in systemic vascular resistance and mean arterial blood pressure that are seen during insufflation. Postulated mechanisms whereby the pneumoperitoneum precipitates release of vasopressin,

include peritoneal stretching, activation of aortic baroreceptors or a decrease in the transmural pressure gradient of the right atrium (Felber *et al,* 1993; Melville *et al,* 1985; Punnonen & Viinamäki, 1982; Solis Herruzo *et al,* 1989 & 1991; Walder & Aitkenhead, 1997).

Evidence is accruing to implicate the renin-angiotensin system in the haemodynamic consequences of pneumoperitoneum. Increased intra-abdominal pressure reduces renal blood flow and stimulates renin release from the juxta-glomerulary apparatus, which in turn activates angiotensin I. This is transformed to angiotensin II that ultimately stimulates the release of aldosterone from the adrenal cortex. Both angiotensin II and aldosterone have marked pressor effects on the vascular system. While the effects of LC and OC on this system have never been compared, the responses of renin and aldosterone to insufflation have been investigated, as have the effects of a gasless technique of laparoscopy (cf. section 1.6.5). Following insufflation, plasma renin and aldosterone levels rise in parallel with systemic vascular resistance and mean arterial blood pressure and return to normal with desufflation (O'Leary *et al,* 1996; Koivusalo *et al,* 1996(b); Koivusalo *et al,* 1998).

1.6 Modulation of the physiological and stress responses to laparoscopic cholecystectomy and the influence on clinical outcome

In view of the haemodynamic and neuroendocrine consequences of pneumoperitoneum described above, investigators embarked on studies to determine if the effects could be modulated. Review of the literature reveals that some of the effects of laparoscopic surgery can be influenced by careful attention to detail.

1.6.1 Positioning of the patient

The commonly practised manoeuvre of "head-up" reverse Trendelenburg tilt, used to allow loops of bowel to fall away from the upper abdomen and away from the operative field, has deleterious effects on cardiorespiratory function when combined with peritoneal insufflation,

as highlighted in "The Report of the National Confidential Enquiry into Peri-operative Deaths 1996/1997" (Gray *et al*, 1997). A reduction in the cardiac index of 30 - 50% has been recorded, in both healthy patients and those with impairment of cardiac function (Iwase *et al*, 1992; Joris *et al*, 1993; Westerband *et al*, 1992). This may be of little consequence to young, fit patients with adequate physiological reserve, but it can result in inadequate oxygen delivery to the myocardium in patients with coexisting cardiac disease. Increases in plasma adrenaline, renin and aldosterone have also been recorded in response to reverse Trendelenburg tilt (O'Leary *et al*, 1996).

The reverse Trendelenburg position increases the functional residual capacity and compliance, but due to the resulting reduction in cardiac output, does not translate to an improvement in gas exchange. Pressure transmitted through the diaphragm by insufflation in the reverse Trendelenburg position also negates any improvement in compliance. The Trendelenburg position ("head down") augments the decrease in functional residual capacity and is compounded by insufflation (Coventry, 1995; Wahba *et al*, 1995). Excessive table tilt should be avoided whenever possible (Gray *et al*, 1997).

1.6.2 Pressure of the pneumoperitoneum

Variations in the pressure of the pneumoperitoneum affect cardiac output and visceral perfusion. Studies using pigs and dogs have derived that there is a linear correlation between the reduction in cardiac output and elevation of total peripheral resistance with increasing pressure in the abdomen (Mikami *et al*, 1998; Richardson & Trinkle, 1976; Shuto *et al*, 1995). In one study, plasma catecholamines remained unchanged from baseline measurements at an intra-abdominal pressure of 10mmHg but increased significantly at a pressure of 20mmHg (Mikami *et al*, 1998). In view of the haemodynamic consequences, there is little advantage to be gained by a pressure above 15 mmHg, as operating space does not significantly increase beyond this (McDougall *et al*, 1994).

The pressure of the pneumoperitoneum affects portal venous blood flow. In a clinical study That involved 11 patients undergoing laparoscopic cholecystectomy, doppler evaluation of the portal vein found that there was a 37% reduction in flow with a pneumoperitoneum of 7mmHg, and a 53% reduction at 14 mmHg (Jakimowicz *et al*, 1998). A team in America has also demonstrated a negative linear correlation between the pressure of insufflation and gastric mucosal pH in pigs (Knolmayer *et al*, 1998). The clinical implications for the splanchnic circulation during cholecystectomy are not known.

A clinical study was performed in Glasgow in which 40 patients were randomised to LC at insufflation pressures of either 7.5mmHg (low) or 15mmHg (standard). Intraoperatively, carbon dioxide levels, end-tidal CO_2 and peak airway pressure rose but there was no significant difference between groups. There was a fall in the cardiac index at the start of insufflation that was more pronounced and lasted a median of 5 minutes longer in the standard pressure group (2 min vs 7 min) but this was not statistically significant. An elevation in the mean arterial pressure coincided with the fall in cardiac index and was slower to occur in the standard pressure group but again this difference was not statistically significant. Postoperatively, pain scores in the low pressure group were significantly better up to 1 week after surgery and there was a tendency for less analgesic consumption and demands than in the standard pressure group. Peak expiratory flow was better (68% vs 53% of baseline values, p=0.04) at six hours in the low pressure group but was similar in both groups at 24 hours (70% vs 62% of baseline, p not significant) (Wallace *et al*, 1997).

A group in Helsinki, Sweden, compared the use of conventional pneumoperitoneum against low pressure CO_2 insufflation (with the aid of an abdominal wall retractor) in 24 patients. Effectively, it was a study of conventional and low pressure insufflation with pressures of 11mmHg in the conventional group and 3mmHg in the low pressure group. The positive intraoperative clinical findings in favour of the retractor-assisted group were better pulmonary compliance, minimal change to minute volume requirements and a slower rise in

mean arterial blood pressure (although it still reached a similar peak level as the conventional group). Postoperatively, the low pressure group was less drowsy and suffered less nausea and vomiting. There were no differences in operating time, heart rate response, pain scores or analgesia requirements. Evaluation of the stress response found similar increases in vasopressin, prolactin and noradrenaline throughout the procedure in both groups, although there was a tendency (non-significant) for the noradrenaline response to be higher in patients who had standard pneumoperitoneum. Urine output during the first 30 minutes of insufflation was significantly lower and the plasma renin activity significantly higher in the conventional group than in the low pressure group (Koivusalo *et al*, 1996(b); Lindgren *et al*, 1995).

1.6.3 Alternatives to carbon dioxide for pneumoperitoneum

As described earlier (cf.section 1.5.5), insufflated CO_2 rapidly dissolves on the moist peritoneal surface to produce carbonic acid and is absorbed systemically. Theoretically, a gas without the potential for systemic absorption and the ability to induce acidosis would be preferable (Eisenhauer *et al*, 1994; McMahon *et al*, 1994(a)).

1.6.3.1 Nitrous Oxide

Gynaecologists and gastroenterologists have used nitrous oxide for many years for outpatient diagnostic laparoscopy under local anaesthesia (Solis Herruzo *et al*, 1989). However, on the basis of a perceived explosion hazard in the event of mixing with methane and hydrogen from the bowel, it failed to gain favour with the general surgical community. Also, there was evidence that it was responsible for a reduction in cardiac output. In a small study (n=7 patients) of the physiological effects of pneumoperitoneum with carbon dioxide, cardiac output fell by a mean of 16% but the difference did not reach statistical significance (Marshall *et al*, 1972(a)). After a similar study of the effects of nitrous oxide (n=8 patients) performed by the same group, it was reported that cardiac output fell by a mean of 24.5% during insufflation and this was statistically significant (Marshall *et al*, 1972(b)). However, the number of patient involved was small, they were involved in two separate studies and

were therefore not randomised and there was no record of the pressure of the pneumo-peritoneum in the group who received nitrous oxide.

Recently, a study of intra-peritoneal gas composition during laparoscopic cholecystectomy (n=14) and anti-reflux procedures (n–6) have cast doubt on the validity of the risks (Hunter *et al*, 1995). For combustion to occur in the presence of nitrous oxide, hydrogen must constitute 5.5% of the gas mixture or methane, 4%. No methane was found in any of the peritoneal samples drawn from 20 patients and in the four cases where hydrogen was detected, it only reached concentrations between 0.016% and 0.075% (70 times lower than the combustion threshold). In the unlikely event of large bowel perforation, 125ml of 100% hydrogen or methane in 3 litres of nitrous oxide would be required to attain minimum combustion levels. These levels are in excess of normal physiological values. The findings corroborated a previous study of gas composition during laparoscopy, which had been summarily dismissed in the past (Robinson *et al*, 1976; Steptoe, 1976). The investigators did not detect any methane and only found hydrogen in one sample at a concentration that was 2,500 times lower than the combustion threshold (Drummond & Scott, 1976(a); Drummond & Scott, 1976(b)).

An investigation of the effects of nitrous oxide for laparoscopic cholecystectomy by a group in Finland has shown that it does not cause the intraoperative respiratory acidosis and hypercarbia, characteristic of CO_2 pneumoperitoneum. In a randomised trial of CO_2 and nitrous oxide pneumoperitoneum, they also demonstrated a reduced requirement for volatile anaesthetic agent (enflurane) and lower postoperative pain scores for up to 24 hours in the nitrous oxide group. Interestingly, the noradrenaline response in this study was statistically higher at the end of pneumoperitoneum (prior to desufflation) and at 8 hours postoperatively in the nitrous oxide group, although there were no differences in the adrenaline and cortisol responses (Aitola *et al*, 1998). An additional benefit of nitrous oxide is that it is does not increase intracranial pressure in the presence space occupying lesions to the same extent as

carbon dioxide pneumoperitoneum, although the clinical implications for healthy patients are unclear (Schöb *et al*, 1996).

1.6.3.2 Helium

The inert properties of the noble gases have prompted evaluation of their use in laparoscopic procedures. Comparisons of helium and CO_2 in humans for laparoscopic cholecystectomy have demonstrated that helium does not cause the acidosis and increased $PaCO_2$ seen with traditional CO_2 pneumoperitoneum (Bongard *et al*, 1993; McMahon *et al*, 1994(a); Naude *et al*, 1996; Neuberger *et al*, 1996). Results are consistent within these studies for a total of 96 patients randomised to helium or CO_2 and 20 who were insufflated consecutively with both gases. As with nitrous oxide, the rise in intracranial pressure caused by helium is less pronounced than CO_2 (Schöb *et al*, 1996).

Evidence from swine suggests that helium causes a more pronounced reduction in hepatic artery blood flow than CO_2 at comparable pressures (Junghans *et al*, 1997(b)). Despite this, total liver blood flow is unaffected so the clinical implications of this latter finding, if any, are not known (Junghans *et al*, 1997(b); Shuto *et al*, 1995).

The stress response to helium pneumoperitoneum has been addressed by only one study. Sixteen patients were randomised to insufflation with helium or CO_2 and the neuroendocrine response was measured preoperatively, during surgery and after desufflation. Adrenaline, noradrenaline and cortisol all increased intraoperatively in both groups but the increase in adrenaline was statistically higher in the patients who received helium pneumoperitoneum ($p=0.03$) (Naude *et al*, 1996).

The main disadvantages of helium are poor water solubility and cost. While there are no reports of gas embolus from insufflation with helium, one patient developed bilateral pneumothoraces that required drainage (Bongard *et al*, 1993) and in two studies,

subcutaneous emphysema required between five days and several weeks to resolve (McMahon *et al*, 1994(a); Neuberger *et al*, 1996). Laboratory data suggest that in a canine model, an embolism of helium is lethal at a dose between 5 to 7.5 ml/kg while a dose of 10 ml/kg of CO_2 is dissipated in minutes and is not fatal (Wolf *et al*, 1994).

1.6.3.3 Argon

As with helium, insufflation with argon does not cause an acidosis or hypercapnia. However, in a study conducted on eight swine, systemic vascular resistance almost doubled and cardiac index fell by 25% upon insufflation with argon to a pressure of 15mmHg (Eisenhauer *et al*, 1994). Insufflation to the same pressure with CO_2 or nitrogen did not cause a statistically significant change in either systemic vascular resistance or cardiac index. The authors therefore concluded that argon is not physiologically inert.

A subsequent study, conducted on 18 adult swine that were randomised to insufflation with CO_2, helium or argon and then placed consecutively in the supine, head up and head down positions, was published in Archives of Surgery and appeared to confirm that there was a greater increase in systemic vascular resistance and mean arterial pressure when pneumoperitoneum was created with argon rather than CO_2 or helium (Junghans *et al*, 1997(a)). In the journal, Surgery, the same data from the same experiments appeared with additional visceral flow data (Junghans *et al*, 1997(b)). In this second article, the authors reported that argon impaired portal venous and hepatic blood flow more than CO_2 or helium and that these effects were augmented by tilt and abdominal pressure. However, the authors also stated that "the type of gas used had a major impact on *neither* cardiac output ($p=0.45$) *norsystemic vascular resistance* ($p=0.7$)" and that the "systemic vascular resistance was directly related to intraabdominal pressure ($p=0.06$)," which contradicted the previous article! On closer inspection, the primary endpoints differed between the two papers for the same set of experiments, the statistical analyses differed with parametric tests used in "Surgery" and non-parametric tests in the article in "Archives of Surgery" and no results of the statistical

analyses were quoted in the "Archives of Surgery" paper to justify the conclusion that argon caused a greater increase in the systemic vascular resistance.

1.6.4 Temperature and humidity of the insufflated gas

Perioperative hypothermia is associated with increased oxygen requirements, cardiac arrhythmias, hypokalaemia, depletion of clotting factors and increased mortality (Bessell *et al*, 1995).

Insufflation with gas at room temperature was found to decrease body temperature at a rate of 0.3°C per 50 litres of CO_2 (Ott, 1991(a)). In a subsequent study by the same author, 40 patients were assigned to receive warmed CO_2 and cold CO_2. Postoperative body temperature was found to be within 0.1°C of preoperative values in the group of patients who received warmed gas whereas body temperature in patients who received gas at room temperature was 0.3°C per 50 litres of CO_2 lower in the recovery room than preoperatively (Ott, 1991(b)). However, the procedures performed during this investigation were different within and between groups and patients were not randomised. A similar, but standardised experiment using swine, failed to record any difference between animals that received warm or cold gas to maintain pneumoperitoneum over a 3-hour period. One clinical study has recorded a reduction in pain scores for up to three days postoperatively in a group randomly assigned to receive warmed gas at a temperature of 31.8°C (Korell *et al*, 1996). However, the control (carbon dioxide at 22.4°C) and study groups contained a mixture of diagnostic and therapeutic gynaecological procedures and the pressure of the pneumoperitoneum was not standardised.

Examination of the thermodynamics revealed that the heat required raise the temperature of CO_2 gas, flowing at 10 l/min, from 25°C to 37°C is 0.9W whereas the latent heat required to humidify the same stream of gas at 37°C is 18W (Bessell *et al*, 1995). Cold, dry gas will exert maximal effects on temperature in long, advanced procedures, especially if there is a

significant gas leak. The impact on the stress response to laparoscopy remains unknown.

1.6.5 Gasless laparoscopy

Due to the inherent physiological disturbances of pneumoperitoneum, abdominal wall retractors have been developed to obviate the requirement for insufflation. One group from Helsinki has assessed these devices in three randomised studies.

The first study (reported twice) compared the use of conventional pneumoperitoneum against low pressure CO_2 insufflation (with the aid of an abdominal wall retractor) in 24 patients and has already been discussed (cf. section 1.6.2)

The second study (also reported twice) compared the retractor without CO_2 insufflation (gasless) against conventional cholecystectomy. As with the previous study, the retractor group had better preservation of pulmonary function with no change in compliance or minute ventilation requirements. The cardiovascular benefits for the gasless group were more pronounced than in the previous study, with a lower increase in the heart rate and no change in mean arterial blood pressure. Intra-operative urinary output was preserved in the absence of pneumoperitoneum, and postoperative recovery time, drowsiness levels and vomiting were reduced. However, the operative time was 23 minutes longer and no differences in pain scores or analgesia requirements were achieved (Koivusalo *et al*, 1996(a); Koivusalo *et al*, 1998).

Analysis of the stress response demonstrated a reduction in the renin plasma activity in the gasless group but found no difference in adrenaline or noradrenaline levels. Surprisingly, vasopressin concentrations were lower in the conventional group but this difference did not reach statistical significance (Koivusalo *et al*, 1998).

A third study in which 30 patients were randomised to abdominal wall retractor or CO_2

pneumoperitoneum confirmed that the gasless approach conferred cardiovascular, respiratory and renal benefits (Koivusalo *et al*, 1997). In addition, gastric mucosal pH and N-acetyl-beta-D-glucosamine (NAG) excretion in the urine (an increase in NAG is deemed a marker of proximal tubular damage of the kidney) were monitored. Gastric pH was found to decrease in both groups during the procedure. Postoperatively, this resolved in the retractor group but persisted and worsened for three hours in the insufflation group. N-acetyl-beta-D-glucosamine rose in both groups but this increase was lower (75% vs 153%) and resolved postoperatively within 180 minutes in the gasless group.

A Japanese group reported a randomised trial that contained 20 patients who underwent LC with abdominal wall retractor or conventional pneumoperitoneum. There were no significant changes in cardiac and respiratory function and no difference in effective renal plasma flow or glomerular filtration rate in the retractor group. In contrast, cardiac output, stroke volume, ejection fraction, pH, effective renal plasma flow and glomerular filtration rate all fell significantly and $PaCO_2$ rose significantly in the conventional group. The Il-6 response was higher in the retractor group than the conventional group (48.2 ± 25.5 pg/ml vs 4.6 ± 2.6 pg/ml respectively) but this did not reach statistical significance, probably due to the small number of patients in the trial (Ninomiya *et al*, 1998).

Another study from Japan contained seventeen female patients who underwent LC and were randomised to CO_2 pneumoperitoneum at a pressure of 8mmHg or a gasless technique. There were no statistically significant differences in the ACTH and cortisol responses between the groups. However, the serum Il-6 was significantly lower at 1 hour and 1 day post-operatively, the IL-10 was lower on the first postoperative day and CRP was lower on days 1 and 3 in the group who had CO_2 pneumoperitoneum. In addition, the postoperative decrease in the lymphocyte count was greatest in the retractor group (Yoshida *et al*, 1997). The results are summarised in table 1.3.

Sample and time		Pneumoperitoneum	Retractor	p value
Il-6 (pg/ml)	1 hr post-op	6.64 ± 1.38	22.1 ± 7.38	0.004
	1 day post-op	10.4 ± 2.75	71.4 ± 39.33	0.002
Il-10 (pg/ml)	1 day post-op	2.23 ± 0.86	6.27 ± 1.44	0.031
CRP (mg/dl)	1 day post-op	0.94 ± 0.26	3.92 ± 1.12	0.027
	3 days post-op	1.7 ± 0.43	6.8 ± 1.44	0.012
WCC % of preop levels	1 hr post-op	82.1 ± 3.6	69.2 ± 4.0	0.027
	1 day post-op	100.1 ± 3.9	82.9 ± 2.7	0.008

Table 1.3. Results of a randomised trial of pneumoperitoneum versus abdominal wall retractor for laparoscopic cholecystectomy (Yoshida *et al*, 1997). Results are expressed as mean ± standard deviation (SD). WCC – white cell count

Although the results of this study initially appear to contradict the data reported by the group from Helsinki, it is corroborated by laboratory evidence that was published in the British Journal of Surgery in 1995 (Watson *et al*, 1995). Four groups of mice were randomised to a control anaesthetic, laparotomy, air laparoscopy or CO_2 laparoscopy. Cytokine and superoxide production by peritoneal macrophages, along with phagocytosis, were similar in the groups assigned to control and CO_2 laparoscopy. Exposure of the peritoneum to air whether by laparotomy or laparoscopy, resulted in high cytokine and superoxide levels and resulted in impaired phagocytosis. A further experiment involved either a "sham" laparotomy (abdominal incision without breach of the peritoneum) or injection of endotoxin (at a concentration found in air) during CO_2 laparoscopy. On this occasion, the "sham" laparotomy had minimal effect on the macrophages but the endotoxin reproduced the responses seen at air laparoscopy or laparotomy. They concluded that air contamination of the peritoneal cavity resulted in an endotoxin induced systemic response and that sterile CO_2 prevented peritoneal contamination.

Protection from the effect of endotoxin is not the only factor. Carbon dioxide causes intracellular acidification that blunts the capacity of peritoneal macrophages to produce cytokines (West *et al*, 1997) and impairs their ability to lyse tumour cells (Puttick *et al*, 1998). Paradoxically, the *absence* of CO_2 may be the cause of the relative increase in the cytokine response to the gasless technique.

1.6.6 Placement and number of cannulae

The "American" and "French" techniques of LC differ in position of the surgeon and placement of cannulae (Figure 1.3). In the "American" technique, popularised by Reddick and Olsen (Reddick & Olsen, 1989), the surgeon stands to the left of the patient and two 10mm cannulae are inserted at the umbilicus and in the epigastrium, while two 5mm cannulae are placed under the costal margin. For the "French" technique, the patient is placed in the Lloyd-Davis position and the surgeon stands between the legs. The cannulae are inserted more caudal to the costal margin and the epigastric cannula is inserted to the left of midline (Kum *et al*, 1996).

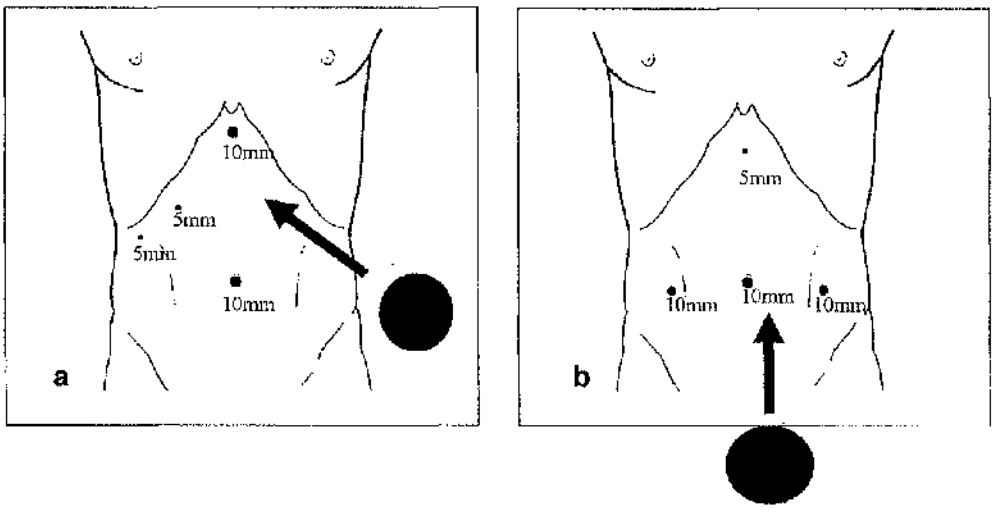


Figure 1.3 Position of the cannulae and surgeon for laparoscopic cholecystectomy using the "American" technique (a) or the "French" technique (b). The circle and the arrow represent the position and direction in which the surgeon stands (Kum *et al*, 1996).

In one study, 49 consecutive patients were randomised to one of the two techniques. Postoperatively, pulmonary function at 6, 24 and 48 hours and visual analogue pain scores at 48 hours were significantly better in the "French" group. It was concluded that the increased distance of the cannulae from the costal margin improved pulmonary function and reduced pain. However, the placement of the cannulae in the "French" technique resulted in a low-angled approach that brought the instruments into contact with the bowel. This was highlighted by an iatrogenic diathermy injury to the intestine in one patient who was withdrawn from the study (Kum *et al*, 1996).

The significance of the location of cannulae was suggested as an important factor in a study that compared pulmonary function after LC, "major" laparoscopic gynaecological procedures and "minor" laparoscopic gynaecological procedures in 30 women (Joris *et al*, 1997). Pulmonary function (FVC, FEV_1, PEFR) were more impaired for two days postoperatively in the LC group, whose cannulae were closer to the costal margin than in either of the gynaecological groups. However, apart from the obvious fact that the procedures differed, the LC group required more cannulae (4 vs 3) and had a longer duration of pneumoperitoneum (57 vs 35 vs 17mins). Opposite directions of Trendelenburg tilt were employed but if this had any influence, it would have further impaired pulmonary function for the gynaecology patients who were placed in the head down position (cf. section 1.6.1). It is therefore likely that the number and placement of the cannulae under the costal margin restricted the ability to breath postoperatively.

1.6.7 Summary

Clinically, laparoscopic cholecystectomy has produced a revolution in patient care with a reduction in wound size, postoperative pain, respiratory compromise and time to convalesce. Biochemically, the effect of the laparoscopic approach on the stress response is fascinating in that there is a schism of the tissue mediated responses and the neurally mediated responses, which has not been seen during conventional surgery. The available evidence suggests that

insufflation stimulates the neuroendocrine response to an extent that is similar to the conventional surgical approach. In contrast though, the cytokine, acute phase and immune responses to surgery (which are dependent on the extent of tissue trauma) are significantly ameliorated.

Despite these improvements for cholecystectomy, review of the literature suggests that with attention to detail, small changes in technique can further improve the clinical outcome. For instance, as discussed earlier, attention to the distortion of the biliary anatomy caused by fundal traction of the gallbladder can reduce the rate of bile duct injury, a reduction in the pressure of the pneumoperitoneum can translate into a reduction in pain (Wallace *et al*, 1997) and attention to the degree of tilt of the operating table can reduce the deleterious haemodynamic effects of pneumoperitoneum (Gray *et al*, 1997).

Although the trocars and cannulae that are used to gain access to the peritoneal cavity are key factors in this surgery, there are some aspects of their design that require further study. While the position of the cannulae has been addressed, the impact of a reduction in the size of the cannulae has not been fully evaluated even though instruments of a smaller diameter are now freely available. In addition, there are potentially serious, albeit rare, complications associated with the process of gaining access to the peritoneal cavity that are directly attributable to the trocars. These aspects will now be reviewed.

1.7 The influence of the diameter of the trocar on laparoscopic procedures

1.7.1 Diagnostic microlaparoscopy

Prospective reports appeared in the 1990's in which a 2mm laparoscope was utilised for diagnostic procedures in a total of 82 patients. Diagnostic accuracy was confirmed immediately with a 10-mm laparoscope (Faber & Coddington, 1997; Haeusler *et al*, 1996; Molloy, 1995), and led one group to conclude, "2mm microlaparoscopy yields sufficient information to abandon the conventional 10mm technique" (Haeusler *et al*, 1996).

Surprisingly, these were not the first reports. Examination of the gynaecological literature reveals a report of "needlescopic" diagnostic laparoscopy and sterilisation published as early as 1976 (Dingfelder & Brenner, 1976)! There is also an early series of fifteen "minilaparoscopies" used to evaluate blunt abdominal trauma that suggested potential for the technique within General Surgery (Sherwood *et al,* 1980).

A study of 135 women undergoing diagnostic microlaparoscopy and 21 who received a standard laparoscopy set out to prospectively compare the feasibility, pain scores and analgesic requirements of the procedures. The authors reported that all procedures were completed satisfactorily and that pain scores and analgesic consumption were lower in the microlaparoscopy group (Kovacs *et al,* 1998). There were several questions concerning methodology that remained unanswered. The definition of a "satisfactorily" completed procedure was not stated and subsequent follow-up to confirm correct diagnosis was not included. The study was not randomised "because the operator decided that microlaparoscopy was safer," leaving another surgeon who "was not converted to microlaparoscopy" to perform conventional procedures. Pain scores and analgesic requirements were assessed and recorded by non-blinded nursing staff, rather than the patients. Lower volumes of CO_2 (and possibly lower pressure) were used for insufflation of the peritoneum during microlaparoscopy, a factor known to reduce postoperative pain (cf. section 1.6.2). Twenty-three patients were withdrawn from the study, as they required an additional operative procedure and pain scores from 39 of the remaining 112 patients were omitted without explanation. Overall, 46% were not included in the final analysis.

Another favourable prospective series of 320 gastroenterological patients undergoing "minilaparoscopy" (1.9mm) with liver biopsy was recently reported. The biopsy failure rate was only 2.8% and mostly due to adhesions. Two complications occurred (0.6%) – one patient with fulminant hepatic failure bled from the abdominal wall and another had an iatrogenic perforation of the transverse colon, which was successfully managed

conservatively. All failures and complications occurred in the first 40 procedures, prompting the authors to suggest a learning curve phenomenon associated with this new approach (Helmreich-Becker *et al,* 1998).

Not all reports were favourable. Concern over image quality was raised by a study evaluating the use of microlaparoscopy for the diagnosis of right iliac fossa pain in 36 general surgical patients (Mutter *et al,* 1998). The diagnostic success rate of microlaparoscopy was only 58%, with complete failure to visualise the appendix in 8% of procedures. Conversely, the appendix visualisation rate was 100% using the 10mm laparoscope among the same patients. This discrepancy was attributed directly to poor image quality and the authors concluded that technology had to improve further before the technique could become a viable diagnostic modality in general surgery. The impact of experience with the new instruments was not considered.

1.7.2 Therapeutic microlaparoscopy

Despite misgivings within the general surgical community, smaller instruments were used to perform cholecystectomy. The first paper in 1997, from Japan, reported a three-cannula technique, performed on 20 consecutive patients, that exclusively employed 2mm cannulae (Watanabe *et al,* 1997). Despite a reduction in area of vision with the 2mm scope, the mean duration of the procedures was 80 minutes, which was similar to the duration of a conventional laparoscopic cholecystectomy (CLC) performed by the authors. They reported that "the 2mm incision had disappeared almost completely on the day of discharge" and that "analgesics were not required postoperatively." As the cannulae were less costly, the authors concluded that micro-laparoscopic cholecystectomy was cheaper than CLC, although no cost analysis was included to support this claim.

A prospective group of 14 patients in Taiwan, selected for mini-laparoscopic cholecystectomy, was compared retrospectively with 31 patients undergoing CLC (Yuan *et*

al, 1997). Both groups were similar with respect to age, ASA status and sex distribution. The authors reported faster resumption of diet, shorter hospital stay, lower analgesic consumption and a cosmetically superior result among the group treated with the mini-laparoscopic technique (Table 1.4).

	Mini-Laparoscopic Cholecystectomy	**Laparoscopic Cholecystectomy**	***p* value**
Operative Time (Hours)	60.8 – 97.8	63.9 – 80.0	p>0.05
Resumption of Diet (Hours)	2.3 – 4.2	5.8 – 10.2	p<0.05
Hospital Stay (Days)	1.2 – 1.7	1.8 – 2.5	p<0.05
Analgesic usage ("Units")	-0.03 – 0.61	0.7 – 1.8	p<0.05

Table 1.4 95% confidence intervals reported by Yuan *et al*, 1997, for a comparative study of mini-laparoscopic cholecystectomy versus laparoscopic cholecystectomy.

However, data for the conventional technique were retrospective, the definition and derivation of analgesic "units" was omitted and no mention was made of how cosmesis was measured or compared. The mini-laparoscopic technique was unusual in that while a 11mm cannula was inserted at the umbilicus, a 2mm laparoscope was used to visualise the procedure from the epigastrium and the dissecting instruments were introduced at the umbilicus. This method reduced the angle of vision and brought the operative instruments closer to the small bowel. All of these factors could theoretically increase the likelihood of iatrogenic visceral injury, although it was not reported in this series. It was also noted that 2mm instruments were not able to grasp a thickened gallbladder and that no instruments of 2mm diameter were available to facilitate exploration of the common duct. A learning curve was also described with a reduction in operating times from 150 minutes for the first case to less than one hour after 10 cases. However, overall operative times were comparable for both techniques.

A larger series of 60 patients was compared with matched patients who had a conventional

laparoscopic procedure (Gagner & Garcia-Ruiz, 1998). While mean operative times were 20% longer for the needlescopic group (98 vs 81mins), analgesia requirements were 70% lower (5 vs 17mg of "morphine equivalents"). Forty-seven percent of patients in the needlescopic group did not require any narcotics compared with 9% in the laparoscopic group. Patients rated the scars on a 10 point score and judged the cosmetic result superior with the needlescopic procedure (mean score of 1/10 vs 5/10). Despite these differences, the mean hospital stay did not vary between the groups (1.2 vs 1.3 days). The same paper also described appendectomy, adrenalectomy, fundoplication, hernia repair and splenectomy, all utilising the new instruments.

Two subsequent series reports of "needlescopic" or "fine-calibre instrument" cholecystectomies documented series of 5 and 20 patients. Both employed a 10mm laparoscope at the umbilicus, one 5mm cannula and two 2.5 to 3mm cannulae (Kimura *et al,* 1998, Tanaka *et al,* 1998). When compared with patients who underwent CLC, operative times, complications, analgesic consumption and postoperative stay were similar. Objective assessment demonstrated that the total size of the wounds was 37.5mm vs 58.5mm and solely on the grounds of cosmesis, the new technique was deemed superior (Kimura *et al,* 1998). As a result, it has become routine within the unit and the technique has spread to other surgical units within Japan (Kimura, 1998).

In correspondence concerning the latter study, an American group reported another variation on the technique that employed one 5mm cannula for the laparoscope and two 2mm cannulae for the instruments (Unger *et al,* 1998). With an experience of 35 consecutive patients, the mean operative time was 68.7 min (+/- SD 23.9 min) and the time to discharge, 1.16 days. Morphine requirements were low (0.24mg/kg) and the cosmetic result was judged "excellent" by the patients. Once again, assessment of cosmesis was subjective.

A technique of micropuncture laparoscopic cholecystectomy (MPLC) has been used since

December 1996 within the Leeds Institute for Minimally Invasive Therapy (LIMIT) (Davides *et al,* 1997(b)). It utilises a 10mm umbilical cannula for the laparoscope, because it is usually necessary to retrieve the gallbladder through an equivalent size of wound, and three 3.3mm cannulae for the instruments. The majority of the procedure is performed with the 10mm laparoscope and a three-chip camera, ensuring optimal image quality. The 3mm laparoscope is only required for clipping after the cystic duct and artery have been widely exposed and subsequently during suturing of the umbilical fascia. The camera is routinely sterilised for all laparoscopic procedures so there is no risk of contamination during changeover.

The initial series of 25 patients was presented to the Joint Euro-Asian Congress of Endoscopic Surgery, Istanbul, June, 1997 (Davides *et al,* 1997(a)). The procedure was completed successfully in all patients with no complications. The duration of surgery was 75 minutes (range 45-180), similar to the conventional laparoscopic technique routinely performed at that time. One patient with common duct stones detected at cholangiography had a successful micropuncture bile duct exploration. Sixteen patients were discharged on the day of surgery and the remainder left within 24 hours. Only eight required analgesia.

1.7.3 Inherent problems with smaller instruments

Several potential problems are apparent with smaller instruments. A reduction in the diameter of the laparoscope reduces the angle of view, light transmission, and image quality (Gagner & Garcia-Ruiz, 1998; Haeusler *et al,* 1996; Hunter, 1998; Molloy, 1995; Yuan *et al,* 1997). Blurring, sufficient to impair the view, can occur during cautery (Dingfelder & Brenner, 1976; Watanabe *et al,* 1997). If a fibre-optic system as opposed to the Hopkins' rod lens system is employed, clarity is further diminished by a "fly's eye" effect (Molloy, 1995; Mutter *et al,* 1998). However, the fibre-optic laparoscope had a degree of inbuilt flexibility that a rod lens system does not (Dingfelder & Brenner, 1976; Molloy, 1995). In view of all these problems, concern has been expressed over the use of microlaparoscopy as a diagnostic modality (Mutter *et al,* 1998).

The difficulties relating to image quality can be overcome by using a 10mm laparoscope. However, a laparoscope with a smaller diameter will still be required to visualise the critical step of clip application to the cystic duct or artery because there are no clip applicators with a diameter of less 5mm that can be used to secure the cystic duct (the duct could be sutured or ligated but this is technically more difficult and time consuming). Changes of laparoscope for this manoeuvre can potentially increase the operative time and introduce opportunities for infection if non-sterile cameras are utilised (Gagner & Garcia-Ruiz, 1998; Kimura *et al*, 1998).

A reduction in the diameter of the instruments to 2mm increases flexibility and reduces the size of "footprint" of the jaws upon the tissue, making retraction and dissection more difficult, especially in the presence of fibrosis or inflammation. There may also be a learning curve for fine calibre instruments. A potential solution is to employ 3mm instruments that deform less during manipulation of the tissues and allow a larger grasping surface (Davides *et al*, 1997(a); Gagner & Garcia-Ruiz, 1998; Kimura, 1998; Tanaka *et al*, 1998; Yuan *et al*, 1997).

In view of the above problems, there has been a degree of caution in the introduction of smaller instruments and calls for careful prospective studies within specialist units (Berci, 1998; Hunter, 1998; Mar Fan & Chan, 1998; Svanvik, 1997)

1.8 The influence of the profile of the tip of the trocar on access to the peritoneal cavity and iatrogenic injury

1.8.1 Complications of access

Review of the literature pertaining to laparoscopic procedures reveals uncommon but potentially life-threatening complications relating to access.

The establishment of primary access is the first stage of any laparoscopic procedure and is

potentially the most dangerous. The most feared complications are inadvertent vascular and visceral trauma. The frequency of visceral trauma is between 0.04% and 0.16% and when it occurs, has a reported mortality of 1.6% to 10% (Bonjer *et al,* 1997; Champault *et al,* 1996; Copeland *et al,* 1983; Deziel *et al,* 1993; Riedel *et al,* 1986; Schrenk *et al,* 1996; Wherry *et al,*1996). Major vascular trauma has a incidence of 0.005 % to 0.11% but mortality ranges from 8.8% to 56% (Champault *et al,* 1996; Deziel *et al,* 1993; Hanney *et al,* 1995; Hashizume *et al,* 1997; Riedel *et al,* 1986; Wherry *et al,*1996). Gas embolism occurs when carbon dioxide enters the venous system and causes profound cardiovascular collapse with the classical triad of hypotension, asystole and cyanosis. The recorded incidence is 0.001% to 0.07% at induction of pneumoperitoneum, but it can also occur during the procedure (Bonjer *et al,* 1997; Hanney *et al,* 1995).

The less serious problem of bleeding at the site of cannulation is more common with an incidence of 0.2% to 0.46% and results in conversion to laparotomy in 5.7 to 11.3% of these patients (Champault *et al,* 1996; Hashizume *et al,* 1997). Most episodes settle spontaneously (Hashizume *et al,* 1997) or are controlled with simple measures such suture ligation, electrocoagulation or tamponade with the balloon of a Foley catheter (Boswell *et al,* 1993; Hashizume *et al,* 1997; Thomas *et al,* 1996).

Incisional hernias are late complications, affecting 0.06% to 3.6% of cases and are mostly associated with cannulae that are 10mm or more in diameter, extension of the wound for specimen retrieval, pre-existing hernias or postoperative infection (Azurin *et al,* 1995; Hashizume *et al,* 1997; Mayol *et al,* 1997; Plaus, 1993). While most are asymptomatic or simply cause discomfort, a potentially life-threatening Richter's hernia can occur (Azurin *et al,* 1995; Plaus, 1993; McGinn *et al,* 1995). Suggestions to minimise the risk include a Z-insertion technique for trocars (Melzer *et al,* 1993; Semm, 1995), closure of defects with a diameter 10mm or greater (Azurin *et al,* 1995) and the use of trocars with conical tips (Semm, 1995). The latter will be discussed separately.

1.8.2. Access

1.8.2.1 Equipment overview – the trocar and cannula assembly

As described in section 1.1.1, trocars are used to facilitate placement of the cannulae, through which the instruments for the operation are inserted. Trocars can be categorised by the profile of the tip **(Figure 1.4)**.

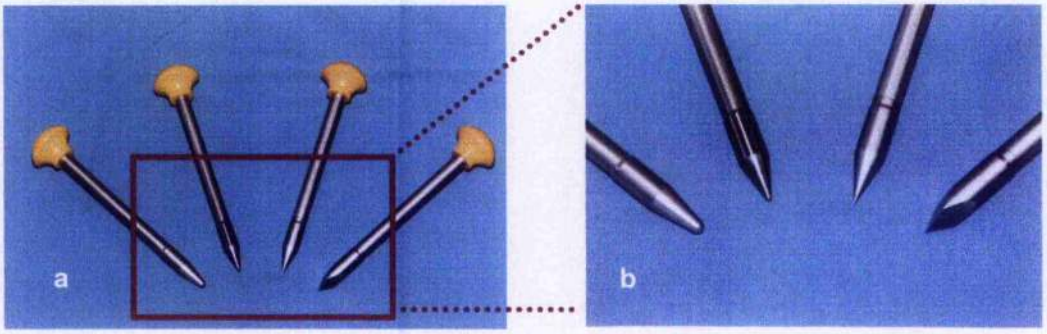


Figure 1.4a The profiles of the non-shielded trocar tips from left to right are blunt (Hasson), blunted conical (pencil point), sharp conical and pyramidal. All come from the "YelloPort"™ range from Surgical Innovations. **b)** Enlarged view of the profiles of the tips of the trocars.

a) **Pyramidal** – This consists of a sharp point and three cutting edges that divide the tissue of the abdominal wall to facilitate entry. This is the oldest design, used by Jacobeus in his original description of laparoscopy in 1910 (Semm, 1995).

b) **Conical** – This tip is tapered and comes with either a sharp or blunt (pencil) point. The tip punctures the abdominal wall and the conical profile stretches the tissue as the trocar is advanced (Semm, 1995). A modification of this design is the "radially expanding trocar," popularised by Professor Lawrence Way of San Francisco. An expandable sheath is inserted using a needle that is removed and replaced by a blunt plastic obturator to dilate the wound to the required size (Bhoyrul *et al,* 1996).

c) **Blunt** – This is principally employed for the open Hasson technique (cf. section 1.8.2.2) and has a rounded, atraumatic end. It requires an initial incision in the fascia with a scalpel before insertion.

Trocars are manufactured as disposable or reusable models. Disposable trocars, made from

aluminium and plastic, are only used once, always have a sharp tip and do not require to be sterilised. Reusable models must be sterilised before each use and as a result, are constructed more robustly with stainless steel and reinforced plastic to withstand the extra handling. They cost more per unit than the equivalent disposable trocar but cost less per procedure as they are used for more than 100 cases. They require careful sterilisation to minimise the risk of cross-contamination and must be sharpened regularly (Corson *et al,* 1989; ECRI, 1998).

Since 1984, a "safety-shield" device has been incorporated into some trocars in an attempt to minimise the risk of visceral injury. This is a spring-loaded cover that retracts on contact with the abdominal wall and exposes the trocar tip (Figure 1.5).

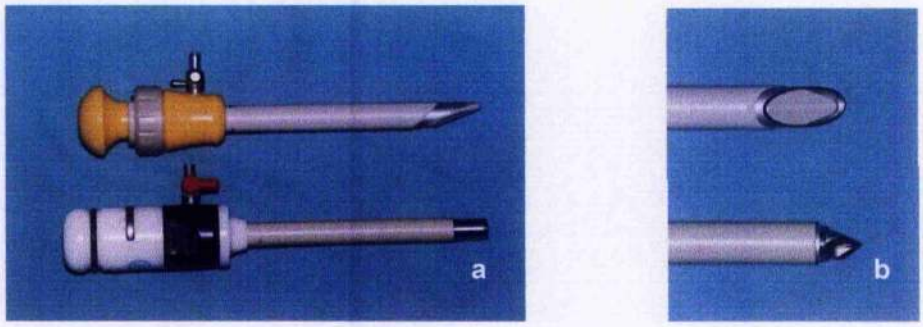


Figure 1.5a Shielded trocars. The upper version has a central, retractable obturator, similar to a Veress needle and the lower version has a shield that surrounds the blade.

Figure 1.5b Enlarged view of the trocars with the shields retracted to reveal the blades.

Once the tip of the trocar has penetrated the peritoneal cavity, the resistance of the abdominal wall against the shield decreases and the spring mechanism pushes the shield over the sharp tip of the trocar. The device locks so that the tip of the trocar cannot be exposed again while it is in the abdomen. However, the so-called "safety-shield" has not prevented serious trocar related injuries or even deaths (Bonjer *et al,* 1997; Champault *et al,* 1996; Dunn & Watson, 1992; Go *et al,* 1993; Hashizume *et al,* 1997; Semm, 1995). There is a delay between initial penetration of the trocar tip and activation of the shield device as it has to overcome the resistance of the peritoneum and abdominal wall and in practice does not activate until most

of the trocar tip is within the abdomen (Dunn & Watson, 1992; Semm, 1995). Failure to realise this "often leads to a false sense of security" and injury (Nathanson, 1995). In America, the Food and Drug Administration has requested that all references to "safety" be removed from shielded trocars due to the lack of evidence of protection from injury (ECRI, 1998).

1.8.2.2 Methods overview – techniques of access

Methods of primary access can be broadly divided into two categories:

a) **Closed access** involves the insertion of the Veress needle (Figure 1.1), usually at the umbilicus, with upward traction on the abdominal wall, to establish pneumoperitoneum, followed by insertion of the primary trocar. This technique appears to predominate in general clinical practice and is used for 60 to 80% of procedures (Borgotta *et al*, 1990; McMahon *et al*, 1993(b); Wherry *et al*, 1996). Intraperitoneal placement is checked by moving the needle to ensure that the tip is free, by injecting saline (which should run without resistance) and the "drop" test where a drop of saline placed on the top of the Veress needle should run into the abdomen on opening the gas tap and elevating the abdominal wall. These tests however, are not infallible and do not exclude visceral trauma (McKernan & Champion, 1995). When insufflation is initiated and the Veress needle is correctly placed, the pressure reading on the insufflator is low and the rate of flow of the gas is high. The converse situation of a high pressure and low flow rate indicates that the tip of the needle is not within the peritoneal cavity or is lodged within the viscera (Thomas *et al*, 1996). An alternative closed approach employed by some surgeons (mostly gynaecologists) is insertion of the primary trocar without prior insufflation (Borgotta *et al*, 1990; Copeland *et al*, 1983; Dingfelder, 1978; Jarrett, 1990; Nezhat *et al*, 1991). Subsequent cannulae are inserted under guidance of the laparoscope.

b) **Open access (or the Hasson technique)** requires a direct cut-down under vision at the umbilicus, incision of the linea alba, followed by incision of the peritoneum, all under

visual guidance. A blunt trocar and cannula are inserted, the trocar is removed and insufflation performed (Hasson, 1971). Subsequent cannulae are inserted under guidance of the laparoscope. Numerous modifications of the original technique are in common use, for example, blunt opening of the peritoneum with artery forceps, addition of an integral thread to screw the cannula into position, sweeping a finger inside the peritoneal cavity to check for adhesions or checking the position of the cannula prior to insufflation (Hurd & Ohl, 1994; Thomas *et al,* 1996). Some surgeons employ open access routinely while others adopt a selective approach, reserving it for patients who have undergone previous abdominal surgery or in whom there is a greater risk of adhesions (McMahon *et al,* 1993(b); McKernan & Champion, 1995; Thomas *et al,* 1996).

1.8.3 Comparison of techniques of access

Considerable controversy exists in the literature over the relative merits of the techniques of open and closed access. Most of the debate centres on the incidence of visceral and vascular trauma. However, due to the infrequent occurrence of these complications, it would require an exceptionally large multi-centre study to address the issue properly (Bonjer *et al,* 1997). Data must therefore be gleaned from published series.

A prospective, consecutive series of laparoscopic cholecystectomies was reported from the McGill University Teaching Hospitals, Toronto (Sigman *et al,* 1993). It contained 1,028 patients who had pneumoperitoneum established by closed (n=781) or open access (n=247). The closed access group contained three visceral injuries and one vascular injury (it was not stated whether the Veress needle or the primary trocar was the cause of the injuries) while the open access group had none. This difference was not statistically significant. Despite this, practice in the unit changed during the study. Initially, the authors preferred closed access, believing that it shortened the duration of surgery. However, as individual surgeons experienced complications related to access, they moved towards an open access technique. Procedures in the open access group were faster (mean 72.6 min vs 81.4 mins, $p<0.001$) but it is not possible to establish from the data whether the reduction in operative time was

related to the method of access or accruing experience with LC. Other studies that have specifically measured the time taken to establish access have shown that in experienced hands, it is similar for both techniques, taking about 3½ to 5 minutes (mean) (Hurd & Ohl, 1994; Hurd *et al,* 1994).

A study from Spain prospectively followed 403 patients and reported a higher incidence of incisional hernias with a closed technique of access (6/203) than an open technique (0/200). However, all of these hernias occurred in patients whose fascial wound at the umbilicus was widened for specimen retrieval. No differences in wound infection, haematoma or visceral injury rates were detected between the techniques (Mayol *et al,* 1997). In another study, the incidence of hernias at the primary site of access was similar whether open or closed access techniques were employed (Azurin *et al,* 1995).

A group in the Netherlands performed a review of the literature and identified papers with a collective total of 489,335 patients who had pneumoperitoneum established by a closed access technique and 12,444 who had open access. In addition, the authors analysed data from their own institution for closed and open access on 1,293 and 438 patients respectively (Bonjer *et al,* 1997).

In the literature, 404 visceral injuries (0.083%) and 368 (0.075%) vascular injuries occurred with closed access. Gas embolism occurred in 0.001% of patients. Among the open access group, visceral injury was recorded in only one study, giving a rate of 0.048%. There were no records of vascular injuries or gas embolism. In the series of procedures reported by the authors, there was one vascular and three visceral injuries among the closed group and none among the open group. It was concluded, using a Pearson χ^2 analysis, that there was no difference in visceral injury rates but that open access prevented vascular injuries and gas embolism (Bonjer *et al,* 1997).

The patients included in this study, both in the literature review and the case series, were not randomised. Some surgeons adopt a selective policy to open / closed access and select open access for patients who have had previous laparotomies or have known adhesions. The data within this study did not take account of this selection bias. As a result, the patients were not matched and it is possible that the open group may have contained a population who were at high risk of visceral injury whichever technique was used.

In addition, most of the series that were examined were retrospective and therefore subject to under-reporting of complications. While no vascular injuries resulting from the Hasson technique were noted in the review, the data only support a conclusion that the Hasson technique may *reduce* vascular injury. The claim that the technique "*prevents*" vascular injury is ill founded as injuries to the aorta and a common iliac vessel during open access, previously reported in an audit performed for the US Department of Defence and in a review of medicolegal claims in Australia, were not included in this review (Hannay *et al*, 1995; Wherry *et al,* 1996). Furthermore, while injuries may be avoided during primary access, care must be exercised to prevent major vascular injuries during subsequent trocar insertions (Hashizume *et al,* 1997).

With closed access, the Veress needle is often cited as the culprit but often, it is the primary trocar to blame. The literature review just discussed, identified the Veress needle as the culprit for 40% of visceral injuries. However, this figure is subject to the accuracy of the original articles that were collected from the literature for this review and the fact that the review was not exhaustive (Bonjer *et al,* 1997). In support of this figure though, a review of patients who sustained iatrogenic injuries while under the care of the Study Group of Endoscopic Surgery in Kyushu, Japan, suggested that the trocar was the cause of injury in 70% of vascular injuries and 100% of visceral injuries (Hashizume *et al,* 1997).

The tendency for gas leak after open access which can occur in up to 14% of cases, with

subsequent difficulty in maintaining pneumoperitoneum, is a factor in the favour of the closed approach, which ensures a tight seal around the cannula (Hurd *et al,* 1994; Thomas *et al,* 1996).

1.8.4 Anatomical considerations during access

Even among proponents of the closed technique, there is contention over the angle of insertion of the Veress needle and the optimal method for insertion of the primary trocar. Kurt Semm strongly advocates perpendicular placement as the best method of avoiding aortic injuries, despite the fact that the umbilicus classically overlies the aortic bifurcation. He argues that angled insertion turns the Veress needle into "an optimal slitting instrument" (Semm, 1995). However, the dangers of perpendicular placement were highlighted during the 1970's in a report of two cases of aortic trauma in thin women. Both injuries were directly posterior to the umbilicus (McDonald *et al,* 1978).

In the last decade, a group from Michigan, USA examined this question with measurements derived from abdominal CT scans and Magnetic Resonance Imaging (Hurd *et al,* 1991; Hurd *et al,* 1992). In non-obese women (normal body mass index), the umbilicus was a mean of 6cm directly anterior to the bifurcation of the aorta and slightly cephalad to the common iliac vein. In obese patients (Body Mass Index over 35kg/m^2), it was situated 2.9cm caudal and 13cm anterior to the aortic bifurcation but was directly anterior to the common iliac vein. In practice, this means that a needle directed at an angle of 90° to the abdominal wall in thin women, is aimed directly at the aortic bifurcation. In obese patients, the common iliac vein is in the path of the needle but is further away from the umbilicus due to the presence of fat in the abdominal wall and the mesentery. The authors therefore recommended an angle of insertion of 45° for thin women but an almost perpendicular technique in obese women, to reduce the instance of insufflation of the thicker pre-peritoneal plane (Hurd *et al,* 1991; Hurd *et al,* 1992). However, pre-peritoneal insufflation with carbon dioxide gas is much less serious than a major vascular injury. Angled insertion of the Veress needle, aiming away

from the vessels into a "triangle of safety," is employed in the Leeds Institute for Minimally Invasive Therapy (LIMIT) (Figure 1.6).

In an attempt to combine the benefits of closed access with direct vision, a number of devices have been introduced that allow the laparoscope to be placed within the trocar during insertion. So far, they have failed to find widespread acceptance, they have a learning curve and do not prevent visceral trauma (Melzer *et al,* 1993; Schaller *et al,* 1995).

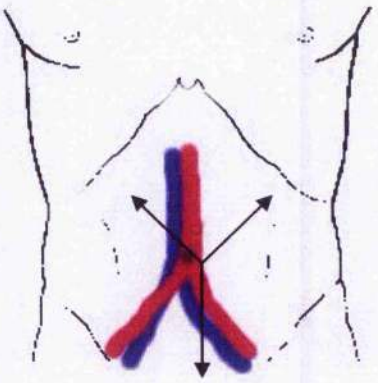


Figure 1.6 The "triangles of safety." Trocars inserted obliquely from the umbilicus into the white areas of the diagram (arrowed) will avoid the major retro-peritoneal vascular structures.

It has been suggested that high force during the insertion of trocars will result in higher rates of visceral injury (Corson *et al,* 1989; Nezhat *et al,* 1991). Presumed mechanisms include deeper inward deflection of the abdominal wall and the "overshoot" phenomenon. "Overshoot" (when the trocar suddenly thrusts forward) is a result of the physiological time lag between the surgeon sensing loss of resistance from the abdominal wall as it is breached, and the release of pressure on the handle of the trocar. If deeper inward deflection of the abdomen has occurred as a result of a high force of insertion, the tip of the trocar will be closer to the underlying viscera or retroperitoneal structures and may cause injury.

To counteract "overshoot" and the inward deflection of the abdominal wall, Dr Harry Reich of New Rochelle, NY, USA, has proposed a high-pressure, two-handed technique for trocar insertion (Reich, 1995). The abdomen is insufflated to 25mmHg with carbon dioxide. The trocar and cannula assembly is taken in two hands, with the palm of the right hand on the

handle of the trocar and the left hand on the cannula handle. The tip of the trocar is engaged with the linea alba, just below the umbilicus, at 90° and pressure is applied to the trocar handle. During insertion, the trocar is tilted by approximately 30° and the wrist of the right hand is rotated by 90° in one thrusting motion. The left hand acts as a restraint to prevent a sudden "overshoot" of the trocar tip as it perforates the peritoneum and the high intra-abdominal pressure reduces the amount of inward deflection of the abdominal wall. Theoretically this should keep the tip of the trocar away from the underlying viscera and vasculature and the manoeuvre to angle the trocar during insertion should direct it away from major blood vessels into a "triangle of safety" (Figure 1.6). Once the primary trocar is in the abdomen, the pressure of the pneumoperitoneum is reduced to 15mmHg or less.

1.8.5 Theoretical advantages relating to the profile of the trocar tip

Proponents of the pyramidal tip insist that it requires the least force to facilitate entry and therefore gives optimal control of the manoeuvre. They also advocate that optimal sharpness is essential, as any blunting of the trocar will increase the force of entry and the likelihood of visceral damage (Corson *et al,* 1989; Nezhat *et al,* 1991). In one study, reusable but regularly and professionally sharpened trocars (n=50) were compared with disposable trocars (n=50). The peak force generated during insertion of the reusable trocars was double that of the disposable devices (mean, 14.55 ± 6.46 (SD) lb vs 7.14 ± 5.35 (SD) lb respectively, $p<0.001$). The authors concluded that the lower force translated into greater control of the trocar during the process of insertion and that female surgeons would benefit from disposable, pyramidal trocars because they did not have the same upper body strength as men (Corson *et al,* 1989)! While there was little doubt that there was a difference in the amount force required for each of the two systems, there were no data to support the claim that this resulted in greater control during the process of insertion and less visceral damage.

For many years, Professor Kurt Semm of Kiel, Germany, has proposed the use of conical trocars. He has argued that the conical trocar only stretches the tissue, allowing it to return to

its normal configuration once the cannula is removed at the end of the procedure. As it does not cut the wound up to the size of the cannula, there should be less tissue injury, a tighter seal and a reduction in hernia formation. In addition, the conical trocar should deflect vessels in the abdominal wall, which would otherwise be sliced if contacted by a blade on the pyramidal trocar. Even if the sharp tip of a conical trocar impinges a blood vessel of the abdominal wall, it should only puncture it rather than divide it, theoretically simplifying haemostasis (Semm, 1995).

1.8.6 Laboratory evidence for the influence of trocar tip profiles on wound characteristics

Laboratory data to endorse these opinions are scarce.

A group from Michigan, USA set up a model using the mesenteric vessels of rabbits (Hurd *et al*, 1995). Using a jig, pyramidal and conical trocars, 5mm and 10mm diameter, were aimed at the vessels. The 5mm trocars were aimed at the centre of the vessels, then 1mm and 2mm from the centre. Similarly, the 10mm trocars were aimed at the centre and then at 1mm increments up to 5mm from the centre point of the vessel.

When the 5mm conical trocar was aimed directly at the centre of the vessels, there was an 88% rate of injury. However, when the trocar came into contact with the vessels at either 1mm or 2mm from the centre, none of the vessels were injured. When a 5mm pyramidal trocar was used, injury rates of 100%, 88% and 62% were noted when the initial point of contact of the trocar was 0, 1 and 2mm from the centre of the vessels, respectively. Introduction of the 10mm pyramidal trocar caused a 100% injury rate at 0mm to 3mm from the centre of the vessels and rates of 80% and 40% at 4 and 5mm from the centre. Whilst rabbit vessels may be more delicate than human vessels, it was claimed that the profile of conical trocars pushed the vessels aside while pyramidal trocars sliced through tissue within their path. An increase in the diameter of the pyramidal trocar also increased the rate of injury of the vessel.

Evaluation of a new radially dilating access system (InnerDyne Medical Inc, Sunnyvale, California, USA) by the team headed by Professor Lawrence Way in San Francisco confirmed some of the theoretical advantages of a dilating system (Bhoyrul *et al*, 1996). Comparison with conventional pyramidal trocars in anaesthetised pigs confirmed a different wound pattern and a lower incidence of bleeding. The cutting trocars caused a stellate wound and bleeding in 21% of trocar sites. The expandable device caused only a slit-like defect that ran in the direction of the muscle fibres, was smaller and was not associated with bleeding. Overall, the defects were 52% smaller than those created by the pyramidal trocar.

A study from Germany has also confirmed that less force is required to insert pyramidal trocars than conical trocars (Böhm *et al,* 1998). A series of 10mm reusable and disposable trocar tips (n=19) were selected and divided into six categories, defined by the profile and the angle of the taper of the tip. Two categories included conical trocars with "blunt" (angle of tip, 30°-45°, group 1) or "sharp" (angle of tip, 18°-30°, group 2) profiles and another two, pyramidal trocars with "blunt" (angle of tip 25°-35°, group 5) or "sharp" (angle of tip, 18°-25°, group 6) profiles. The two remaining categories (groups 3 and 4) contained six different trocars that were specially manufactured for the study. These trocars had a range of conical profiles with different angles of taper, but the extreme tip on each was ground into a sharp, pyramidal shape that was 5 to 10mm in length (group 3) or 12 to 15mm in length (group 4). All trocars were inserted into the abdominal wall of anaesthetised swine and the force of entry, removal force and wound sizes were all recorded, with four measurements made for each trocar. The results are shown in table 1.5.

Pyramidal trocars required the least mean force of insertion ($p<0.001$), were removed most easily ($p<0.01$) and created a wound the same diameter as the trocar. Conical trocars on the other hand, required a higher mean force of insertion, were more difficult to remove and created a smaller defect. The highest mean removal force though was recorded in group 3, one of the groups of specially prepared trocars with a combination of conical and pyramidal profiles. The conclusion was that a low insertion force cannot be combined with a high

removal force by simply changing the profile of the trocar tip and that no tip was optimal. Overall, the authors suggested, "that some kind of conical shaped trocar should be preferred."

Group	Entry force (Newtons)	Removal force (Newtons)	Wound size (mm)
1	82.0 ± 15.3	6.8 ± 1.3	8.5 ± 0.9
2	53.8 ± 24.3	7.6 ± 2.4	7.8 ± 0.6
3	54.2 ± 7.8	9.1 ± 2.8	7.5 ± 1.8
4	29.2 ± 13.6	8.4 ± 2.6	9.1 ± 2.5
5	23.4 ± 2.7	6.6 ± 2.1	10.1 ± 0.6
6	29.4 ± 10.7	4.7 ± 0.5	10.2 ± 0.3

Table 1.5 Entry force, removal force and size of abdominal wound in relation to different profiles of trocar tips (Böhm *et al,* 1998). For explanation of the groups, see the preceding paragraph.

The concept of the study was good but its execution lacked uniformity. Although each category contained similar profiles of trocar tips, the categories were not uniform as there were subtle intra-group differences in the angle or length of the tip. Ideally, each individual trocar should have been compared so that the effect of changing the angle of taper could have been assessed more accurately. Further breakdown of the results for the specially prepared trocars (groups 3 and 4) would have been an interesting attempt to explain why the entry force was less than for conical trocars yet the removal force was much higher. In fact, the results from groups 4 would appear to contradict the conclusion that a low insertion force cannot be combined with a high removal force by simply changing the profile of the trocar tip (Table 1.5).

During the discussion of this study, the theoretical relationship between increased force for insertion and higher rates of injury was mentioned. However, no data were collected during the study to examine if and by how much, the higher force of insertion for conical trocars translated into less control, greater displacement of the abdominal wall and deeper

penetration of the peritoneal cavity by the tip of the trocar.

1.8.7 Clinical studies of different trocar tip profiles

Clinical data concerning the merits of pyramidal and conical trocars are even sparser than laboratory data.

One clinical but non-randomised series compared pyramidal and blunt trocars for closed primary access in 2,457 laparoscopies. There were no complications among 1,889 laparoscopies that were performed with the blunted conical trocar and one perforation of the intestine from 568 insertions of the pyramidal trocar (Tews *et al,* 1991). The authors concluded that the blunted trocar was safer. However, the fact that no mention was made of any minor complications (e.g. wound haematomas) suggests that follow-up and data collection were less than rigorous. Furthermore, the data presented in the paper do not support the conclusion that the blunted trocar was safer. When subjected to statistical analysis, the difference in the rate of bowel injury between the two groups was not statistically significant (p=0.231, Fisher's exact test).

In a survey of 103,852 operations in France, there were 131 episodes of haemorrhage from the abdominal wall. Although pyramidal trocars were implicated in 104 cases and conical trocars in the remaining 27 instances, no conclusions can be drawn from these figures. There was no mention of the total numbers of pyramidal and conical trocars that were used, which means that the frequency of these episodes cannot be calculated or compared (Champault *et al,* 1996).

A small, non-randomised trial (n=19 patients) was performed in which the InnerDyne radially expanding access system (InnerDyne Medical Inc, Sunnyvale, CA, USA) was compared with size-matched, disposable, shielded, pyramidal trocars in patients who underwent a variety of gynaecological procedures. The radially expanding access system was

alternated between the right and left sides of the abdomen in consecutive patients and size-matched, pyramidal trocars were placed in the contralateral side. The women, who were unaware of the orientation of the trocars, were followed for one month and were asked to rate the severity of pain in each wound. Consistently, after one day, one week and one month, the side on which the radially expanding device had been used was associated with less pain ($p<0.001$). There were five complications in the series, all related to the pyramidal trocar, which just reached statistical significance ($p=0.046$). These included bleeding ($n=2$) and cannula slippage with loss of pneumoperitoneum ($n=3$) (Turner, 1996).

1.9 Summary of aspects of trocar and cannula design that require further study

1.9.1 Diameter

Recently, the use of small diameter trocars and instruments (3.3mm or less) has been described for laparoscopic cholecystectomy. Data from case series and cohort studies have lent credence to suggestions that smaller wounds may result in up to 70% less pain and analgesic consumption, a faster recovery and virtually invisible wounds (cf. section 1.7.2).

However, a reduction in the diameter of the laparoscope reduces the image quality and the consequent reduction in the diameter of the instruments increases flexibility and makes retraction and dissection more difficult, especially in the presence of fibrosis or inflammation. There may also be a learning curve associated with smaller instruments (cf. section 1.7.3).

As a result, there is uncertainty over the clinical benefits of laparoscopic cholecystectomy with small instruments and calls for randomised controlled trials in specialist units (Berci, 1998; Hunter, 1998; Mar Fan & Chan, 1998; Svanvik, 1997). No data are available about the impact on the stress response, if any, of the smaller trocar and cannula systems.

1.9.2 Profile

Some authors argue that increased force during the insertion process will result in higher rates of visceral injury (Böhm *et al*, 1998; Corson *et al*, 1989; Nezhat *et al*, 1991). Presumed mechanisms include deeper inward deflection of the abdominal wall and the "overshoot" phenomenon (cf section 1.8.4).

While it has been shown that trocars with a conical profile require more force to traverse the abdominal wall, the assumption that this translates to a higher rate of visceral or vascular injury has not been proven. In fact, there is some evidence that injury is less likely, less serious and smaller with a conical trocar than a pyramidal trocar (cf. section 1.8.6). The evidence also alludes to a lower rate of injury with trocars of a smaller diameter (Hurd *et al*, 1995). Whether the findings of these studies can be applied to bowel or major vessels is not known. Since bowel and major vascular injuries cause the most serious morbidity and mortality, this is an important omission in the literature that requires further study.

1.10 Hypotheses and Aims

1.10.1 The trauma of access in Minimally Invasive Surgery can be reduced through the use of thinner instruments

As discussed earlier, the advantages of laparoscopic cholecystectomy over open cholecystectomy are now well established. These include lower release of cytokines, less impairment of cell-mediated immunity, less pain, better pulmonary function, faster postoperative recovery, fewer complications and improved cosmetic appearance. Data from case series and cohort studies suggest that a further reduction in the size of the wounds could result in greater patient comfort and a faster postoperative recovery.

The effect of the use of thinner instruments will be investigated in a randomised controlled trial of conventional laparoscopic cholecystectomy (performed with two 10mm and two 5.5mm cannulae) and micropuncture cholecystectomy (performed with on 10mm and three

3.5mm cannulae). The aims of the study are to compare patient recovery, the stress response to surgery and the relative difficulty of the two procedures. These objectives will be achieved by measurement of:-

1. Visual analogue pain scores.
2. Analgesic requirements.
3. The presence of nausea and vomiting.
4. Pulmonary function as measured by peak expiratory flow rate (PEFR), forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1).
5. Quality of life, using the EuroQol EQ-5D assessment tool.
6. Postoperative function of the patients.
7. The responses of interleukin-6, adrenocorticotropic hormone and vasopressin over the first 24 hours after induction of anaesthesia.
8. Total operative times and times taken to perform each step of a cholecystectomy.

1.10.2 Iatrogenic visceral injury, sustained during the process of gaining access to the abdomen in Minimally Invasive Surgery, can be influenced by the choice of profile of the trocar tip

In the literature, it has been established that conical trocars require a higher force of entry but cause smaller wounds and are less likely to injure small vessels that they encounter during the process of insertion. Cutting trocars slice through tissue, create a wound of the same diameter and are more likely to injure small blood vessels. However, it has been assumed from these data by some authors that the higher force required to insert a conical or blunt trocar results in deeper incursion into the abdominal cavity and higher rates of visceral or vascular injury, while other authors have suggested that conical trocars may push aside viscera upon contact and are less likely to cause major vascular trauma. There are no data to support these assumptions.

The influence of the profile of the tip of the trocar on the depth of penetration of the abdomen during the process of insertion will be studied in-vitro, using an abdominal wall simulator designed for the experiment. The aim is to compare the distance of travel of the tip of pyramidal, sharp conical and blunt conical trocars when:-

1. The tip of the trocar initially penetrates the peritoneum.
2. The leading edge of the cannula is first observed to breach the peritoneum.
3. The entire cannula has penetrated the peritoneum.

In the subsequent experiments, the influence of the profile of the tip of the trocar on the rate and severity of bowel and aortic injury will be examined in-vitro, using models designed for the experiments. The aims of these studies will be to compare:-

1. The incidence of deflection and injury.
2. The size and shape of the injuries.

CHAPTER 2

THE IMPACT ON POSTOPERATIVE OUTCOME AND THE SURGICAL STRESS RESPONSE OF A REDUCTION IN THE DIAMETER OF THE TROCARS, CANNULAE AND INSTRUMENTS.

A RANDOMISED COMPARISON OF CONVENTIONAL LAPAROSCOPIC AND MICROPUNCTURE LAPAROSCOPIC CHOLECYSTECTOMY.

2.1 Introduction

Recently, the use of trocars, cannulae and instruments with a diameter of 3.3mm or less has been described for laparoscopic cholecystectomy. Although data from case series and cohort studies have lent credence to suggestions that smaller wounds may result in less pain and analgesic consumption, a faster recovery and virtually invisible wounds, uncertainties over the feasibility and benefits of such surgery remain (cf. section 1.7). As the technique of micropuncture laparoscopic cholecystectomy (MPLC) has been used within the Leeds Institute for Minimally Invasive Therapy since 1996, it was decided to conduct a randomised trial to compare it with conventional laparoscopic cholecystectomy.

2.2 Hypothesis and aims

2.2.1 Hypothesis

The trauma of access in Minimally Invasive Surgery can be reduced through the use of thinner instruments

2.2.2 Aims

The effect of the use of thinner instruments will be investigated in a randomised controlled trial of conventional laparoscopic cholecystectomy (performed with two 10mm and two 5.5mm cannulae) and micropuncture cholecystectomy (performed with on 10mm and three 3.5mm cannulae). The aims of the study are to compare patient recovery, the stress response to surgery and the relative difficulty of the two procedures.

2.3 Methods

2.3.1 Operative procedures

2.3.1.1 Conventional laparoscopic cholecystectomy : The Leeds technique

Under general anaesthesia and with the patient in the supine position, pneumoperitoneum was established using the Veress needle. A 10mm cannula was inserted at the umbilicus and general laparoscopy was performed. The remaining three cannulae were inserted as per the Reddick-Olsen technique (Figure 2.1) with one cannula of 10mm diameter in the epigastrium and a further two 5.5mm cannulae in the right upper quadrant (Reddick & Olsen, 1989). All cannula sites were pre-emptively infiltrated with a total of 20 mls of 0.5% plain bupivicaine. The pressure was reduced from 15mmHg to 7mmHg once the cannulae had been inserted. Conical trocars were used throughout the study.

A Diamond-Flex™ retractor (Snowden Pencer, Tucker, GA, USA) was placed through the lateral cannula to retract the liver and facilitate dissection of Calot's triangle. These retractors have a blunt profile and can be placed under the liver without causing trauma (Figures 2.2 and 2.3). They avoid the distortion of Calot's triangle caused by fundal traction and facilitate opening of the angle between the cystic duct and bile duct (M°Intyre *et al*, 1996). In the presence of severe inflammation, they facilitate a fundus-first dissection (Martin *et al*, 1995).

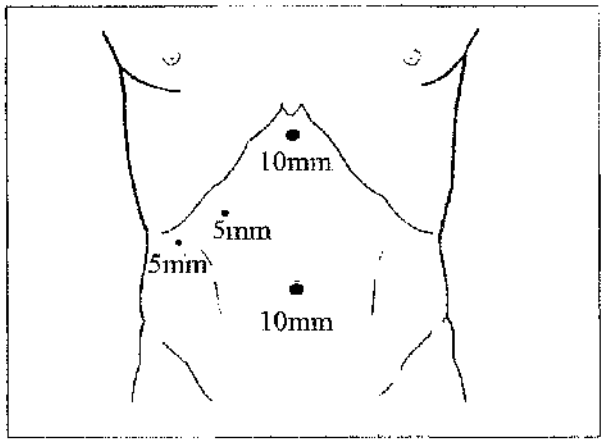


Figure 2.1 Position of the cannulae for conventional laparoscopic cholecystectomy.

Dissection was commenced at Calot's triangle and a window equating to 50% of the gallbladder length was created to identify the cystic duct and artery and any anomalous, anatomical features. Routine intraoperative cholangiography was used (Martin *et al,* 1992). Images were produced by fluoroscopy and printed as a permanent record (Figure 2.3).

The gallbladder was placed in an impervious bag (Cook, Bloomington, IN, USA) for retrieval through the umbilical cannulation site and a 3mm silicone drain (Osteotec Ltd, Christchurch, Dorset, UK) was inserted via the lateral subcostal cannula site. The fascial defect at the umbilicus was closed with '0' calibre polydioxanone sutures (PDS, Ethicon, Edinburgh, West Lothian, UK), inserted by an Endoclaw device (Surgical Innovations, Leeds, West Yorkshire, UK) under direct vision. The skin was closed with 4/0 subcuticular sutures. All wounds were dressed with opaque dressings (Op-site, Smith and Nephew Medical Limited, Hull, UK).

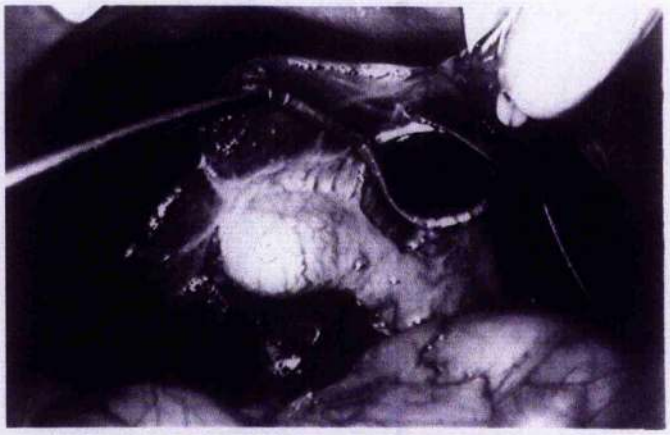


Figure 2.2 A 5mm Diamond-Flex™ retractor, placed under the liver

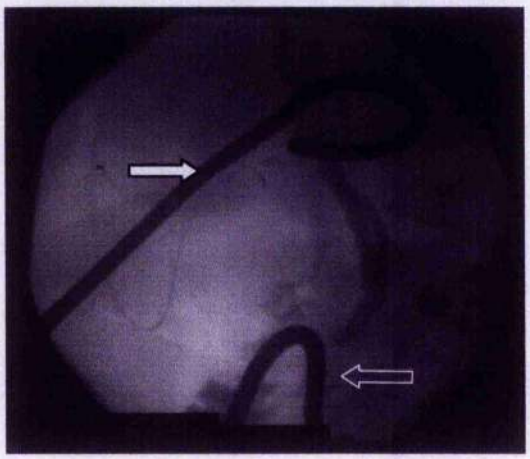


Figure 2.3 An intraoperative cholangiogram taken during CLC. The liver retractor can be seen clearly (solid arrow). In this film, a second retractor (outline arrow) is retracting the omentum that was obscuring the view of Calot's triangle.

2.3.1.2 Micropuncture laparoscopic cholecystectomy

The technique described above was modified by using three, 3.3mm cannulae (with conical trocars) subcostally and in the epigastrium (Figure 2.4). The liver was retracted with a 3mm Diamond-Flex™ retractor (Snowden Pencer, Tucker, GA, USA). Cholangiography was performed after securing a catheter in the cystic duct with a grasping clamp (Surgical Innovations, Leeds, West Yorkshire, UK), inserted through the epigastric cannula (Figure 2.5). The cystic duct and artery were clipped with a 10mm clip applicator, placed through the umbilical cannula and guided by a 3mm laparoscope in the epigastric cannula (Expanded Optics, Barnet, Hertfordshire, England).

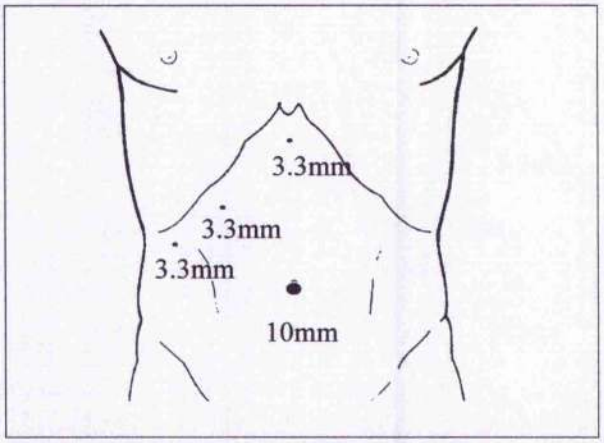


Figure 2.4 Position of the cannulae for the Micropuncture technique. Note that all three sub-costal cannulae are the same diameter.

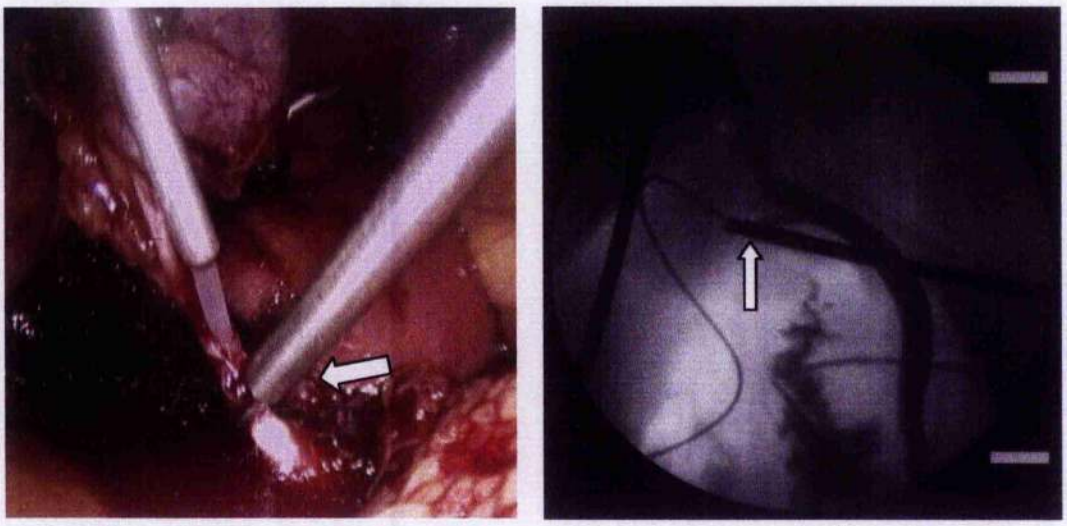


Figure 2.5 An intraoperative cholangiogram obtained during MPLC. The catheter is secured within the cystic duct by the grasper (arrow).

2.3.2 Inclusion and exclusion criteria

Patients with an American Society of Anesthesiologists Physical status score (ASA) of 1 or 2 (cf. appendix 1) and listed for cholecystectomy were considered. Patients with evidence of choledocholithiasis, acute cholecystitis, previous abdominal surgery or who were consuming regular opiate analgesia, were excluded. Patients with an ASA status of 3 or higher (cf. appendix 1) were excluded to enable standardisation of anaesthesia.

2.3.3 Randomisation

A randomisation list was generated by The North Yorkshire Clinical Trials Unit with separate stratification for consultant and trainee. Patients were randomised at the time of induction of anaesthesia.

2.3.4 Anaesthesia and analgesia

The anaesthetists who regularly provide cover for the elective operating lists agreed a standardised protocol of anaesthesia (cf. appendix 1). Intraoperatively, all cannula sites were pre-emptively infiltrated with a total of 20 mls of 0.5% plain bupivicaine and each patient received a diclofenac suppository (100mg) and 5mg of intravenous diamorphine. Postoperatively, all patients were prescribed co-codamol 30/500 as required for pain and cyclizine 50mg as required for nausea. If the oral medication was inadequate, patients could request 10mg of intramuscular morphine from a nurse, who was blinded to the procedure. Analgesic and anti-emetic requirements were recorded on the hospital drug administration chart and after discharge, patients recorded their consumption of analgesia on a pain score sheet (cf. appendix 2). Three patients preferred "weaker", non-prescription opiate analgesia at home. To accommodate this, opiates were converted into morphine equivalents using standard published values (Table 2.1, Twycross *et al,* 1998). The presence of nausea and vomiting was also recorded (cf. appendix 2).

Opiate	Morphine equivalent
Diamorphine 5mg	10mg
Codeine 30mg	3mg
Dihydrocodeine 30mg	3mg
Dextropropoxyphene 32.5mg	1.5mg

Table 2.1 Morphine equivalents for opiate analgesia (values from Twycross et al 1998).

2.3.5 Operative time

The total time for the procedure was recorded, from skin incision to skin closure. In addition, the procedure was sub-divided and when the surgeon completed each step, the circulating nurse recorded the time. These steps were:-

1. Time to establish pneumoperitoneum and insert four cannulae.
2. Time to complete the dissection of Calot's triangle (i.e. to open a "window" equivalent to 50% of the length of the gallbladder) and to correctly identify the anatomy.
3. Time to successfully complete cholangiography. If cholangiography was unsuccessful, the time this step was abandoned was recorded.
4. Time from the completion of cholangiography, to clip application and division of the cystic duct.
5. Time to remove the remaining attachments of the gallbladder from the liver.
6. Time to insert the specimen retrieval bag and place the gallbladder within it.

2.3.6 Pain scores

Pain is a highly personal and subjective experience that is difficult to quantify objectively. It is influenced by previous experience, ethnicity, affect and anxiety. The fact that so many systems have been developed to facilitate comparative measurement for clinical and research purposes speaks volumes to their limitations. However, there are specific clinical settings where one system will have an advantage over another. Common categories of scoring systems are:

a) Visual analogue pain scale (VAPS) – This system employs an unmarked 10cm line, labelled at either end with the extremes of "no pain" and "worst pain" (Collins *et al,* 1997; Scott & Huskisson, 1976). Patients have to place one mark, to record current pain intensity and this is measured from the left side, in millimetres (Figure 2.6).

The advantages of this system are that is easy to use, provides an infinite number of responses without restrictive subcategories and has been shown to be reproducible (Choinière & Amsel, 1996; Scott & Huskisson, 1976). Older patients may find it more difficult to use (Kremer *et al,* 1981; Jensen *et al,* 1986) but this can be circumvented when instructions are implicit or supervision is available (Choinière & Amsel, 1996). Potential disadvantage are that verbal responses are not possible in the clinical setting, care must be exercised during production of the VAPS (photocopies can alter the length of the baseline) and errors can occur during measurement of the response (Jensen *et al,* 1986). It is therefore used primarily as a research tool rather than a clinical aid to pain management.

Figure 2.6 Example of a completed Visual Analogue Pain Scale. The mark represents a score of 38.

b) Numerical scales – These are systems with anchored numerical points which operate on a similar principle to the VAPS, except that patients choose a number on a predefined scale instead of placing a mark on a line. This has been validated as easy to use, sensitive, reliable and reproducible. It is advantageous in the clinical setting as it can be given verbally, although it has been criticised because the values are fewer, absolute and subject to numerical preference by patients (Scott & Huskisson, 1976). While good correlation between the results of the two methods exists, the numerical scale is not directly interchangeable with the VAPS (Choinière & Amsel, 1996; Jensen *et al,* 1986; Kremer *et al,* 1981).

c) Multi-dimensional assessment tools – The most widely accepted and respected example is the McGill Pain Questionnaire (Melzack, 1975). Unlike the VAPS and numeric scales that only record intensity, this system uses pain descriptors to collect and score detailed information about several aspects of the personal pain experience (the categories are labelled "sensory", "affective" and "evaluative"). This makes the McGill Pain Questionnaire score less susceptible to alterations of the psychological state of the patient. However, there are some disagreements over appropriateness and comprehension of the vocabulary employed and one study has demonstrated that 40% of sensory descriptors are subject to incomprehension, underuse and ambiguity (Fernandez & Towery, 1996). Due to its length, repeated measurements can be cumbersome - it takes between 10 to 20 minutes to complete (Melzack, 1975). Also, if a patient chooses a word from a category that was not selected at an earlier time point, the scoring system records an infinite increase in the pain score – such values must be omitted from analysis. Careful interpretation is therefore required (Choinière & Amsel, 1996).

For the purposes of this trial, the VAPS was chosen due to its ease of use, sensitivity and reproducibility. Documentation by the patient in written as opposed to verbal format was considered essential for accurate and impartial data collection and ease of analysis. Participants were given explicit oral and written instructions to minimise the risk of incorrect responses due to misunderstanding (cf. appendix 2). Measurements were made preoperatively to act as baseline controls, then at eight, twelve and 24 hours to assess the time period during which "day-cases" could potentially be discharged. Further measurements were recorded daily for one week.

2.3.7 Pulmonary function

Laparoscopic cholecystectomy is associated with better preservation of postoperative respiratory function compared with open cholecystectomy (cf. section 1.4.3). Pulmonary function tests were measured in the sitting position, with a portable Vitalograph 2120

Electronic Storage Spirometer and results were downloaded onto 2170 Serial Spirotrac Software (Vitalograph Ltd, Buckingham, UK). All patients were taught the technique preoperatively and were given the opportunity to practice until the spirometer confirmed correct technique and consistent results. Measurements were made preoperatively to act as baseline controls, then at eight and 24 hours to assess the time period during which "day-cases" could potentially be discharged. Further measurements were recorded one week and four weeks later.

2.3.8 Quality of life assessment: The EuroQoL EQ-5D questionnaire

The EuroQoL EQ-5D questionnaire is a generic measurement tool for recording health status, developed by an international research network group (EuroQoL). It is designed for self-completion and enables patients to record information concerning their health, simply and quickly with completion typically taking less than five minutes (Brooks *et al,* 1996; Kind *et al,* 1998; MacDonagh *et al,* 1997;).

On the first page, there is a list of five "dimensions"; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are sub-divided into three categories; no problems, some problems, and extreme problems. The respondent ticks one box that corresponds to the category that best applies to them at that moment in time and from this, a total combination of 243 health states can be defined (if death and unconsciousness are included, 245 states can be ascertained). Each of these states has a weighted index, derived from population data that are used to score the response, with a value of "1" representing perfect health. The third page comprises of a vertical, visual analogue "health thermometer," with "0" representing the "worst imaginable health state" and "100" the "best imaginable health state." (cf. appendix 4) The weighted index and the health thermometer scores can be analysed as ordinal data. The responses to the dimensions can be compared with the Chi-squared test (Brooks *et al,* 1996; Kind *et al,* 1998). The chief statistician at EuroQoL advised further analysis with the χ^2 test, with the dimensions

regrouped as "problem present" and "problem absent" (Kind P, personal communication).

The tool is available in all major languages and a published review of the available literature has confirmed that:-

a) the instrument is "user-friendly" due to its simplicity and that completion rates of 98-100% can be achieved,

b) response rates are not affected by age or educational level,

c) test-retest reliability has been ascertained by the EuroQOL groups in York, UK and Rotterdam, Holland,

d) comparison of the EuroQoL questionnaire with the SF-36 and the Nottingham Health Profile demonstrate broad agreement (Brooks *et al,* 1996).

Some surgical studies have already employed the EQ-5D questionnaire and reported that it has sufficient sensitivity to detect differences in the study populations (Sculpher *et al,* 1996; MacDonagh *et al,* 1997). As patients participating in this study would supply blood samples, VAP scores, undergo respiratory function testing and assessment of functional activity, the EuroQOL EQ-5D was selected for its simplicity and speed of completion. Measurements were made preoperatively to act as baseline controls, then at eight and 24 hours to assess the time period during which "day-cases" could potentially be discharged. Further measurements were recorded one week and four weeks later.

2.3.9 Stress response

It is normal practice within LIMIT for most routine ASA 1 and 2 patients to be discharged within 24 hours. In order not to interfere with this practice, it was decided prior to the trial that blood sampling would not occur beyond 24 hours.

Interleukin-6 (Il-6), adrenocorticotropic hormone (ACTH) and arginine vasopressin (AVP) were measured as markers of the cytokine and neuro-humoral responses to surgical stress.

These were specifically chosen because ACTH, AVP and Il-6 all rise and fall within 24 hours of surgery and correlate with the degree of trauma (cf. section 1.5.2). The sample times were selected on the basis that ACTH and AVP are highest in the immediate postoperative period (around 2 hours after induction), Il-6 peaks by eight hours after induction and all return towards baseline concentrations within 24 hours of a laparoscopic procedure. Samples were collected at the following time points:-

Sample 1 - preoperatively (baseline),

Sample 2 - after induction of anaesthesia but prior to surgery,

Sample 3 - two hours after induction

Sample 4 - eight hours after induction

Sample 5 - twenty-four hours post induction.

Samples were collected in pre-chilled EDTA and lithium heparin tubes and were spun at 3000 rpm for 7 minutes at 4°C. Aliquots of plasma were frozen within 20 minutes of collection to –20°C then transferred to a freezer in the main laboratory at Leeds General Infirmary within 48 hours where they were stored at –70°C until they were analysed in batches.

Interleukin-6 and ACTH were analysed using quantitative sandwich enzyme-linked immunosorbent assay kits (ELISA). The technique is summarised in appendix 3.

Vasopressin assays were not performed with a commercial kit as it is technically difficult to achieve adequate quality control for a single batch. Samples were therefore couriered on dry ice to an external laboratory (Department of Biochemistry, Royal Gwent Hospital, Newport, UK) in which a reproducible technique for extraction and analysis of vasopressin by radioimmunoassay has been developed. This has been demonstrated to result in a mean

recovery of 96.4% (±5.5%) of vasopressin from plasma samples and to have an assay detection limit of 0.25pmol/L (Penney *et al*, 1992).

2.3.10 Postoperative function

Patients must be able to mobilise and perform basic activities of daily life to ensure a safe discharge from hospital. Review of the literature revealed no simple, satisfactory tests, specific to cholecystectomy that would allow a comparison of postoperative function of patients undergoing different techniques of laparoscopic cholecystectomy. Exercise tests with a treadmill and measurement of maximum oxygen uptake require specialised equipment, are not easily performed on the ward setting and are not affected by laparoscopic cholecystectomy (cf. section 1.4.4). However, studies of inguinal hernia repair have effectively incorporated a functional comparison of treatment groups with straight leg raising and sit-ups. The rationale for these tests is that that postoperative pain restricts the use of the muscles that are involved in these activities (Liem *et al*, 1997; Payne *et al*, 1994).

Advice was sought from Professor CB Cooke of the Sports Science Department of Leeds Metropolitan University. Ideally, any tests for cholecystectomy should assess the function of the rectus abdominis, transversus abdominis and the internal and external obliques, without inducing maximum effort. Suggestions for tests included timing patients to rise from the supine position in bed, to stand from a chair and walk a set distance of 20m (equivalent to the distance from a ward bed to the toilet). A further repetitive test to measure impairment of torso rotational movements (i.e. using the external and internal oblique muscles) was devised whereby patients would move 10 objects of equivalent size and weight from right to left with their left hand, then back again with their left hand. A cheap, reliable and robust source of objects of identical shape and size was chosen (Baked Beans, HJ Heinz Company Limited, Hayes, Middlesex, UK). Preoperative testing was used to ensure that each patient acted as his or her own control, then as with pulmonary function, measurements were recorded at eight hours, 24 hours, one week and four weeks.

2.3.11 Statistics

2.3.11.1 Study size

This was estimated in collaboration with the hospital biomedical statistician at the outset. Among published studies of laparoscopic versus open cholecystectomy, patients who underwent a laparoscopic procedure typically reported mean visual analogue pain scores (VAPS) of around 40mm to 50mm during the first 24 hours after the operation (Joris *et al,* 1992; Mealy *et al,* 1992; McMahon *et al,* 1994(b); Karayiannakis *et al,* 1997). As no such VAPS data were available for the micropuncture or needlescopic techniques, an estimate of the score had to be made.

Using the VAPS system, pain that does not require analgesia or a pain that has been successfully relieved by analgesia is widely accepted to be represented by a score of less than 30mm. Moderate pain is represented by a score of 30mm to 54mm and severe pain by scores of 55mm or more (Collins *et al,* 1997; George *et al,* 1992; Mantha *et al,* 1993; Salomäki *et al,* 1991; Tauzin-Fin *et al,* 1992).

As 17 of 25 patients (68%) in the pilot study of the micropuncture technique performed in Leeds required no analgesia (Davides *et al,* 1997b), it was therefore assumed for the purposes of the power calculation that their mean visual analogue pain score would have been 30mm or less. This meant that to have 80% power to detect a 25% reduction in pain scores from a mean of 40mm to 30mm, the study required a minimum of 17 patients in each group. This assumed equal patterns of distribution and a two-tailed significance level of 0.05.

2.3.11.2 Methods of analysis

The Mann-Whitney test was used for metric and ordinal data and the χ^2 test for categorical data, unless a cell frequency was less than five, in which case Fisher's exact test was employed. Where repeated metric or ordinal samples were encountered, comparisons of the

areas under the curves (AUC) were made (Matthews *et al* 1990). Intra-group comparisons were made with the Wilcoxon signed ranks test. All data were analysed using SPSS software (Statistical Package for Social Sciences v 9.0, SSPS UK Ltd, Woking, Surrey, UK). Analyses were conducted on an "intention to treat" basis.

2.3.12 Ethics committee approval

Approval was obtained from the local ethics committee. All patients received an information sheet and gave their written informed consent to participate in the study (cf. appendix 5).

2.4 Results

Forty-four patients agreed to participate in the trial. Four were withdrawn; three due to unsuspected choledocholithiasis detected during intraoperative cholangiography with the need for duct exploration and one because it was necessary to reschedule the operation. Three of the four withdrawn patients were in the CLC arm and one in the MPLC arm of the trial (p=0.607, Fisher's exact test). Forty patients were entered into the study; nineteen to CLC and 21 to MPLC.

2.4.1 Patient characteristics

Both groups of patients were well matched by body mass index, length of symptoms, time on the waiting list, presence of calculi or polyps, stone size, thickening or contraction of the gallbladder wall, adhesions or presence of a dilated common bile duct (Tables 2.2 and 2.3). The median ages of the groups differed by 9 years, but the range of ages was wide and did not reach statistical significance. More patients in the CLC group had previous emergency admissions, (6 vs 2) but this was not statistically significant (p=0.120, Fisher's exact test).

Variable	CLC (n=19)	MPLC (n=21)	p value
Age (years)	**49** (47 – 54)	**58** (44 – 63.5)	0.193†
Sex (male:female)	**4:15**	**1:20**	0.172‡
Body Mass Index (kg/m^2)	**27.7** (24.6 – 30.8)	**24.5** (23.2 – 32.45)	0.440†
Symptom time (months)	**12.5** (9.5 – 21.25)	**18** (7.0 – 33.0)	0.429†
Time on list (months)	**7** (3.1 – 12.2)	**6.9** (2.0 – 9.8)	0.481†
ASA status (ASA 1:ASA 2)	**13:6**	**15:6**	1.000‡

Table 2.2 Comparison of the characteristics of the patients within the two groups. Values are medians with the interquartile range (IQR). †-Mann-Whitney test, ‡-Fisher's exact test

Variable	CLC (n=19)	MPLC (n=21)	p value
Emergency admissions	4 BC, 2AC	2 BC	0.120‡
Calculi present	18	19	1.000‡
Stone size (cm)	0.5 (0.4 – 1.5)	1.0 (0.25 – 2.0)	0.380†
Polyps present	1	1	1.000‡
Contracted GB	3	2	0.654‡
Thick walled GB	13	12	0.527‡
Adhesions present	10	11	1.000‡
Dilated CBD (>0.8cm)	1	1	1.000‡

Table 2.3 Comparison of the extent of biliary disease in the two groups. Single figures denote the total numbers of patients in each group. Stone size is expressed as median (IQR). AC – acute cholecystitis, BC – biliary colic, CBD – common bile duct, GB - gallbladder

† - Mann-Whitney test, ‡ - Fisher's exact test

2.4.2 Operative details, times and complications.

There were no significant differences between groups with respect to the grade of the operating surgeon, number of cannulae used or the pressure of pneumoperitoneum. Apart from the size of the instruments, both CLC and MPLC were performed in a similar manner.

All micropuncture procedures were completed without conversion to CLC. However, in two procedures, one 3.3mm cannula was changed to a 5mm cannula to facilitate control of refractory haemorrhage from the gallbladder bed with the argon diathermy (a 3.3mm argon probe was unavailable). An extra cannula was used in the left upper quadrant in five patients in each group, to retract a bulky omentum that was obscuring the view of Calot's triangle. This is standard practice in the unit to avoid the need to struggle and to maintain safe visualisation of the cystic duct.

Cholangiography was successfully completed in 15 patients in each group but there were four failures in the CLC group and five in the MPLC group due to the presence of a narrow or occluded cystic duct. Cholangiography was not performed in one patient in the MPLC group because of an iodine allergy (Table 2.4)

There were no major complications and only eight minor complications. In the CLC group, there was a minor bile leak that spontaneously resolved, three haematomas and two infections of the umbilical wound. In the MPLC group, one patient had post-cholecystectomy diarrhoea and another was readmitted with abdominal pain. This settled spontaneously and no cause was established (Table 2.4). The study was not powered to detect any difference in the rate of complications.

There was no significant difference in total operative time. However, breakdown of the times taken to perform individual stages of the procedure demonstrated that it took almost 2 minutes longer to establish pneumoperitoneum and place the cannulae with the micropuncture technique ($p=0.015$, Mann-Whitney test). In addition, it took over 2 minutes longer to clip the cystic duct after cholangiography in the MPLC group ($p<0.001$, Mann-Whitney test). There were no differences in time to dissect Calot's triangle, perform cholangiography or remove the gallbladder from the liver (Table 2.5).

Variable	CLC (n=19)	MPLC (n=21)	p value
Consultant operator	**16**	**17**	1.000‡
Trainee operator	**3**	**4**	
Number of cannulae	**4** (4 – 5)	**4** (4 – 5)	0.787†
Number requiring extra cannula	**5**	**5**	1.000‡
Working pressure (mmHg)	**7** (7 – 7)	**7** (7 – 7)	0.657†
Peak pressure (mmHg)	**7** (7 – 10)	**7** (7 – 7.5)	0.512†
CO_2 Volume (litres)	**92.3** (66.6 – 130.2)	**76.2** (59.3 – 125.0)	0.370†
Successful cholangiograms	**15**	**15**	1.000‡
Complications	**6**	**2**	0.12‡

Table 2.4 Comparison of operative details. When medians are quoted, the interquartile range follows in brackets. Solitary values represent absolute numbers in each group.

† - Mann-Whitney test, ‡ - Fisher's exact test.

Time period	CLC (minutes)	N	MPLC (minutes)	N	p value†
Total Operative Time	**62:59** (52:23 – 81:00)	16	**74:00** (57:46 – 94:56)	19	0.126
Cannula insertion	**5:42** (3:45 – 6:37)	16	**7:38** (5:57 – 10:15)	19	**0.015**
Calot's triangle dissection	**19:29** (12:17 – 27:05)	13	**20:13** (14:37 – 37:18)	18	0.573
Cholangiogram	**6:04** (5:23 – 8:36)	16	**8:04** (6:50 – 11:51)	19	0.139
Clip applied to cystic duct	**1:05** (0:40 – 1:35)	16	**3:45** (2:26 – 7:49)	19	**<0.001**
Gallbladder off liver bed	**4:49** (3:20 – 7:55)	15	**7:30** (3:51 – 14:38)	18	0.254
Gallbladder into specimen bag	**1:17** (1:00 – 1:49)	15	**2:00** (1:24 – 2:22)	19	0.095

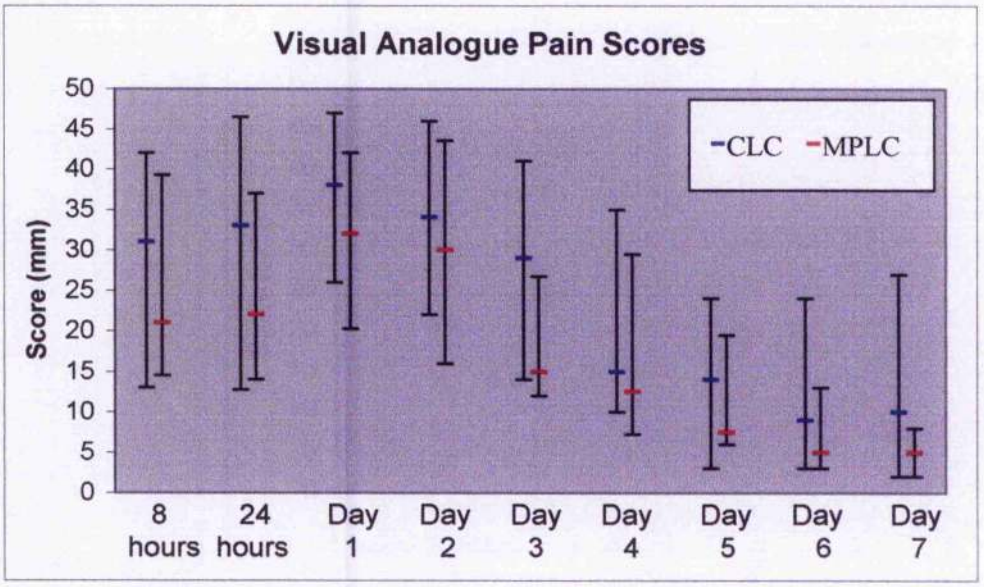
Table 2.5 Comparison of total operative time and the times taken for each step of the procedure. Values are the median (IQR).

N – number of times recorded. † - Mann-Whitney test.

The need to collect the data was realised after five patients had already been enrolled into the study and was therefore collected for 35 patients. Seven time points out of a possible 245 were missed because the circulating nurse was out of theatre on an errand. For five patients, a fundus-first dissection was performed due to the presence of inflammation, with the result that full and safe dissection of Calot's triangle occurred after the gallbladder had been removed from the liver. In these patients the time to remove the gallbladder was designated as a missing value.

2.4.3 Visual analogue pain scores

Two patients (one in each group) did not record entries for the 12-hour pain score and one patient in the micropuncture group failed to return the sheet at either follow-up visit. Median visual analogue pain scores were lower in the MPLC group on every occasion but due to the large variation there was no statistically significant difference between the groups (Figure 2.7, Table 2.6).



CLC	19	18	19	19	19	19	19	19	19
MPLC	20	19	20	20	20	20	20	20	20

Figure 2.7 Visual analogue pain scores for the first postoperative week. Values are the median with the interquartile range. The number of responses at each time point is annotated below the graph.

Time period	CLC (mm.hr)	MPLC (mm.hr)	p value†
First 24 hours	**25.5** (18.8 – 34.7)	**20.3** (16.2 – 32.1)	0.325
First three days	**85.5** (59.1 – 108.0)	**75.0** (44.0 – 86.0)	0.249
1 week	**146.3** (104.6 – 231.0)	**119.3** (78.6 – 191.6)	0.431

Table 2.6 Comparison of the median areas under the curves (interquartile range) for visual analogue pain scores for CLC and MPLC. †-Mann-Whitney test.

2.4.4 Analgesic requirements

As described in the methods section, opiates were converted into morphine equivalents using standard published values (Table 2.1). It was intended to count the number of tablets remaining on day seven to check the total recorded on the pain sheets but very few of the patients returned with their medication so this was not possible. One patient in the MPLC group did not return their data sheet.

Total opiate consumption - There were no statistically significant differences in total opiate consumption (sum of parenteral and oral, intra-operative and postoperative) over the initial 24 hours or during the first postoperative week (Table 2.7).

Time period	CLC (mg of morphine)	MPLC (mg of morphine)	p value†
24 hours	**22** (22 – 32)	**22** (16 – 28)	0.099
1 week	**67** (38 – 100)	**40** (23.5 – 82)	0.205

Table 2.7 *Total* consumption of opiate analgesia (intra-operative and postoperative doses, parenteral and oral) measured as morphine equivalents (mg). Values are expressed as the median with the interquartile range. † - Mann-Whitney test.

Oral and parenteral opiate consumption – There were no differences in total consumption of oral codeine based opiates during the initial 24 hours or the following week. However, during the initial 24 hours on the ward, 6 patients in the CLC group but only one patient in the MPLC group required parenteral opiate (p=0.04, Fisher's exact test). The quantity of parenteral opiate used was also significantly lower for the MPLC group (Table 2.8).

Oral / Parenteral	CLC (mg of morphine)	MPLC (mg of morphine)	p value†
Parenteral consumption	**0** (0 -10)	**0** (0 - 0)	**0.038**
Oral intake - 24 hours	**12** (12 – 18)	**12** (6 –18)	0.481
Oral intake - 1 week	**57** (24 – 84)	**30** (15 – 69)	0.217

Table 2.8 Breakdown of post-operative parenteral and oral analgesic consumption (intra-operative diamorphine not included). Values are expressed in milligrams as the median morphine equivalent (interquartile range). †-Mann-Whitney test.

2.4.5 Nausea and vomiting

One patient in the MPLC group failed to return the data sheet and one patient in each arm of the trial did not respond at 12 hours. Review of the contingency tables prepared for analysis of the data with the χ^2 test, revealed that between 50 – 75% of cells contained an expected frequency count below five (cf. appendix 6). The data were therefore re-categorised to the presence (score of 1,2 or 3) or absence (score of 0) of nausea and vomiting and were analysed with the Fisher's exact test which demonstrated no statistically significant differences between the groups at any time point (Table 2.9). Likewise, there was no difference in the number of patients in each group who requested an anti-emetic (CLC 5 patients vs MPLC 8 patients, p=0.511, Fisher's exact test).

Time	Group	Number with no N/V	Number with N/V	p value†
8 hours	CLC	11	8	0.751
	MPLC	10	10	
12 hours	CLC	13	5	1.000
	MPLC	14	5	
Day 1	CLC	12	7	0.301
	MPLC	16	4	
Day 2	CLC	13	6	0.127
	MPLC	18	2	
Day 3	CLC	13	6	0.273
	MPLC	17	3	
Day 4	CLC	17	2	1.000
	MPLC	17	3	
Day 5	CLC	15	4	0.407
	MPLC	18	2	
Day 6	CLC	18	1	1.000
	MPLC	18	2	
Day 7	CLC	17	2	0.605
	MPLC	19	1	

Table 2.9 Presence or absence of nausea and vomiting (N/V). † - Fisher's exact test.

2.4.6 Pulmonary function tests

Three patients did not attend for follow up at four weeks, two patients refused spirometry at 8 hours and one at 24 hours. One patient refused to undergo further spirometry because she did not enjoy it. The number of patients who completed spirometry at each time point is annotated below the graph of peak expiratory flow rate (Figure 2.8).

Results were converted to a percentage of the pre-operative values so that every patient acted as their own control and the trends could be directly compared. Comparisons of the areas under the curves for Peak Expiratory Flow rate (PEFR), Forced Vital Capacity (FVC) and Forced Expiratory Volume over one second (FEV_1) showed no difference between the two groups (Figure 2.8, Table 2.10).

Function	Time	CLC	MPLC	p value†
PEFR (%day)	**24 hours**	**70.3** (61.6 – 90.4)	**76.5** (64.8 – 86.2)	0.832
	1 week	**576.8** (485.9–669.1)	**595.4** (510.2-622.0)	0.715
	4 weeks	**2585.0** (2211.3-2772.6)	**2553.8** (2277.7-2677.0)	0.629
FVC (%day)	**24 hours**	**78.0** (70.7 – 90.1)	**82.0** (75.3 – 93.1)	0.316
	1 week	**612.0** (567.8-637.6)	**621.4** (564.8-677.2)	0.543
	4 weeks	**2585.7** (2479.3-2763.8)	**2584.4** (2475.2-2682.5)	0.918
FEV_1 (%day)	**24 hours**	**82.3** (71.8 – 94.0)	**84.9** (78.1 – 93.4)	0.601
	1 week	**628.5** (580.9-677.5)	**610.7** (586.2-666.5)	0.887
	4 weeks	**2663.0** (2499.7-2752.4)	**2561.0** (2518.4-2728.6)	0.691

Table 2.10 Comparison of the areas under the curves for pulmonary function in the two groups, expressed as a percentage of preoperative values. The values in the table represent the median areas under the curves (with interquartile ranges) for 24 hours, one week and four weeks. † - Mann-Whitney test

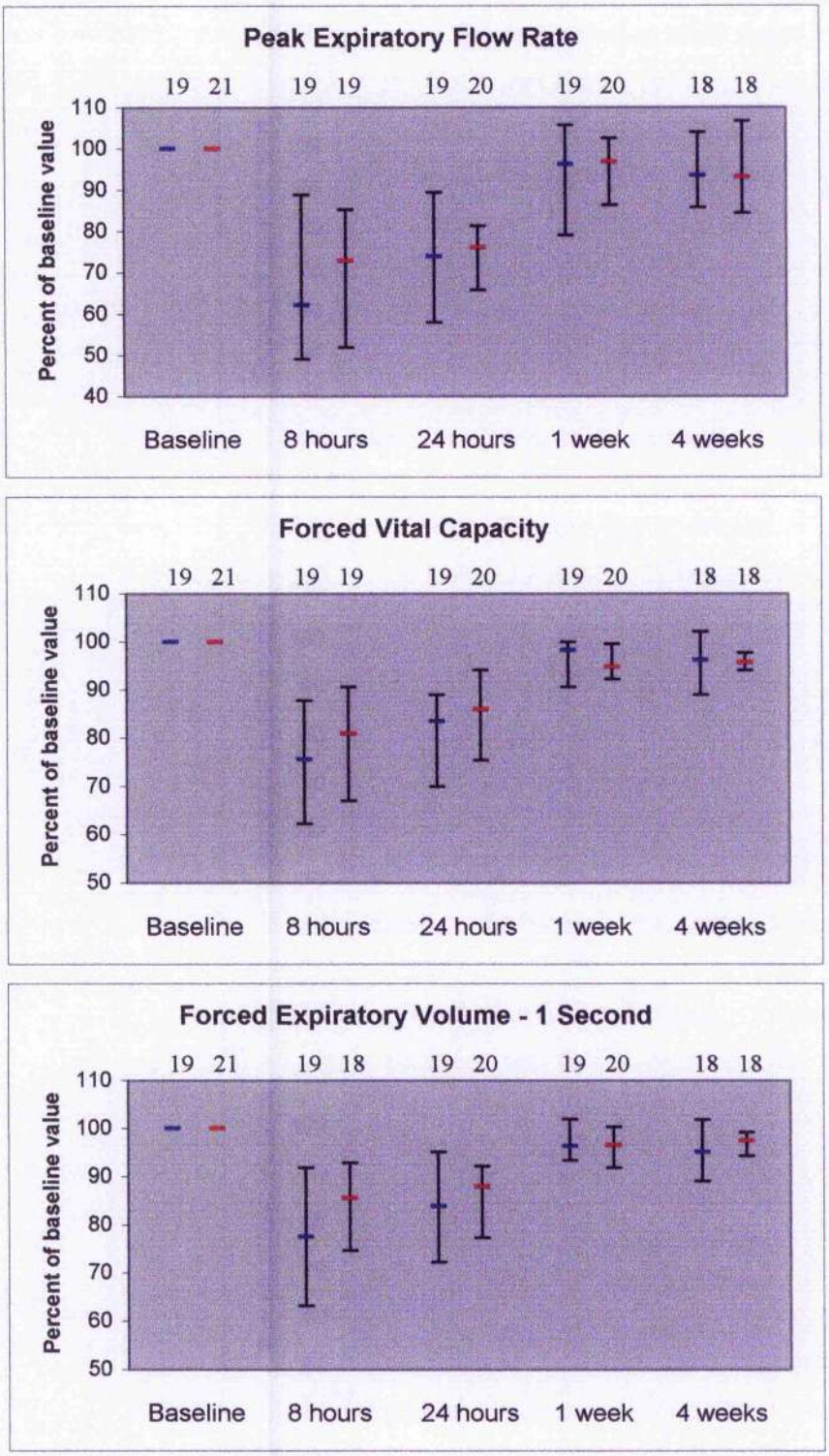


Figure 2.8 Comparison of the trend of change (% of preoperative values) for PEFR, FVC and FEV_1 in CLC (blue) and MPLC (red) groups. Values are medians (interquartile ranges). The number of patients who performed the tests is listed above each time point.

2.4.7 Quality of life

Two patients did not complete a questionnaire (one prior to theatre and the other at the final follow-up visit) and three defaulted from follow-up. One patient ticked two boxes in the activity dimension of the first post-operative questionnaire so this was treated as a missing value in accordance with the recommended instructions for the tool. Review of the contingency tables prepared for analysis with the χ^2 test revealed that for most of the dimensions, more than 20% of the cells would contain an expected frequency count of less than five (cf. appendix 6). The data were therefore re-categorised to the presence or absence of problems and analysed with Fisher's exact test. There were no differences between the groups, either preoperatively or postoperatively for any of the dimensions (Figure 2.9, Table 2.11), weighted indices (Figure 2.10, Table 2.12) or the health thermometer scores (Figure 2.11, Table 2.12).

Comparison of preoperative and postoperative Health Thermometer Scores demonstrated a reduction in the perceived health state by the patients in both groups 8 hours and 24 hours after surgery with a return to baseline values at one week postoperatively. Four weeks after surgery, both groups reported an improvement in their perceived health state from preoperative values (Figure 2.11).

Dimension	Preop	8 hours	24 hours	1 week	4 weeks
Mobility	1.000	1.000	0.333	1.000	0.487
Self-care	1.000	0.755	0.281	1.000	0.487
Activities	1.000	0.716	0.738	0.750	1.000
Pain	0.488	1.000	0.331	1.000	0.299
Anxiety/ Depression	0.290	1.000	0.607	0.233	0.231

Table 2.11 Probability values derived from comparison of the dimension responses for the CLC and MPLC arms of the trail. Values were derived with Fisher's exact test. The responses are portrayed graphically in Figure 3.9.

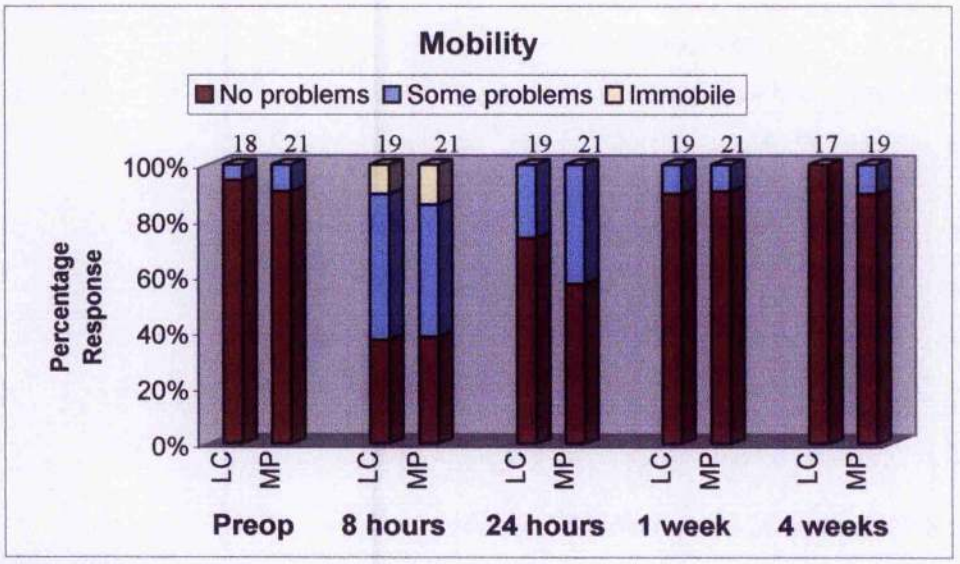


Figure 2.9a

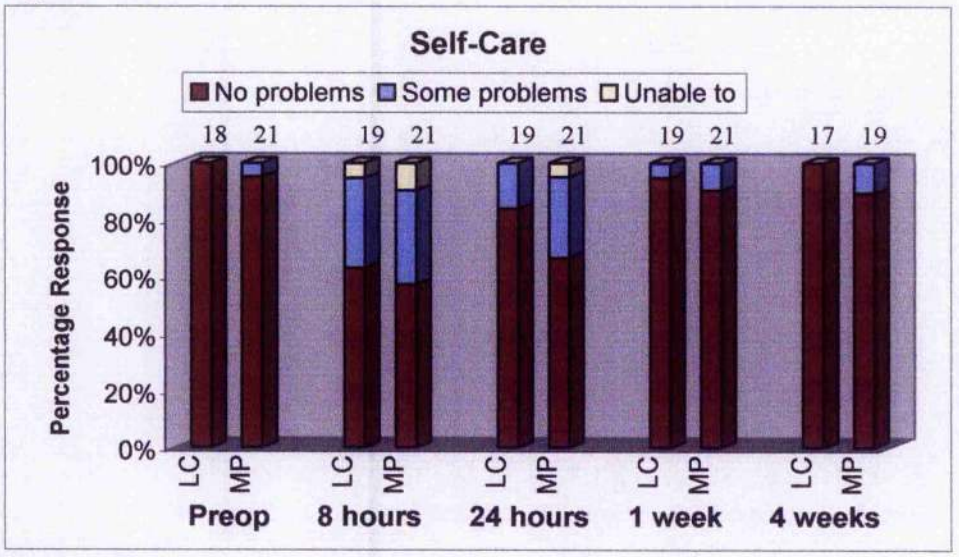


Figure 2.9b

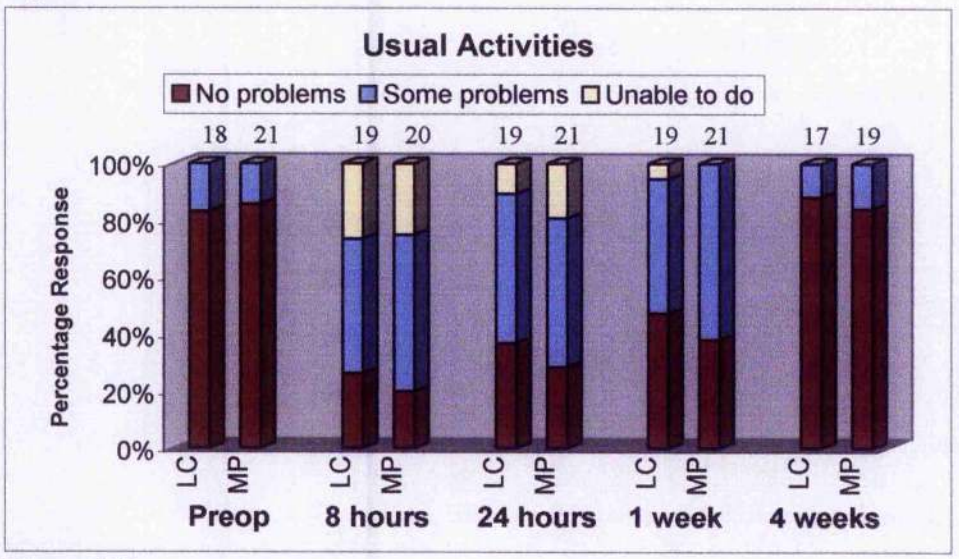


Figure 2.9c

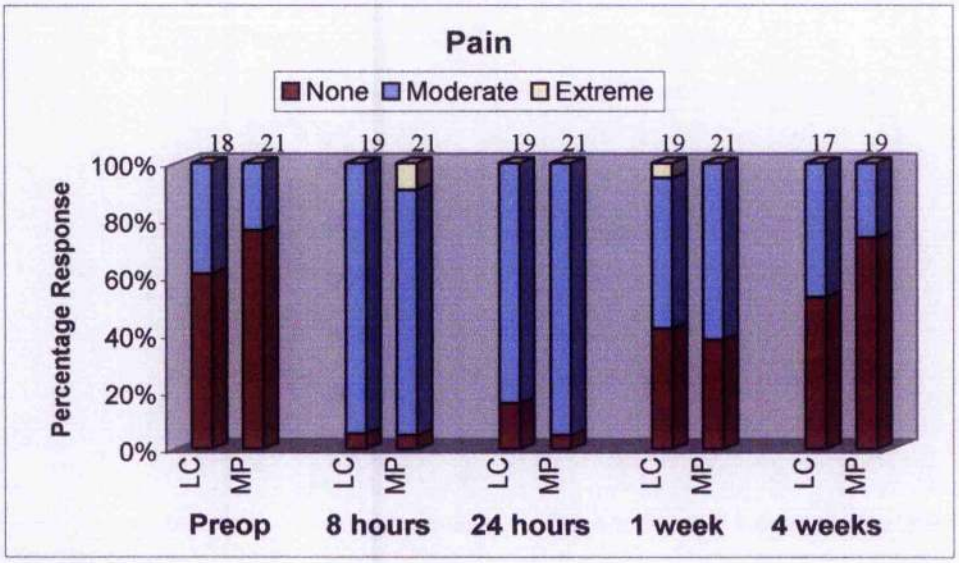


Figure 2.9d

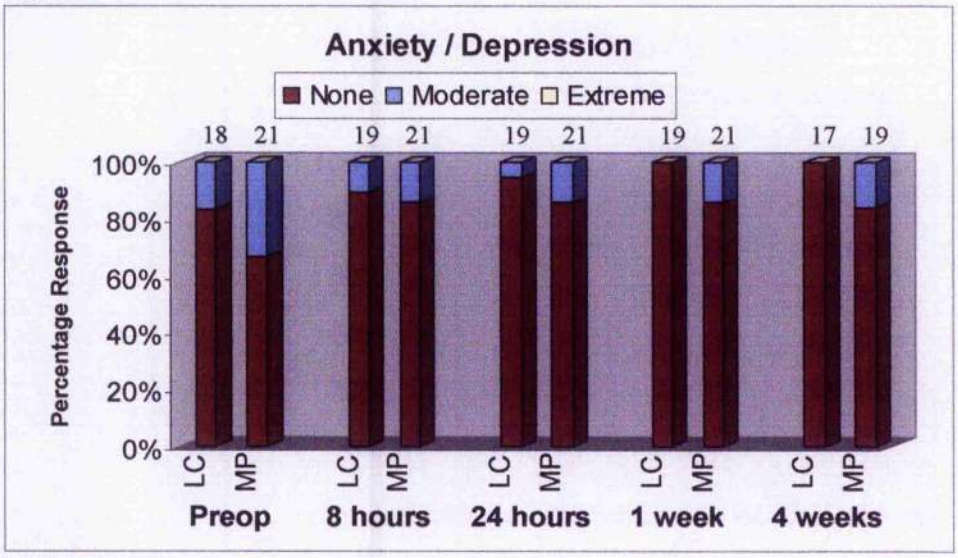


Figure 2.9e

Figure 2.9 (a-e) Graphical representation of the responses to each of the dimensions in the EuroQoL questionnaire. The number of responses for each time point is recorded above each bar. There were no statistically significant differences between the two groups.

LC - conventional laparoscopic cholecystectomy

MP - micropuncture cholecystectomy

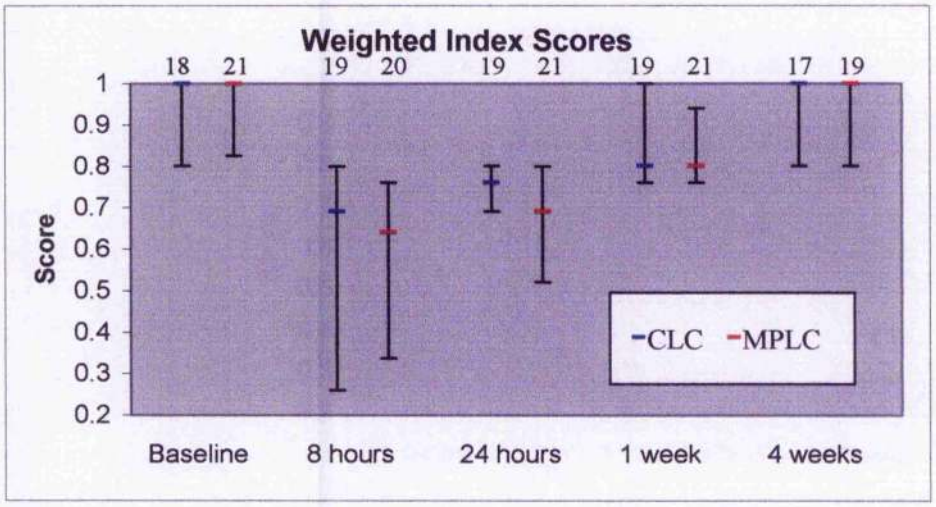


Figure 2.10 Median Weighted Health Index Scores with interquartile ranges.

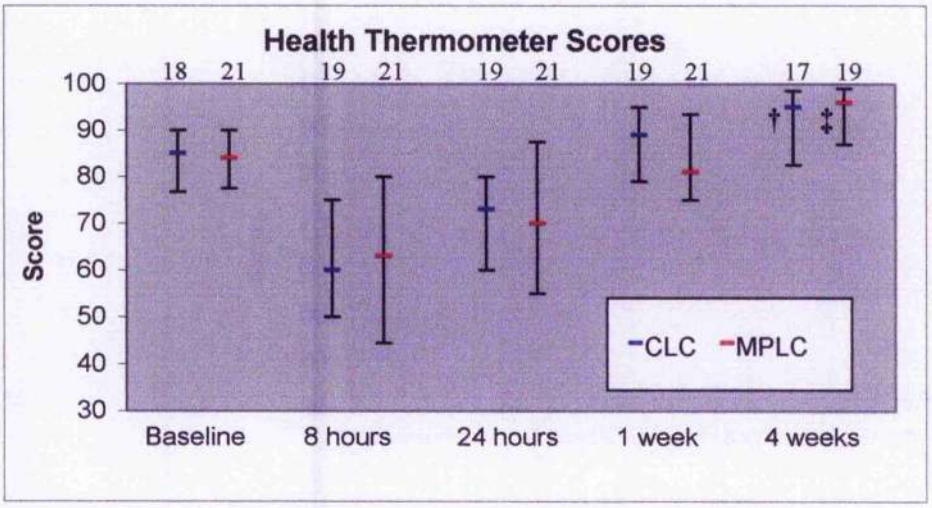


Figure 2.11 Median Health Thermometer Scores with interquartile ranges.

† - p = 0.026, ‡ - p = 0.002, positive ranks from preop values, Wilcoxon signed ranks test.

Score	CLC	MPLC	p value†
Weighted Index	**22.85** (21.18 – 26.15)	**24.10** (21.78 – 25.9)	0.581
Health Thermometer	**2494** (2191 – 2572)	**2367** (2124 – 2615)	0.921

Table 2.12 Median values (interquartile range) of the areas under the curves for the EuroQoL weighted index scores (days.units) and health thermometer scores (days.units) for the two groups of patients. † - Mann-Whitney test.

2.4.8 Stress response

Only one sample was omitted. In preparation for discharge, the nursing staff removed a venflon from a patient (in the CLC group) before the 24-hour sample was collected. Due to a needle phobia, she refused further venesection.

2.4.8.1 Interleukin 6

The highest concentrations of Il-6 were measured eight hours after induction of anaesthesia. Analysis of the areas under the curves demonstrated no significant difference between the groups (Figure 2.12, Table 2.13).

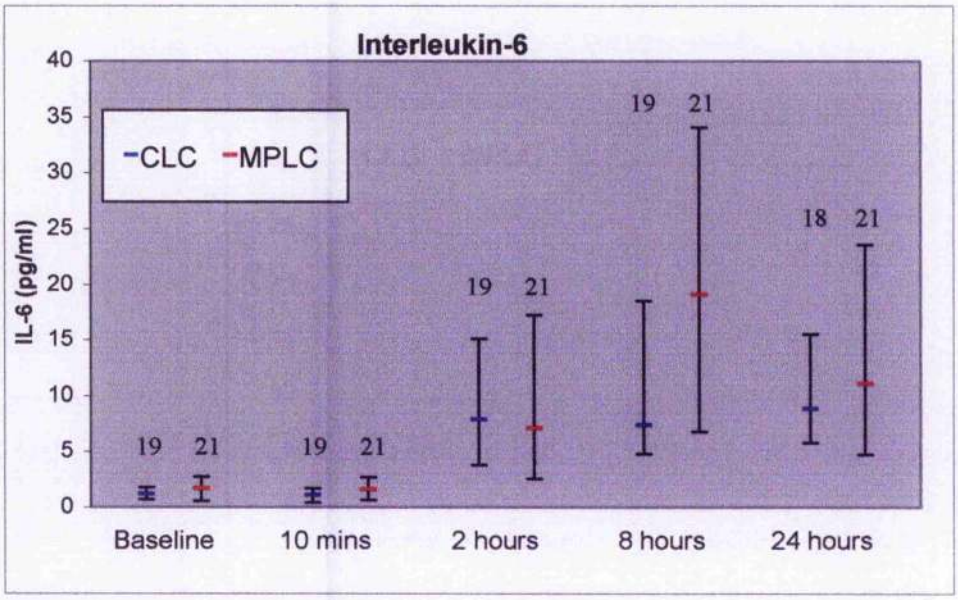


Figure 2.12 Median interleukin-6 concentrations with interquartile ranges. Sample times were relative to induction and the number of samples collected is recorded above each bar.

	CLC	MPLC	P value†
Area under the curve (hr.pg.ml^{-1})	**190.0** (142.7-354.7)	**342.3** (157.6-673.7)	0.185

Table 2.13 Median areas under the curves (interquartile range) for Il-6.

† - Mann-Whitney test.

2.4.8.2 ACTH

ACTH concentrations were highest in the samples taken two hours after induction. Analysis of the areas under the curves demonstrated no significant difference between groups (Figure 2.13, Table 2.14).

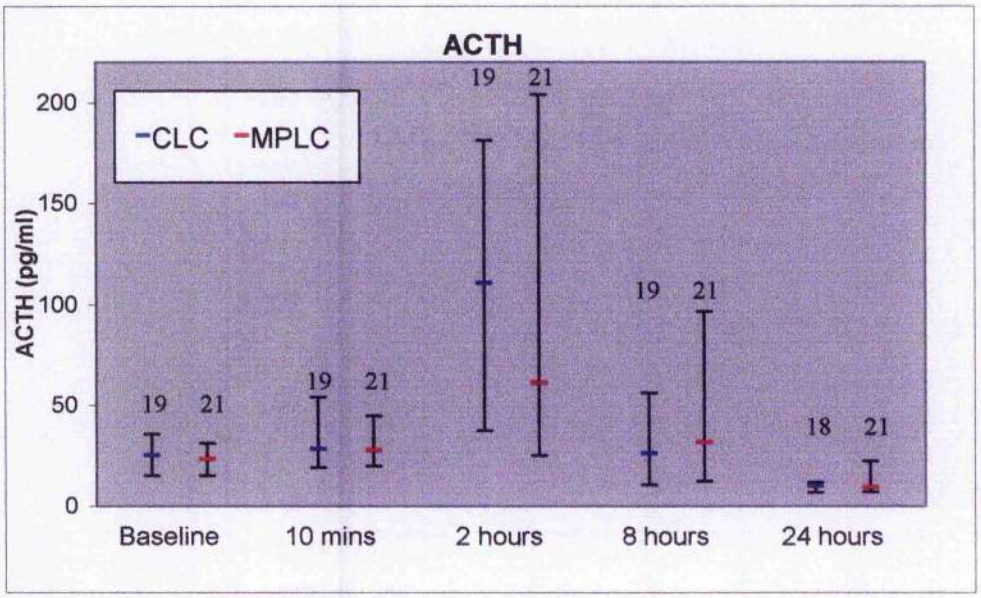


Figure 2.13 Median ACTH concentrations with interquartile ranges. Sample times were relative to induction and the number of samples collected is recorded above each bar.

	CLC	MPLC	p value†
Area under the curve (hr.pg.ml^{-1})	**1335.4** (474.8-2139.6)	**1014.4** (477.4-1872.8)	0.778

Table 2.14 Median areas under the curves (interquartile range) for ACTH.

† - Mann-Whitney test.

2.4.8.3 Vasopressin

Levels were elevated in samples collected from both groups at two hours and eight hours after induction of anaesthesia, although the median values did not exceed 10 pg/ml. Analysis of the areas under the curves demonstrated no significant difference between the groups (Figure 2.14, Table 2.15).

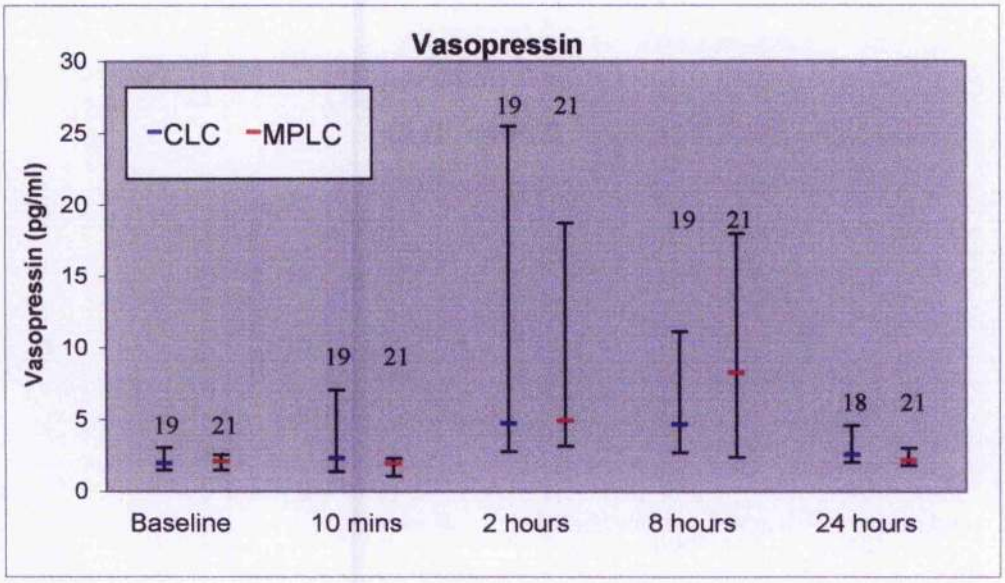


Figure 2.14 Median vasopressin concentrations with interquartile ranges. Sample times were relative to induction and the number of samples collected is recorded above each bar.

	CLC	MPLC	p value†
Area under the curve (hr.pg.ml^{-1})	**187.6** (89.4 – 229.2)	**145.8** (61.6 – 303.0)	0.800

Table 2.15 Median areas under the curves (interquartile range) for vasopressin.

† - Mann-Whitney test.

2.4.9 Postoperative function

One patient in the CLC group and four in the MPLC group felt unable to get out of bed eight hours after induction of anaesthesia (p=0.345 Fisher's exact test). There were no statistically significant differences between the MPLC and CLC groups for any of the baseline times. Analysis of the areas under the curves for each exercise demonstrated no statistically significant difference between the groups (Figure 2.15 to 2.19, Tables 2.16 to 2.20).

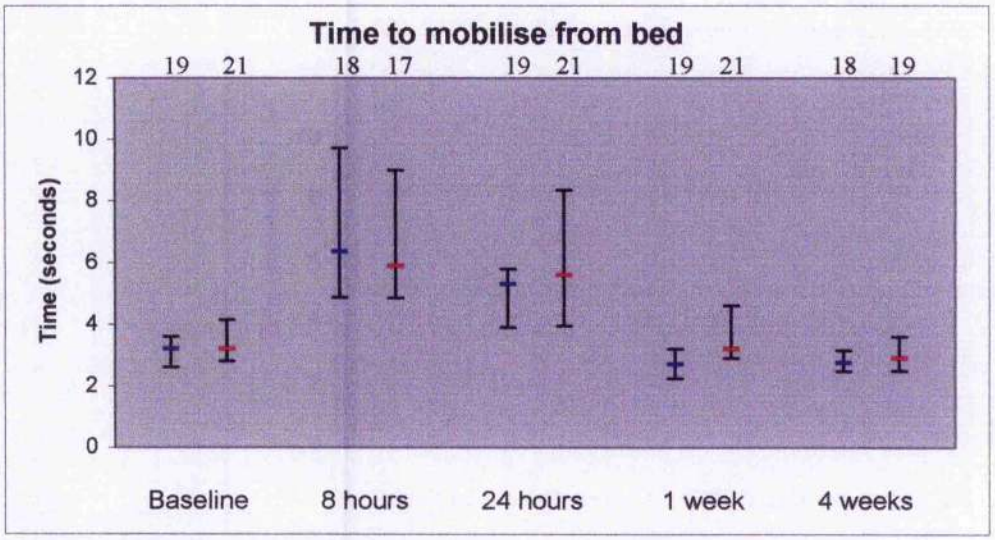


Figure 2.15 Median times (interquartile range) to rise from bed.

AUC (days.seconds)	CLC	MPLC	p value†
Rise from bed	**90.8** (80.6 – 100.9)	**90.4** (85.2 - 121.2)	0.806

Table 2.16 Median areas under the curves (interquartile range) for time to rise from bed.

The number of completed tests is stated above each time point. †-Mann-Whitney test.

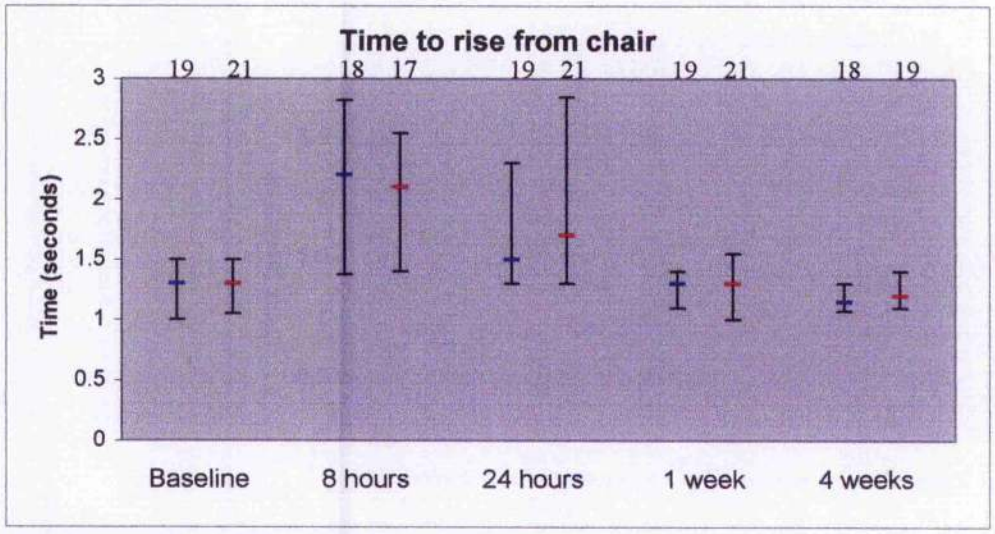


Figure 2.16 Median times (interquartile range) to rise from chair.

AUC (days.seconds)	CLC	MPLC	p value†
Rise from chair	**37.5** (31.4 – 40.4)	**35.7** (29.8 – 47.2)	0.748

Table 2.17 Median areas under the curves (interquartile range) for time to rise from chair.

The number of completed tests is stated above each time point. † - Mann-Whitney test.

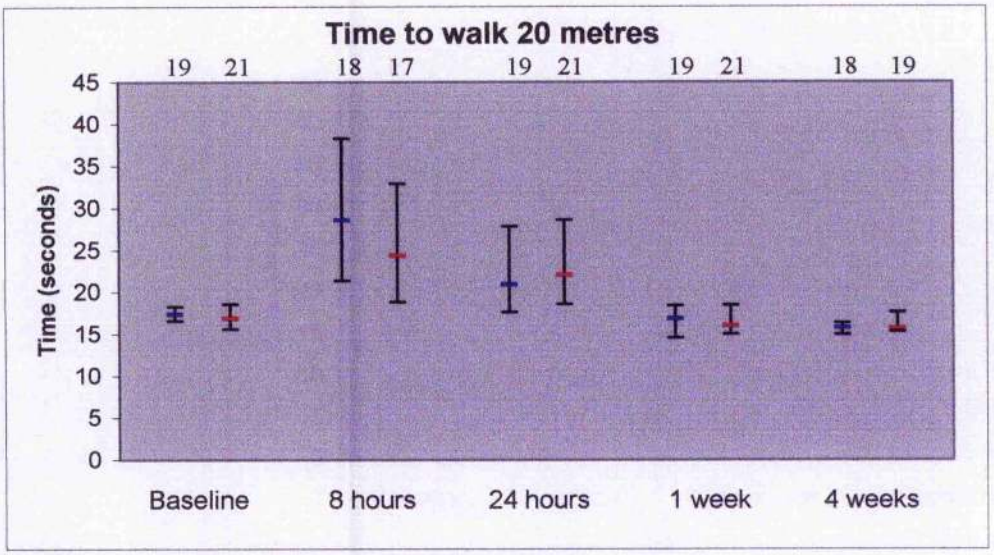


Figure 2.17 Median times (interquartile range) to walk 20 metres.

AUC (days.seconds)	CLC	MPLC	p value†
Walk 20 metres	**479.0** (447.7 – 519.6)	**464.7** (442.2 – 514.8)	0.610

Table 2.18 Median areas under the curves (interquartile range) for time to walk 20 metres. The number of completed tests is stated above each time point. † - Mann-Whitney test.

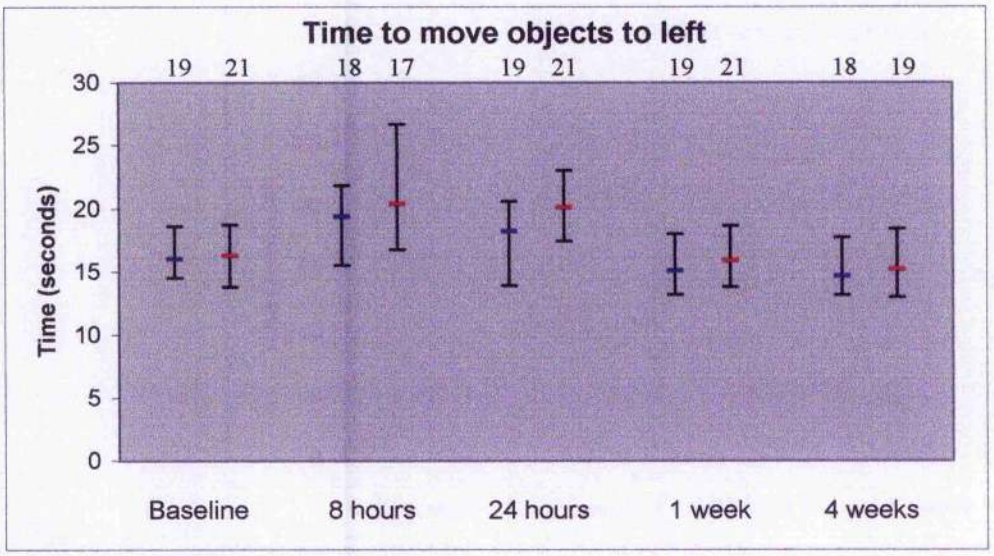


Figure 2.18 Median times (interquartile range) to move objects to left.

AUC (days.seconds)	CLC	MPLC	p value†
Move objects to left	**427.5** (377.3 – 492.1)	**433.8** (396.7 – 522.5)	0.777

Table 2.19 Median areas under the curves (interquartile range) for moving objects left. The number of completed tests is stated above each time point. † - Mann-Whitney test.

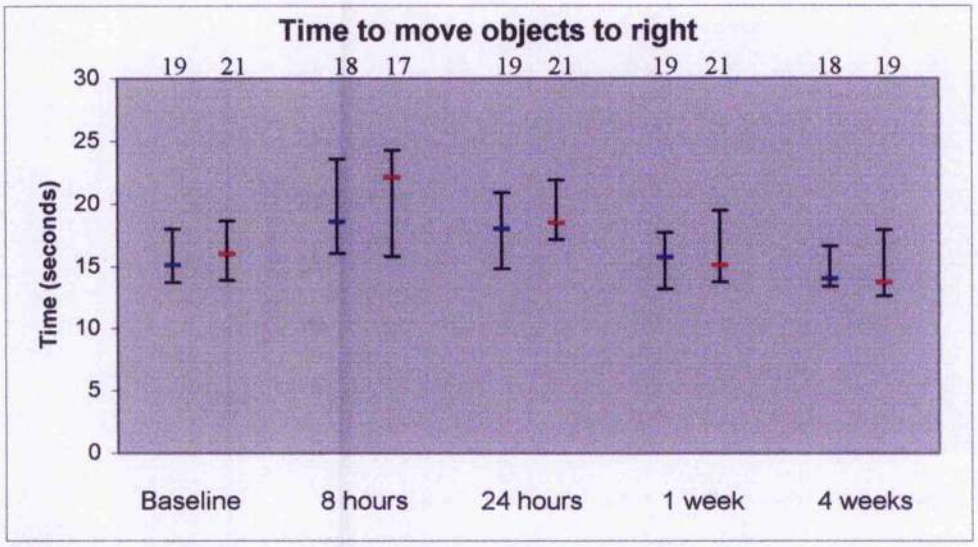


Figure 2.19 Median times (interquartile range) to move objects to right.

AUC (days.seconds)	CLC	MPLC	p value†
Move objects to right	**423.9** (370.8 – 482.8)	**416.1** (367.8 – 516.8)	0.955

Table 2.20 Median areas under the curves (interquartile range) for moving objects right. The number of completed tests is stated above each time point. † - Mann-Whitney test.

2.5 Discussion

This study demonstrates that MPLC is feasible for the majority of elective cholecystectomies. MPLC was completed in 90% of patients randomised to the procedure and it was not necessary to convert to CLC or open cholecystectomy in any patient, although two cases did require conversion of one 3.3mm cannula to a 5mm cannula. If a 3.3mm argon diathermy probe had been available, this could have been avoided. This figure compares favourably with the five randomised trials that have been published in the literature since the inception of this study, in which the conversion rates to CLC or open cholecystectomy range from 3% to 38%(Bisgaard *et al,* 2000; Bisgaard *et al*, 2002; Cheah *et al,* 2001; Look *et al,* 2001; Schwenk *et al,* 2000).

In one randomised study, the duration of the operation was a median of 30 minutes longer when performed with 2mm instruments and was associated with a 38% conversion rate to

CLC (Bisgaard *et al,* 2000). In the present study and the other four trials, there were no significant increases in the overall times for micropuncture cholecystectomy and conversion rates were lower (Bisgaard *et al,* 2002; Cheah *et al,* 2001; Look *et al,* 2001; Schwenk *et al,* 2000). The common factor among these latter trials was the use of at least one 3mm or 5mm cannula for the grasping instruments. It is probable that the use of more rigid instruments is an important factor in ensuring adequate traction and manipulation of the tissue during dissection.

The anticipated reduction in analgesia of up to 70%, suggested by our pilot series and an earlier cohort study (Davides *et al,* 1999; Gagner & Garcia-Ruiz, 1998) was not apparent in this study. While median pain scores were consistently lower at all time points in the MPLC group there was no statistically significant difference between the groups. However, parenteral analgesic consumption was significantly less in the MPLC group.

Four of the five published randomised studies have detected small, statistically significant differences in pain. The first trial in the literature that used 2mm instruments, ended prematurely due to a conversion rate of 38% to CLC. However, the authors noted a reduction in pain among the eight patients who had a completed "micro-LC" (Bisgaard *et al,* 2000). Another study that compared a technique of cholecystectomy that used a combination of two 2mm and two 5mm cannulae, with CLC, reported lower VAPS scores while coughing, on the evening of surgery that persisted until the third postoperative day (Schwenk *et al,* 2000). In the largest study so far, with 75 patients (using a 10mm, one 3mm and two 2mm cannulae), there was a statistically significant reduction in pain scores at 24 hours (2.2 versus 3.6; $p<0.003$) and a lower consumption of parenteral analgesia (7 versus 12 injections; $p=0.05$) in the "needlescopic" group when compared with the CLC group (Cheah *et al,* 2001). Bisgaard and colleagues, undaunted by previous difficulties with 2mm instruments, went on to compare 3.5mm instruments with CLC in a randomised trial that contained 60 patients. Patients in the microlaparoscopic group recorded significantly lower total incisional

pain scores on a visual analogue scale for the first 24 hours than patients in the CLC arm of the trial (39 vs 66; $p<0.05$) and lower incisional pain scores over the first postoperative week ($p<0.01$). However, there were no statistically significant differences between the two groups for overall pain scores ($p=0.42$). Analgesic consumption was not recorded. The clinical significance of such small differences in pain scores and/or analgesic consumption in these studies is uncertain.

The breakdown of the operative times was used to objectively compare the difficulty of cholecystectomy using micropuncture and conventional instrumentation. The rationale behind this approach was that any increase in the difficulty of the procedure caused by the smaller instruments would be manifest by an increase in operative times. There were no statistically significant increases in time taken to perform the dissection of Calot's triangle, remove the gallbladder from the liver, perform cholangiography or manipulate the gallbladder into the retrieval bag.

The finding of an increase in time taken to insert the cannula with the MPLC technique is probably an artefact. A similar analysis of operative times in a recent, large cohort study found that the smaller cannulae were inserted more quickly than historical controls from an earlier, multi-centre study (Traverso *et al,* 1997; Unger *et al,* 2000). The data from the original series also demonstrated that operative times could be affected by the familiarity of the theatre staff with the procedure (Traverso *et al,* 1997).

However, the extra two to three minutes required with MPLC to apply clips the cystic duct after cholangiography is readily explained by the need to change to the 3mm laparoscope and reorientate the view of the operative field. This difference is of minor significance though, because the overall operative times did not differ significantly between the groups in this study.

Pulmonary function was remarkably similar in the two groups and these results are comparable to those of two recently published trials of microlaparoscopic cholecystectomy (Bisgaard *et al*, 2002; Schwenk *et al*, 2000). This suggests that the reduction in size of the incisions is too small to have much impact on postoperative pulmonary function.

The stress response to cholecystectomy with small calibre instruments has not been previously reported. The profile of the interleukin-6, ACTH and vasopressin responses was similar in both groups, suggesting that like pulmonary function, the reduction in the size of the incisions had little impact on the response.

There are also no reports on the influence of smaller instruments on quality of life scores. Similar results were obtained in both groups of patients for overall scores, health thermometer ratings and each of the individual dimensions. Self-assessed overall health ratings at four weeks postoperatively were better than those taken preoperatively.

There were some difficulties that were encountered while setting up and running this study.

While the study size was estimated at the outset with a biomedical statistician, the calculation assumed normal variance and was based on estimated pain scores among the micropuncture patients for the first 24 hours (cf. section 2.3.11.1). Re-analysis of the scores obtained for the first 24 hours, has suggested that this study was underpowered and that a 25% reduction in pain was over optimistic. A sample size of 82 in each group would have had 80% power to detect a 20% reduction in the mean area under the curves for pain scores over the initial 24 hours.

Due to the limited number of personnel within the unit and the timings of the operating lists, it was not possible to blind the principle observer. Where possible, data that could be subject to observer bias were avoided. The circulating nurse recorded operative times. Blood

samples were collected at preset times and the patient recorded pain and quality of life scores without assistance. Analgesia was requested by the patient and was administered and recorded by nursing staff who were blinded to the procedure. Pulmonary function tests were collected on a portable, computerised device that independently monitored the quality and consistency of the tests.

Although the study was randomised, there were some factors that interfered with consecutive recruitment of patients. Firstly, 10 patients refused to participate in a trial. In addition, after the study commenced, a new anaesthetist who did not agree with the concept of standardisation of anaesthesia, was assigned to one of the operating lists. This meant that it was not possible to recruit nine further patients. However, as all 40 patients who were enrolled into the study received a standardised anaesthetic and similar perioperative care, this ensured that the two groups were tightly controlled and that opportunities for extraneous factors other than the size of the instruments to impact on the outcome measures of the study were minimal. In this respect, refusal to recruit these nine patients and tolerate any deviation from the anaesthetic protocol was a strength of the study.

Four different surgeons participated in this trial (three consultants and one trainee). All were competent at both techniques prior to the study and stratification was employed so that procedures undertaken by a consultant or trainee had an equal chance of allocation to either arm of the trial. In this way, experience was equally apportioned between the two groups and the results were representative of clinical practice within the department.

As no suitable functional tests for recovery from cholecystectomy were found despite extensive literature searches, the concept was adapted from tests devised for patients undergoing inguinal hernia repair. Advice was sought from a Professor in Sports Science and simple tasks that are necessary to allow independent function were selected. All patients must be able to get out of a bed or chair, walk to the toilet or move small objects in order to

function effectively outside the hospital. Failure to perform these tasks would deem a patient unsuitable for discharge. However, the functional tests were not previously validated and the only control built into the measurements was the preoperative baseline assessment. Most measurements returned to normal by the end of the first postoperative week, but at the final visit four weeks after surgery, the times were faster than the baseline values. This would indicate that the tests were subject to an element of increased familiarity due to repetition and not suitable for sequential assessment of postoperative functional recovery. As a result, no conclusions concerning the procedures were derived from the data.

While this study suggests that elective cholecystectomy using 3.3mm instruments is feasible in a westernised population and may be associated with a reduction in the consumption of parenteral analgesia, it has not demonstrated any obvious, major clinical benefits for patients who stay in hospital overnight.

CHAPTER 3.

THE EFFECT OF TROCAR TIP PROFILE ON ABDOMINAL WALL PENETRATION

3.1 Introduction

There are several schools of thought concerning the advantages and disadvantages of trocar tip profiles (cf. section 1.8). 'Pyramidal-shaped' cutting trocars incise the tissue as it is traversed by the trocar and create a defect of the same diameter. The sharp profile ensures a low entry force against tissue resistance but the cannula is easily removed, sometimes accidentally during an operation. Trocars with a conical, non-cutting profile stretch the tissues, thereby creating a smaller wound with a tighter seal around the cannula. They are associated with a reduction in bleeding from the abdominal wall but require a higher force of insertion (Bhoyrul *et al*, 1996; Böhm *et al*, 1998).

It has been suggested that increased force during the insertion process will result in higher rates of visceral injury (Corson *et al*, 1989; Nezhat *et al*, 1991). Presumed mechanisms include deeper inward deflection of the abdominal wall and the "overshoot" phenomenon (cf. section 1.9.2).

3.2 Hypothesis and Aims

3.2.1 Hypothesis

The tip of a conical trocar passes more deeply into the abdominal cavity than the tip of a pyramidal trocar during the process of cannula placement.

3.2.2 Aim

The aim of the study is to compare the distance of travel into the abdominal cavity of the tip of pyramidal, sharp conical and blunt conical trocars when the tip of the trocar initially penetrates the peritoneum, the leading edge of the cannula is first observed to breach the peritoneum and the entire cannula has penetrated the peritoneum.

3.3 Materials and methods

3.3.1 Trocars and cannulae

Trocars with pyramidal, sharp conical and blunt conical profiles were selected from the 10.5mm "YelloPort"™ range (Surgical Innovations, Leeds, West Yorkshire, UK) (Figure 3.1). Only one range was used to ensure that the sole variable was the design of the tip. The outer diameter and surface profile of the cannula, factors that could influence friction between the tissue and the cannula, were therefore standardised.

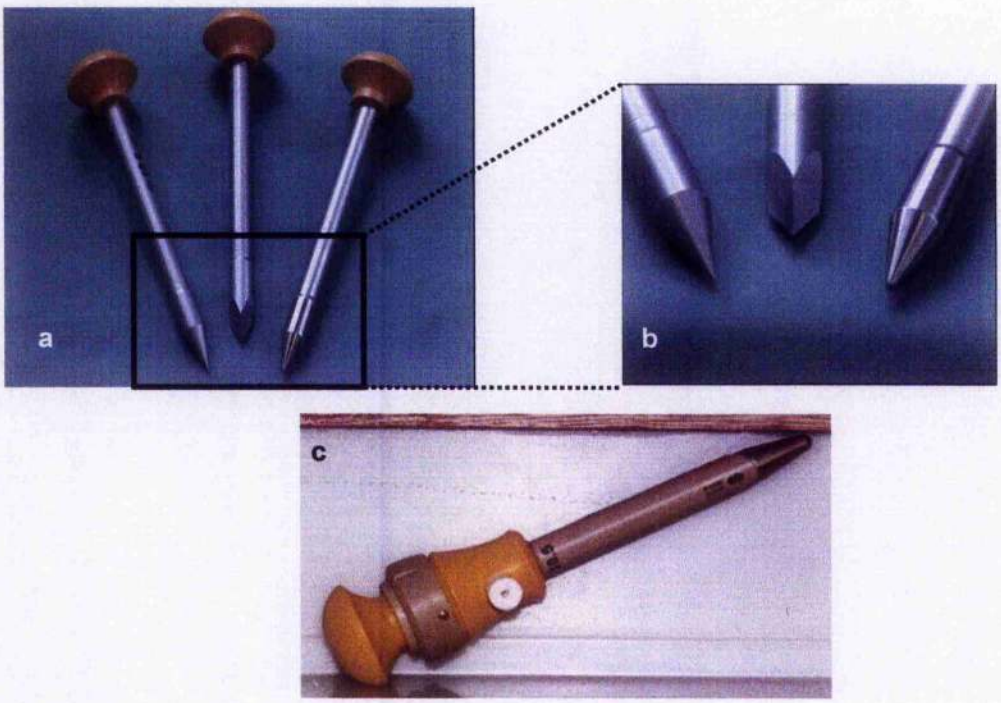


Figure 3.1a The profiles of the trocar tips from left to right are sharp conical, pyramidal and blunt conical. They are all part of the standard "YelloPort" ™ range.

Figure 3.1b Inset. Enlarged view of the profile of the trocar tips.

Figure 3.1c The "YelloPort" ™ trocar and cannula assembly. In this example, a Hasson trocar has been used.

3.3.2 Development of the abdominal wall model and insertion technique

Fresh sections of abdominal wall from pigs, obtained from an abattoir, were stretched across

and clamped to the metal bars of a jig (prepared from an obsolete laparoscopic trainer), which allowed the skin and peritoneal surfaces to be visualised (Figure 3.2). A ruler was attached to the posterior wall of the device to facilitate the measurement of abdominal wall deflection during insertion of the trocars and cannulae. Each insertion was recorded on video using a camera (Handycam PRO Hi8, Sony, Japan) that was placed level with the peritoneal surface at a distance of 3 metres on a tripod stand. All levels were confirmed to be horizontal with a spirit level.

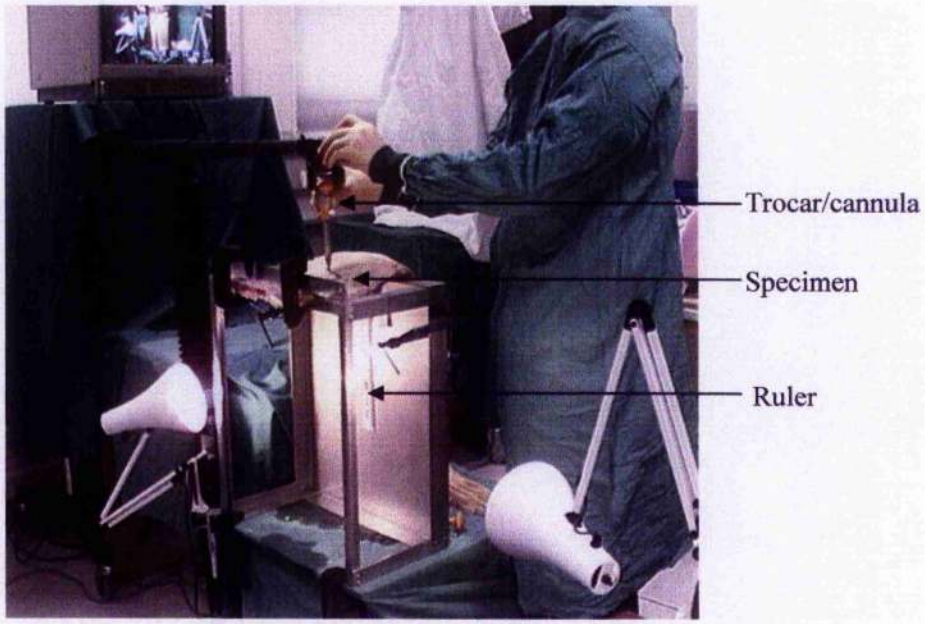


Figure 3.2 Insertion of a trocar and cannula with the "Laparolift"™ arm. The abdominal wall specimen was clamped firmly to the modified laparoscopic trainer. The ruler was attached to the posterior wall of the apparatus.

Transverse incisions of length 20mm were made in the skin and adipose tissue to the level of the muscle, so that the cannula would not snag or grip on the wound edge. The trocars, with a cannula placed over them, were pushed through the fascial and muscle layers until the peritoneum was breached. The three types of trocar were inserted in rotation, ensuring that the sites were evenly spread over the specimen to minimise any effect of inherent variations in the physical structure of the abdominal wall and any effect that previous trocar insertions

would have had on the tension of the specimen.

This model evolved from a number of different attempts to create a reproducible simulation of the abdominal wall that would facilitate measurement of the relative depth of the tips of the trocars during insertion. It became evident early in the process that the concept of a sealed unit, insufflated with CO_2 and covered by a "skin" to represent the abdominal wall through which the trocars would be inserted, was not practical for several reasons.

In order to guarantee consistency in the thickness, resistance and elasticity of the "abdominal wall" through which the trocar and cannula systems would be inserted, two types of synthetic material were initially tested. The first was black neoprene rubber sheeting as used on some of the laparoscopic training boxes within the department (Diver's Warehouse, Bradford, West Yorkshire, UK). Subsequently, "Training Box Skin," a laminate of high density, low density and high density foam with a base layer of thin latex rubber, designed to simulate the skin, subcutaneous fascia, deep fascia and peritoneum for surgical training courses, was assessed (Limbs & Things Ltd, Bristol, Somerset, UK). These materials had the advantage that they could be clamped to a laparoscopic trainer to maintain an airtight seal. However, they could not be used for multiple insertions because of gas leak from the "wound" inflicted by the first trocar. Moreover, repair of the puncture site with patches to the inner aspect of a sheet risked interfering with the resistance, tension and elasticity of the model to subsequent trocar insertions. Replacement with a new sheet of material was a possible, albeit costly option but there was no simple method to measure and standardise the tension across the sheet with each change. It was also found that that there was a disproportionately high degree of friction between the material and the cannula-sleeve that increased the resistance to the leading edge of the cannula as it followed the tip of the trocar through the specimen. This could have affected the measurements of depth of the trocar tip.

Porcine abdominal wall, obtained from the abattoir was therefore tested as it had been used

in a laboratory by several authors as an alternative to human tissue because of a similar, although thinner, anatomical structure (Bhoyrul *et al*, 1996; Böhm *et al*, 1998; Tarnay *et al*, 1999). While no direct comparisons between the insertion characteristics of trocars in humans and swine exist in the literature, two separate studies have recorded a mean pressure of 7.14 lbs to place a reusable, pyramidal trocar in humans (Corson *et al*, 1989) and a mean pressure of 9.01 lbs to place a similar, disposable pyramidal trocar in swine (Tarnay *et* al, 1999).

It was not possible to place a specimen of porcine abdominal wall across a jig or a laparoscopic trainer and produce a seal for insufflation with carbon dioxide. It was therefore decided to produce tension in the specimen by clamping it tightly across the open-frame trainer with G-clamps and a metal bar. As there was no pneumoperitoneum to escape after insertion of the first trocar, multiple trocar insertions could be performed on each abdominal wall specimen, so that every insertion within the experiment would be standardised as it had been performed on tissue with similar characteristics and held under similar tension. This method also had the advantage of displaying the undersurface of the specimen so that measurements of the depth of penetration of the trocar tip could be made with a video camera as the trocar / cannula assembly breached the peritoneum. This was not possible with a closed, insufflated system without the addition of a small Perspex window through which there would have been limited vision.

Initially, as a pilot study, trocars were inserted by hand but the experiment was subsequently modified to incorporate an automated insertion device. The "Laparolift"™ (Origin Medsystems Inc, California, USA) is normally employed for gasless laparoscopy and consists of a "T" arm which is raised and lowered by a motor at a speed of 1.2cm/s and generates a force of up to 18kg (Laparolift manual, Origin Medsystems Inc, California, USA). A miniature vice was attached to the undersurface of the arm and was used to grasp

the trocar handle. This standardised the insertion technique and force and removed the human element with potential for inconsistency and bias (Figure 3.2).

3.3.3 End-points

3.3.3.1 Definition of the end-points

The distance of travel of the tip of the trocars below the starting level of the peritoneal surface (baseline) of the abdominal wall was derived using superimposed lines on the video monitor. The travel of the tip was measured at:-

a) Stage 1 - when the tip initially penetrated the peritoneum (Figure 3.3a),

b) Stage 2 - when the leading edge of the cannula was first observed to breach the peritoneum (the tip of the "YelloPort"™ cannula is bevelled) (Figure 3.3b),

c) Stage 3 - when the entire cannula penetrated the peritoneum (Figure 3.3c).

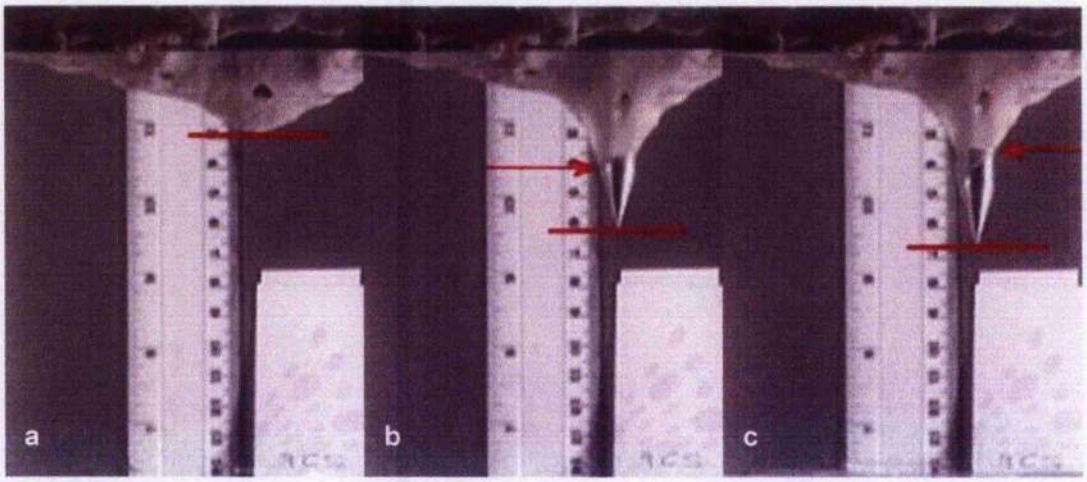


Figure 3.3(a-c) Stages of the insertion process at which the travel of the tip of the trocar was recorded. Each stage is described in section 3.3.3.1. The horizontal line represents the measurement that was recorded for each stage. The arrows point to (b) the leading edge of the cannula and (c) the point at which the entire cannula breached the peritoneum. In this example, the cannula had a sharp, conical tip.

3.3.3.2 Measurement and calculation of the end-points

The measurement taken from the monitor screen was scaled due to the effect of perspective. To rectify this, a simple mathematical equation was devised. The distance (f) between the camera and jig, and the visualised deflection (d) created a right-angled triangle with the hypotenuse running between the lens and the observed measurement on the posterior wall of the jig. Tan α is equal to f / d, and is common to the right-angled triangle created by the true deflection (D) and the distance from the lens to the trocar (f – p), where p is the distance from the trocar and the posterior wall of the jig (Figure 3.4). This created the formula:-

D (millimetres) = d (3000 – p) / 3000

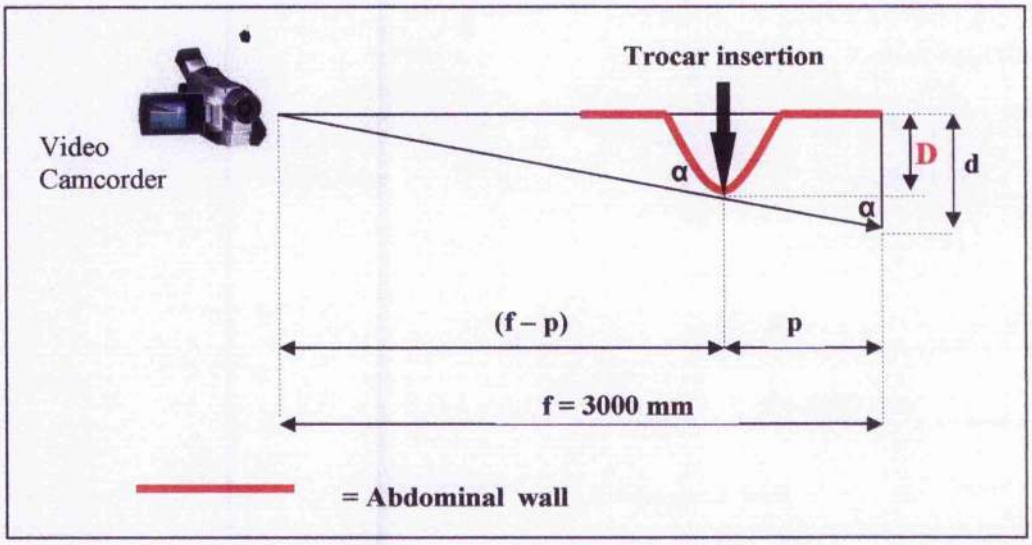


Figure 3.4 Measurements required to correct the error incurred by perspective. The values were used to calculate the true penetration of the tip of the trocar below the baseline level of the peritoneum (**D**).

3.3.4 Statistics

3.3.4.1 Selection of sample size

No literature or prior experience was available to assist in the calculation of a suitable sample size. It was therefore elected to introduce each trocar ten times during this pilot study.

3.3.4.2 Method of analysis

Statistical analysis was performed using the Mann-Whitney test for inter-group comparisons. All data were analysed on SPSS (Statistical Package for Social Sciences v 9.0, SSPS UK Ltd, Woking, Surrey, UK). Results were considered significant at the 5% level (i.e. $p < 0.05$).

3.4 Results

3.4.1 Experiment 1 – Manual insertion of trocars

All trocar insertions were performed on the one specimen of abdominal wall. The depth of penetration of the tip of the pyramidal trocar was significantly less at all three stages than that recorded for the sharp and blunt conical trocars. There were no statistically significant differences in the depth of penetration between the sharp and blunt conical groups. Using the Mann-Whitney test, p-values for comparisons of the distance of the trocars from the posterior wall of the apparatus were not statistically significant. This indicates that the trocars were inserted in similar positions on the abdominal wall model. (Tables 3.1 and 3.2, Figures 3.5 to 3.8).

Trocar tip	Stage 1 (mm)	Stage 2 (mm)	Stage 3 (mm)	Distance from posterior wall (mm)
Pyramidal	**21.0** (15.9 - 25.5)	**40.6** (38.7 – 45.6)	**55.2** (50.7 – 57.6)	**142.5** (116.2 –168.8)
Conical Sharp	**37.0** (31.2 – 40.6)	**60.6** (57.9 – 65.8)	**71.0** (65.2 – 76.7)	**142.5** (116.2-153.8)
Conical Blunt	**40.6** (38.0 – 51.6)	**58.8** (55.2 – 68.6)	**68.8** (66.1 – 76.6)	**127.5** (116.2-153.8)

Table 3.1 Experiment 1 (manual insertion). The median and interquartile values of trocar tip depth from baseline levels of the peritoneum at each stage of insertion (for the definition of the stages, see section 3.3.3.1). The column on the right lists the median distances of the trocars from the posterior wall of the apparatus.

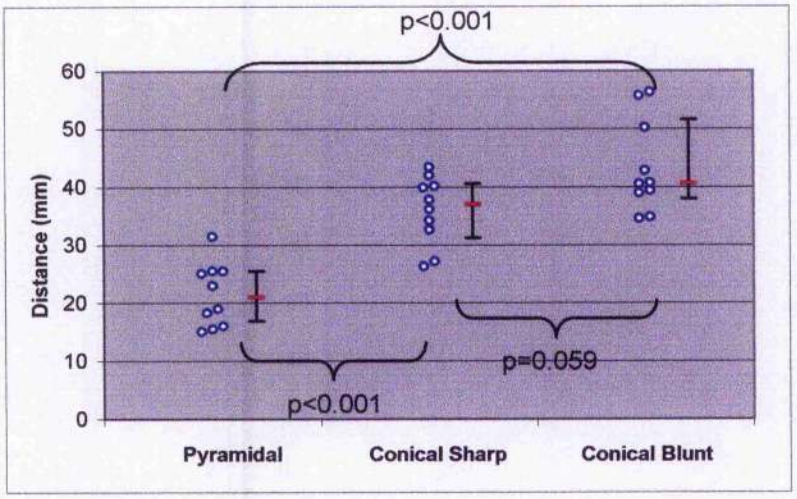


Figure 3.5 Scatterplot of the depth of the tip of each type of trocar at the point of initial penetration of the peritoneum (manual insertion, stage 1). The median and interquartile ranges are displayed to the right. Inter-group comparisons were made with the Mann-Whitney test.

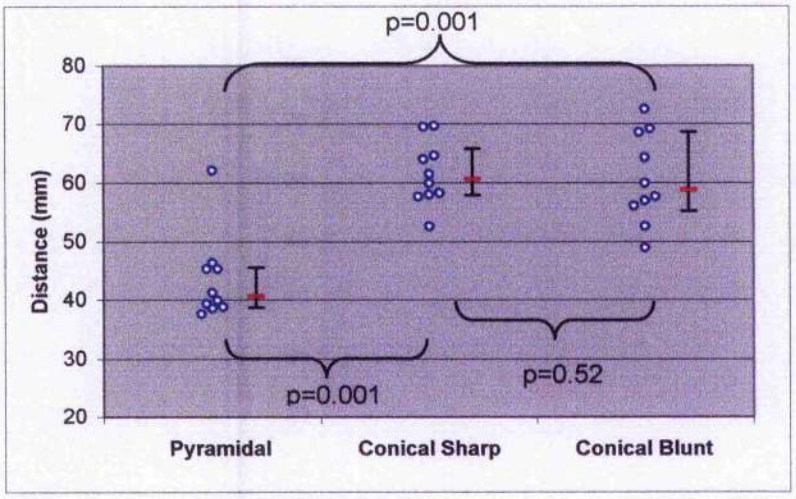


Figure 3.6 The depth of the tip of each type of trocar, when the leading edge of the cannula initially appeared through the peritoneum (manual insertion, stage 2). The median and interquartile ranges are displayed to the right. Inter-group comparisons were made with the Mann-Whitney test.

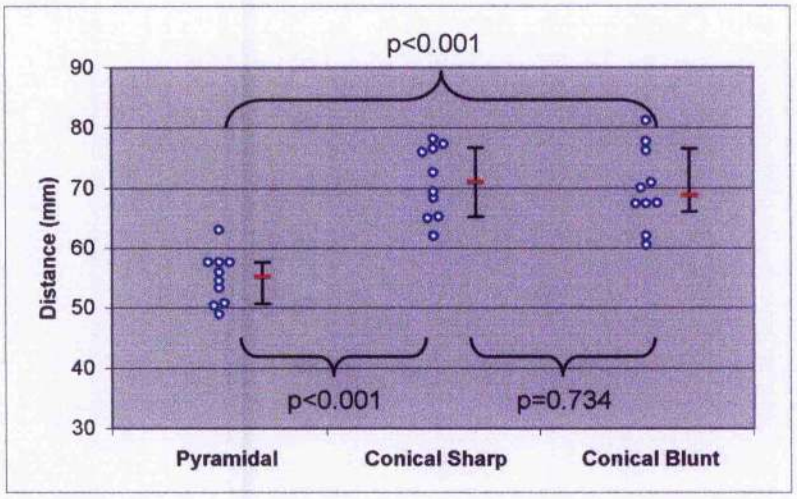


Figure 3.7 The depth of the tip of each type of trocar, when the cannula had completely penetrated the peritoneum (manual insertion, stage 3). The median and interquartile ranges are displayed to the right. Inter-group comparisons were made with the Mann-Whitney test.

Trocar tip	Stage 1	Stage 2	Stage 3	Distance from posterior wall
Pyramidal vs Conical (sharp)	**<0.001**	**0.001**	**<0.001**	0.789
Pyramidal vs Conical (blunt)	**<0.001**	**0.001**	**<0.001**	0.618
Conical (sharp) vs Conical (blunt)	0.059	0.52	0.734	0.73

Table 3.2 Experiment 1 (manual insertion). Probability values, derived with the Mann-Whitney test, for comparisons of the depth of the trocar tip at each stage of insertion and the distance of the trocars from the reference point on the posterior wall of the apparatus. Statistically significant results are highlighted in bold text.

3.4.2 Experiment 2 – Insertion of trocars using a mechanical device

All trocar insertions within this experiment were performed on the one specimen of abdominal wall. As before, there was a statistically significant difference between pyramidal and conical trocars at stages 1 and 2, with penetration occurring earlier in the pyramidal group (Tables 3.3 and 3.4, Figures 3.8 to 3.10). While this difference was preserved between

pyramidal and sharp, conical trocars at stage 3, the difference between pyramidal and blunt, conical trocars just failed to reach significance. However, two inadequate penetrations of the blunt trocar, as a result of a technical error, were not noticed during the experiments. There was a significant difference between conical sharp and blunt trocars in the depth of the tip of the trocar at initial penetration but not at stages two and three.

Trocar tip	Stage 1 (mm)	Stage 2 (mm)	Stage 3 (mm)	Distance from posterior wall (mm)
Pyramidal	**20.6** (17.8 – 23.7)	**42.2** (37.4 – 45.2)	**53.6** (51.0 – 56.8)	**150** (120 – 180)
Conical (sharp)	**34.6** (28.0 – 36.5)	**58.4** (51.9 – 65.2)	**66.0** (60.4 – 72.3)	**150** (120 – 180)
Conical (blunt)	**39.2** (35.4 – 43.2)	**55.1** (48.0 – 61.9)	**60.2** (53.8 – 70.5)	**150** (120 – 180)

Table 3.3 Experiment 2 (mechanical insertion). The median and interquartile values of trocar tip depth from baseline level of the peritoneum at each stage of insertion (for the definition of the stages, see section 3.3.3.1). The column on the right lists the median distances of the trocars from the posterior wall of the apparatus that served as the reference point for the calculations. All measurements are in millimetres (mm).

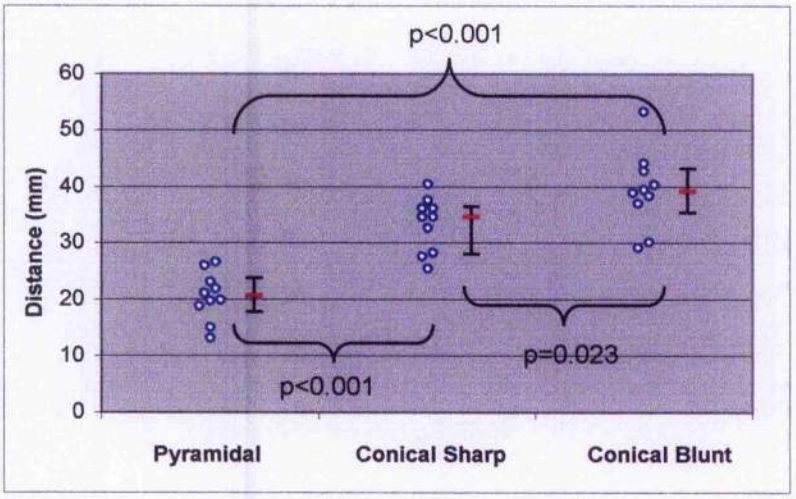


Figure 3.8 Scatterplot of the depth of the tip of each type of trocar at the point of initial penetration of the peritoneum (mechanical insertion, stage 1). The median and interquartile ranges are displayed to the right. Inter-group comparisons were made with the Mann-Whitney test.

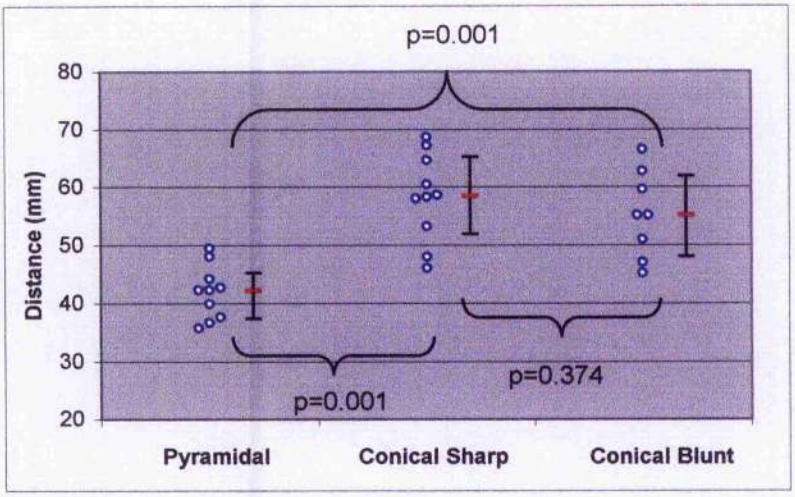


Figure 3.9 The depth of the tip of each type of trocar, when the leading edge of the cannula initially appeared through the peritoneum (mechanical insertion, stage 2). The median and interquartile ranges are displayed to the right. There are only eight data points for the blunt conical group due to incomplete insertion. Inter-group comparisons were made with the Mann-Whitney test.

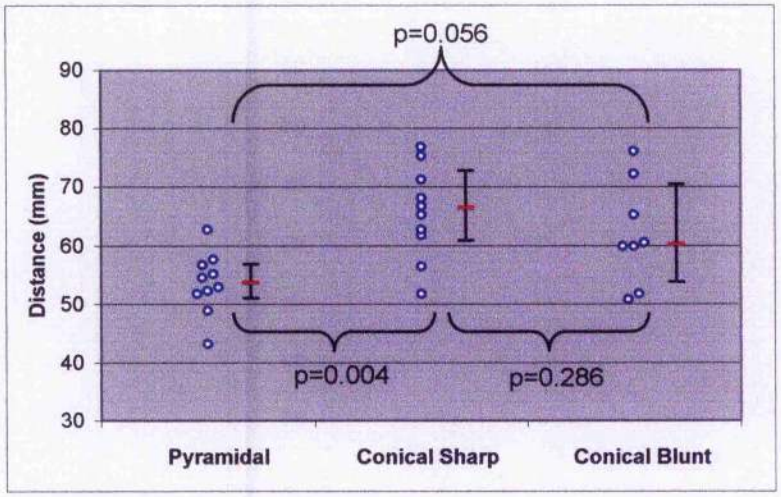


Figure 3.10 The depth of the tip of each type of trocar, when the cannula had completely penetrated the peritoneum (mechanical insertion, stage 3). The median and interquartile ranges are displayed to the right. Again, there are only eight data points for the blunt conical group. Inter-group comparisons were made with the Mann-Whitney test.

Trocar tip	Stage 1	Stage 2	Stage 3	Distance from posterior wall
Pyramidal vs Conical (sharp)	**<0.001**	**0.001**	**0.004**	1.000
Pyramidal vs Conical (blunt)	**<0.001**	**0.001**	0.056	0.779
Conical (sharp) vs Conical (blunt)	**0.023**	0.374	0.286	0.779

Table 3.4 Experiment 2 (mechanical insertion). Probability values, derived with the Mann-Whitney test, for comparisons of the depth of the trocar tip at each stage of insertion and the distance of the trocars from the reference point on the posterior wall of the apparatus. Statistically significant results are highlighted in bold text.

3.5 Discussion

Trocars with a conical tip are known to require more force for insertion than trocars with a pyramidal tip (Böhm *et al*, 1998). In this study, it was noted that this difference in profile and force translated into deeper ingression of the abdominal cavity by the tip and cannula, prior to complete penetration of the peritoneum. The difference in the depth of initial penetration of the peritoneum by the trocar tip was up to 93% more for the blunt conical and 76% more for the sharp conical trocar than the pyramidal trocar and equated to a difference of almost 2cm. However, when complete entry of the trocar and cannula assembly was attained, this difference only equated to approximately 30% extra distance for both types of conical trocar (1.2 to 1.6 cm).

In the normal abdomen (i.e without a pneumoperitoneum), the abdominal aorta lies between 6 to 13cm behind the base of the umbilicus, depending on the degree of obesity (Hurd *et al*, 1991). Bowel will obviously lie more anteriorly. This distance increases with the introduction of pneumoperitoneum but no data for this measurement are available. It would be tempting to make direct comparisons of these measurements with the results of this current study but this is not appropriate for several reasons.

Firstly, the abdominal wall of pigs is thinner than the human equivalent but it has however, been previously regarded as an acceptable alternative for experimental purposes (Bhoyrul *et al*, 1996; Böhm *et al*, 1998; Tarnay *et al*, 1999).

Also, under normal circumstances, the pneumoperitoneum exerts an outward force that distends and places the abdominal wall under tension. Without the creation of a closed compartment (that would make measurement of displacement from within extremely difficult), it is not possible to exactly mimic this clinical situation. The force of the pneumoperitoneum, as it pushes against the surgeon who is inserting the trocar, provides resistance that will influence the depth of penetration. Within the model used for this study, the tension in the abdominal wall was created in a longitudinal plane and maintained with clamps, attached to the modified laparoscopic trainer. All 30 trocar insertions within each experiment were performed on the one specimen to ensure consistency of the thickness of tissue through which they had to pass. It is conceivable though, that both the position of and the multiple insertions and extractions of the trocars could have affected abdominal wall tension as the experiments progressed. For this reason, the insertion order of the trocars was performed sequentially rather than in batches to minimise and evenly spread any possible changes.

A further aspect that this study does not address is the influence of a rotational movement during the insertion of the conical trocar. Rotation of the trocar is used in the clinical setting to facilitate its passage. Despite the intention to avoid rotation and therefore standardise the technique of insertion, this may have occurred while inserting trocars by hand in experiment 1. The mechanical insertion of the trocars for experiment 2 ensured that there was no rotational element, but this deviates from clinical practice.

Despite its shortcomings, this study suggests that the sharpness of the leading point of the trocar and the profile of the remainder of the tip both exert an influence on the passage of the

trocar through the abdominal wall.

The pyramidal trocar with a sharp point and three sharp blades created the least deflection of the tissue at all stages of insertion. The sharp, conical trocar, known to require a higher force for insertion (Bölm *et al,* 1998), caused a greater deflection at all stages. However, the deflection at stage 1 (i.e. the point at which the tip breached the peritoneum) was significantly less in experiment 2 and when compared with the degree of deflection caused by the conical trocar with a blunt tip. This difference vanished once the tip had progressed beyond the peritoneum and the conical component of the trocar tip passed through the wound. In other words, the sharp tip passed more easily through the tissue than the blunt tip but the resistance of the conical profile as it stretched the tissue apart impeded both trocars to a similar extent. This difference failed to reach statistical significance in experiment 1 but further study will be required to assess whether or not this was a type 2 error.

This study has not evaluated the effect of the "shielded trocar," which was introduced in an attempt to obviate worry about an unprotected tip in the abdominal cavity. This was not studied because the resistance of the shield would have introduced another variable in addition to the profile of the tip of the trocar. Neither has it considered the effect of a disposable sharp blade, which is known to reduce the resistance to insertion (Corson *et al,* 1989). The latter would have introduced the new variables of slightly different diameter and surface profile of the trocar and cannula. It would be interesting though in future work to evaluate these aspects of trocar and cannula design.

While differences are evident among the groups, the experiments have not evaluated any potential injury pattern to the underlying viscera. Since it is this aspect of trocar insertion that has the most potential for serious morbidity and even mortality, it is necessary to investigate this further before conclusions are drawn over the clinical significance of the findings within this study.

CHAPTER 4

THE EFFECT OF TROCAR TIP PROFILE ON BOWEL INJURY

4.1 Introduction

In the last chapter, it was noted that the depth of penetration of the trocar tip, during the process of insertion into the abdominal cavity, was affected by both the sharpness and the profile of the tip of the trocar. It is assumed in the literature that a sharp pyramidal trocar is more easily inserted and is therefore less likely to thrust forward and penetrate the viscera (Corson *et al*, 1989; Nezhat *et al*, 1991). It would also seem logical to assume that minimal incursion of the peritoneal cavity should reduce the opportunity for a trocar to come into contact with the bowel. However, there are no data available that describes the pattern or severity of any injury sustained by the bowel upon contact with a trocar.

4.2 Hypothesis and Aim

4.2.1 Hypothesis

Iatrogenic injury, sustained during the process of gaining access to the abdomen in Minimally Invasive Surgery can be influenced by the choice of profile of the trocar tip.

4.2.2 Aim

The aim of this study is to compare the incidence and characteristics of any injury sustained by the bowel, when impinged centrally or off-centre, by pyramidal, sharp conical and blunt conical trocars.

4.3 Materials and methods

4.3.1 Trocars and cannulae

The same trocars from the 10.5mm "YelloPort"™ range (Surgical Innovations, Leeds, West Yorkshire, UK), as described in section 3.3.1, were used (Figure 3.1). Only one range was used to ensure that the sole variable was the design of the tip.

4.3.2 Bowel model and insertion technique

Small bowel from pigs, complete with the mesentery, was obtained from the local abattoir. Lengths of bowel, 20cm long were filled with 20mls of 0.9% normal saline (Baxter Healthcare Ltd, Thetford, Norfolk, UK), dyed with red food colouring (Supercook, Leeds, West Yorkshire, UK) to highlight any leakage that may occur. The ends were tied and rendered watertight with 2.0 prolene (Ethicon, Edinburgh, West Lothian, Scotland).

A section of firm, foam material was placed across the bottom of a box and was covered by a layer of mesentery so that a layer of peritoneum lined the base of the apparatus. Each specimen was placed into the box, on top of the mesentery and both the bowel and mesentery were lubricated with 0.9% saline to minimise friction and allow free movement of the specimen. A perspex cover, with a central hole just wide enough for the trocar and cannula assembly, was placed over the box and lined up with either the centre of the bowel (experiment 1) or 5mm from the midline, towards the anti-mesenteric border (experiment 2). To aid in the process of alignment, the ends of the prolene ties on the specimens were left long and were brought up through additional small holes in the perspex cover. Once the specimen was in the correct position, all tension on the prolene was released so that the bowel was not tethered and the ties were kept away from the centre of the jig with clips.

The "Laparolift"™ device, as modified for the previous set of experiments (section 3.3.2), was used to ensure perpendicular insertion and standardise the rate and force of trocar insertion. A restraint was placed to ensure that the tip of the trocar was inserted to a constant depth, just level with the upper aspect of the foam base in the box (Figure 4.1).

4.3.3 End-points

The rates of injury and deflection were recorded. The characteristics of the wounds were also noted.

4.3.4 Statistics

4.3.4.1 Selection of sample size

While the clinical literature suggests that bowel injury occurs with a frequency between 0.4 to 1.5 / 1000 cases during laparoscopy (Bonjer *et al*, 1997; Champault *et al*, 1996; Copeland *et al*, 1983; Deziel *et al*, 1993; Riedel *et al,* 1986; Schrenk *et al*, 1996), no literature was available to assist in the calculation of a suitable sample size for an experiment where the bowel was deliberately targeted. It was therefore elected to introduce each trocar ten times.

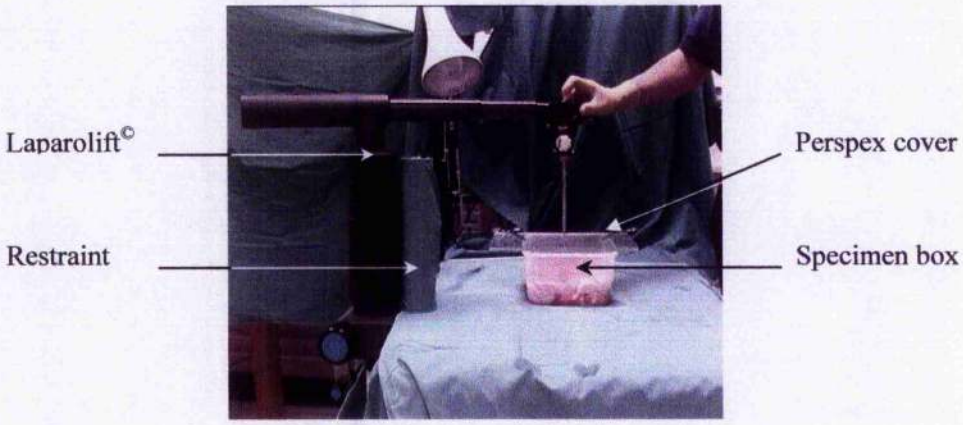


Figure 4.1 General view of the jig used to ensure perpendicular and standardised placement of the trocars. Each specimen was lined up with the tip of the trocar so that it impinged the bowel on the centre of the specimen or 5mm towards the anti-mesenteric border. The buttons to raise and lower the "Laparolift"™ on the upper surface were activated by hand.

4.3.4.2 Methods of analysis

Fisher's exact test was used for comparisons between the groups. All data were analysed using SPSS (Statistical Package for Social Sciences v 9.0, SSPS UK Ltd, Woking, Surrey, UK). Results were considered significant at the 5% level (i.e. $p < 0.05$).

4.4 Results

4.4.1 Experiment 1 – Central bowel injury

4.4.1.1 Deflection

Only one specimen of bowel, in the blunt conical group, deflected when impinged by a

trocar. This was not statistically significant (Figure 4.2).

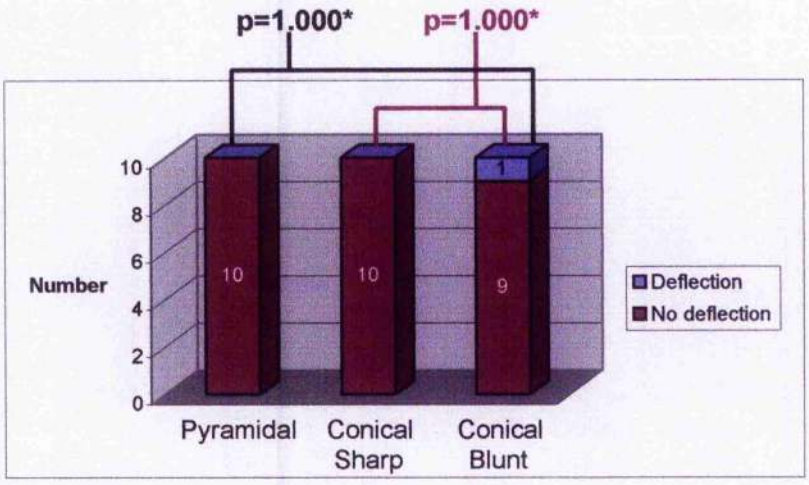


Figure 4.2 The incidence of deflection of the bowel when impaled centrally. As there were no episodes of deflection among the specimens impaled by the pyramidal and conical sharp trocars, it was not possible to calculate a probability value. By definition, there was no statistically significant difference between these two groups.

*Fisher's exact test.

4.4.1.2 Penetration of the bowel wall

Every pass with a sharp tipped trocar punctured both the anterior and posterior walls of the bowel and resulted in leakage of the saline. None of the sections of bowel impinged by the blunt conical trocars were penetrated although a small, non-penetrating crush mark could be seen at the site of contact. The difference in the incidence of penetration between sharp tipped and blunt tipped trocars was statistically significant (Figure 4.3). This difference occurred although there were no differences among the groups in the incidence of visible evidence of contact with a trocar on one or both walls of the bowel (Figure 4.4).

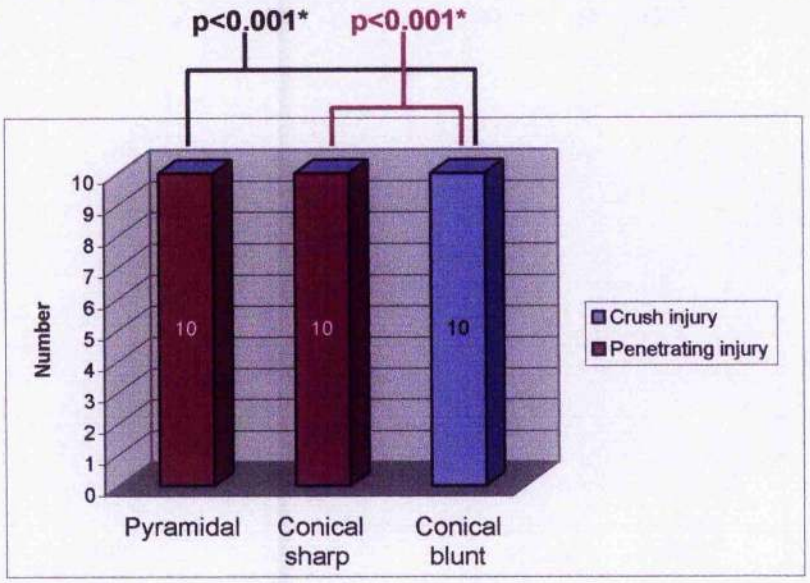


Figure 4.3 The incidence of central penetrating and crush injuries. *Fisher's exact test.

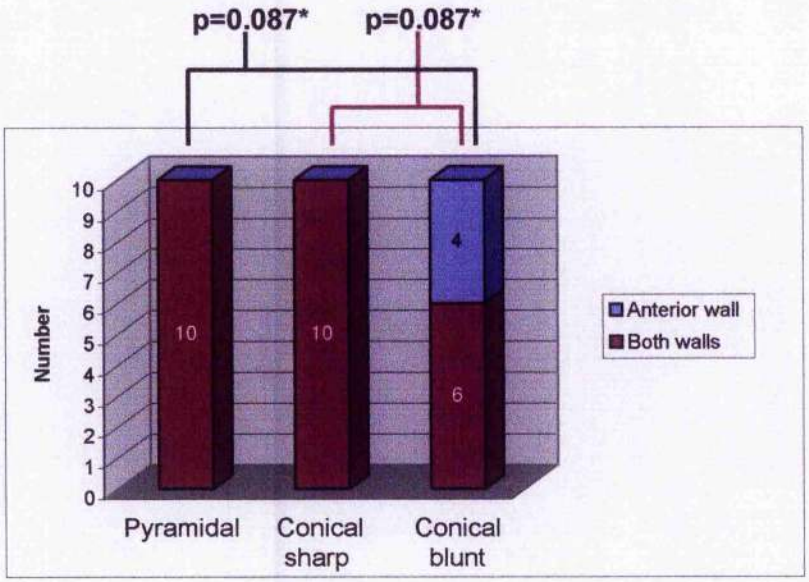


Figure 4.4 The incidence of visible evidence of contact with a trocar on one or both walls of the bowel when caught centrally by a trocar. The pyramidal and conical sharp groups caused a penetrating injury whereas the conical blunt group only caused a non-penetrating indentation (see Figure 4.3). *Fisher's exact test.

4.4.1.3 Shape of the injury

All ten passes with a trocar with a pyramidal tip created tri-radiate wounds (Figure 4.5a). The sharp conical trocar caused a small round puncture wound (Figure 4.5b) and the blunt conical trocar, a small, non-penetrating dimple.

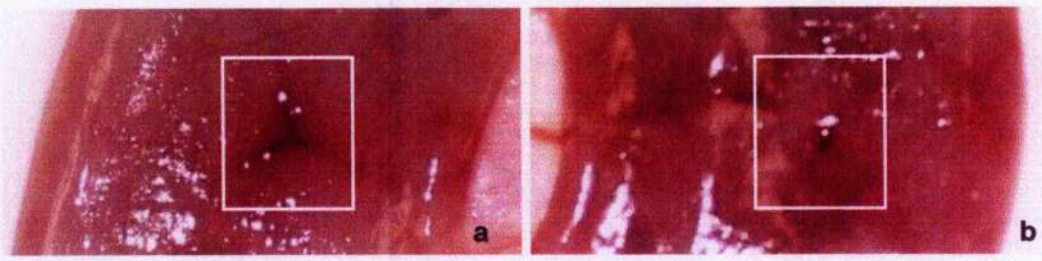


Figure 4.5a Stellate injury caused by a pyramidal trocar.

Figure 4.5b Small round puncture wound caused by a sharp conical trocar.

4.4.2 Experiment 2 – "Off-centre" bowel injury

4.4.2.1 Deflection

Seven sections of bowel deflected when they were impinged by a blunt, conical trocar, whereas none of the specimens in the pyramidal or sharp conical groups moved aside. This was statistically significant (Figure 4.6).

4.4.2.2 Penetration of the bowel wall

Again, every pass with a sharp tipped trocar punctured the bowel and resulted in leakage of the saline. None of the sections of bowel impinged by the blunt conical trocars were penetrated but evidence of indentation was visible in all cases. The difference in the incidence of penetration between sharp tipped and blunt tipped trocars was statistically significant (Figure 4.7). Both anterior and posterior walls were pierced by all of the pyramidal and sharp conical trocars. Crush marks were evident on both walls in eight of the specimens and on the anterior wall only in two specimens in the blunt conical group. There were therefore no statistically significant differences among the groups in the incidence of visible evidence of contact with a trocar on one or both walls of the bowel (Figure 4.8).

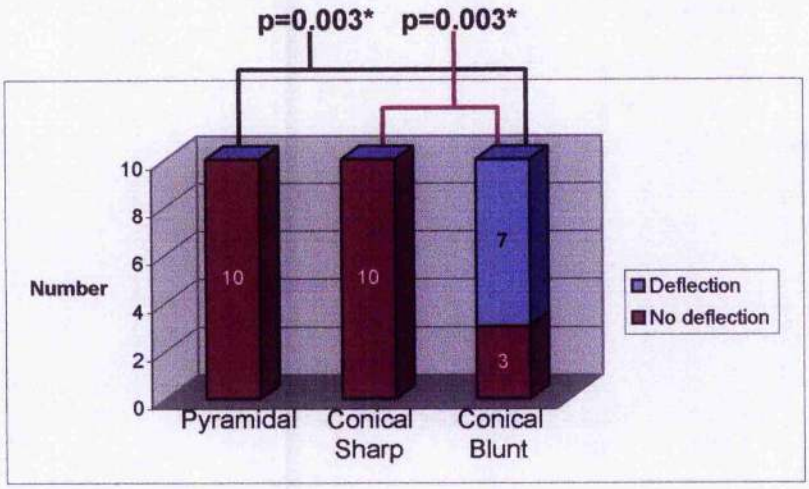


Figure 4.6 The incidence of deflection of the bowel when it was contacted "off-centre." As there were no episodes of deflection among the specimens impaled by the pyramidal and conical sharp trocars, it was not possible to calculate a probability value. By definition, there was no statistically significant difference between these two groups. *Fisher's exact test.

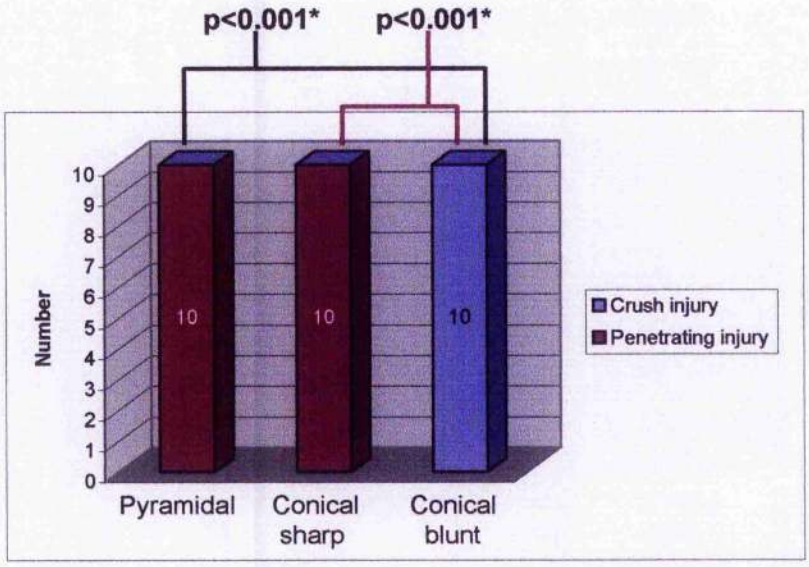


Figure 4.7 The incidence of penetrating and crush wounds for "off-centre" injuries. *Fisher's exact test.

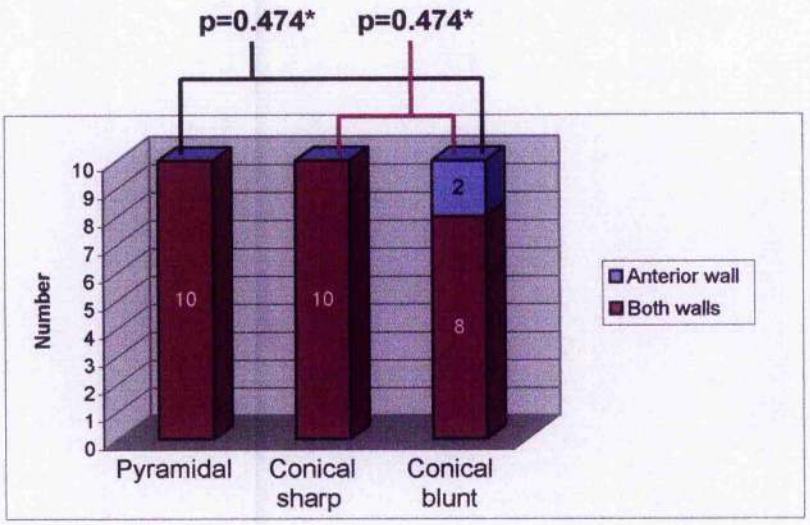


Figure 4.8 The incidence of injury to one or both sides of the bowel wall when impaled "off-centre." *Fisher's exact test.

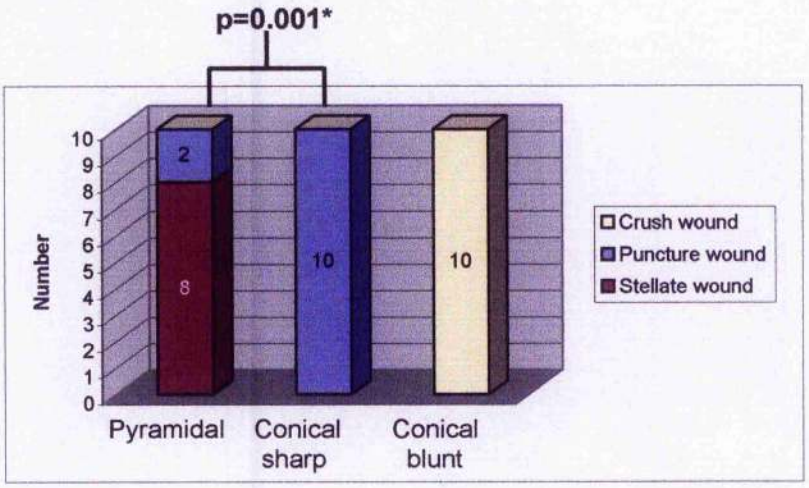


Figure 4.9 Characteristics of the wounds obtained with different shapes of trocars. For probability values derived from comparisons of the rates of penetrating and crush injuries between pyramidal / conical blunt and conical sharp / conical blunt trocars, see Figure 4.7. * Fisher's exact test - comparison of the incidence of puncture and stellate wounds between pyramidal and conical sharp trocars.

4.4.2.3 Shape of the Injury

Eight out of ten passes with a trocar with a pyramidal tip created tri-radiate wounds. In two cases, a small puncture wound was obtained. As previously noted, the sharp conical trocar caused a small round puncture wound and the blunt conical trocar, a small, non-penetrating

dimple. Non-penetrating crush injuries occurred exclusively with the conical blunt trocar. The characteristics of the wounds were related to the profile of the tip of the offending trocar (Figure 4.9).

4.5 Discussion

Once again, there was a clear difference in the injury pattern related to the profile of the tip of the trocar. The most important factor though in this experiment was the sharpness of the extreme tip of the trocar. Both the pyramidal and sharp conical trocars perforated all specimens of bowel, albeit with different shapes of wounds. None of the blunt trocars caused a penetrating injury, even though there was evidence of pressure on the posterior wall of the bowel in most cases. In fact, it was noted in this latter group that the crush mark disappeared within a few minutes of the trocar injury. Due to the use of cadaveric tissue, it is not possible to determine whether or not in-vivo, this area would heal spontaneously or perforate at a later date. This is a potential weakness of the experiment but it does not detract from the findings.

It is difficult to recreate the exact environment of the abdomen. However, the current experiment was set up in a manner that allowed freedom of movement of the bowel over a peritoneal surface as found in-vivo yet allowed standardisation of the technique, position and depth of trocar insertion that would have been virtually impossible in a live model.

The theoretical advantage of a conical trocar is that it will encourage mobile viscera to deflect (Semm, 1995; Tews *et al*, 1991). This only occurred when a blunt conical trocar was used and was most pronounced when initial contact was made away from the centre of the bowel. Bowel was impaled by the conical trocar with a sharp tip regardless of whether the injury was central or off-centre, suggesting that the sharp tip caught the serosa and prevented lateral movement. Contrary to the opinions of some authors (Corson *et al*, 1989; Nezhat *et al*, 1991), the presence of a sharp tip actually facilitates visceral injury and should be avoided if at all possible.

CHAPTER 5

THE EFFECT OF THE TROCAR TIP PROFILE ON THE PATTERN OF VASCULAR INJURIES

5.1 Introduction

In Chapter 1, it was noted that the profile of the tip of the trocar influences the ease of passage through the tissue and the nature of the wound. Cutting pyramidal trocars incise tissue within their path and create a defect that is the same diameter. Conical trocars stretch the tissue aside thereby creating a smaller wound. It has also been proposed that conical trocars can deflect both the abdominal viscera and blood vessels (cf. section 1.8).

5.2 Hypothesis and Aim

5.2.1 Hypothesis

Iatrogenic injury, sustained during the process of gaining access to the abdomen in Minimally Invasive Surgery can be influenced by the choice of profile of the trocar tip.

5.2.2 Aim

The aim of this study is to compare the incidence and characteristics of any injury sustained by the aorta when impinged by pyramidal, sharp conical, blunt conical and Hasson trocars.

5.3 Materials and Methods

5.3.1 Trocars and Cannulae

Trocars with pyramidal, sharp conical and blunt conical profiles were selected from the 10.5mm "YelloPort"™ range (Surgical Innovations, Leeds, West Yorkshire, UK). In addition, because a trocar can potentially come in contact with the aorta during open access, a rounded Hasson trocar was included for these experiments (Figure 5.1). Only one range was utilised to ensure that the sole variable was the design of the tip.

5.3.2 Abdominal Aorta

Abdominal aortas from pigs, reared for heart valve xenografts, were obtained from the abattoir. Each aorta was carefully examined for lumbar and mesenteric branches, all of which were clipped. Proximally, an intravenous giving set, attached to a bag of normal (0.9%) saline (Baxter Healthcare Ltd, Thetford, Norfolk, UK) was secured with No.1 prolene (Ethicon, Edinburgh, UK). Five millilitres of red food colouring (Supercook, Leeds, West

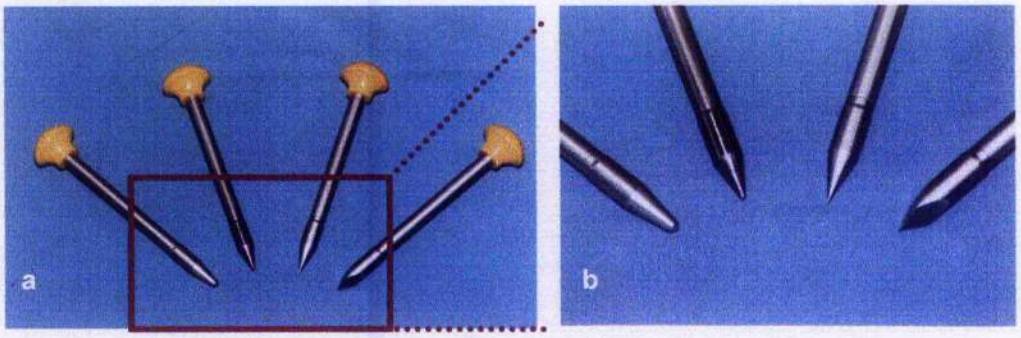


Figure 5.1a The profiles of the trocar tips from left to right are rounded (Hasson), blunt conical, sharp conical and pyramidal. All come from the "YelloPort"™ range (Surgical Innovations, Leeds, West Yorkshire, UK).

Figure 5.1b Enlarged view of the trocars that displays the different profiles.

Yorkshire, UK) were added to the saline to highlight any leakage. The fluid was run through the aorta to expel air and the distal aorta was cross-clamped to create a closed system. A pressure infusion cuff (Medex Medical Ltd, Rossendale, Lancashire, UK) was used to create a pressure of 120mmHg, the peak of the normal aortic wave-form. The aorta was placed in the centre of a jig.

5.3.3 Development of the Apparatus for the Study

Initially, the aortas were pinned to a wooden backplate and placed within an abdominal simulation box (AnnexArt, Beaumaris, Anglesey, UK). A neoprene skin (Diver's Warehouse, Bradford, West Yorkshire, UK) was placed over this to represent the abdominal wall. Markers placed on this surface were used to indicate the location of the aorta. However,

early trials of this device demonstrated that it was not possible to ensure consistent perpendicular and central placement of the trocar in relation to the specimen.

An alternative device was designed. It consisted of a wooden back plate that served as a base to which the specimen was secured and also represented the vertebral column. An inverted "U"-shaped cover was constructed, with enough space to permit lateral deflection of the aorta, when this occurred. In the roof, a central hole was drilled to allow the insertion of a trocar and cannula. This was 24.5mm thick and was a snug but not a tight fit, to ensure consistent perpendicular, central placement of the trocar (Figure 5.2). A dial calliper gauge was used to ensure the specimen was equidistant from the sides of the device and therefore central.

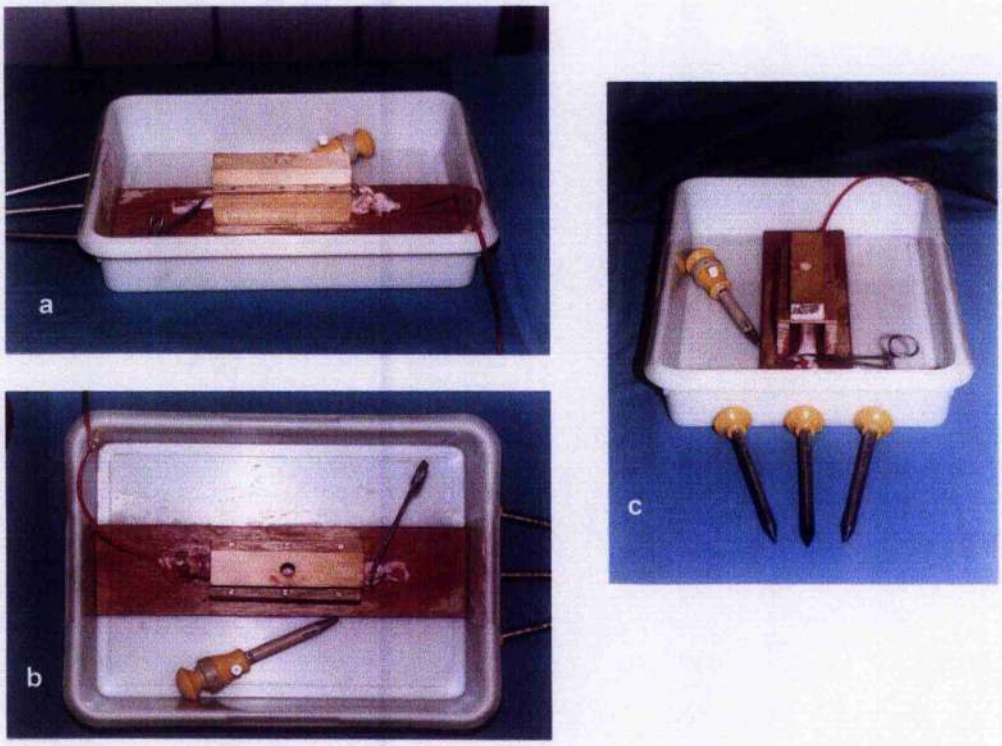


Figure 5.2(a-c) Superior, anterior and side elevations of the apparatus used for the series of experiments. The aorta was situated within the device, directly below the hole in the upper surface (b) and with sufficient space to deflect (c). The infusion line, from the pressurised reservoir of 0.9% saline, entered from the right.

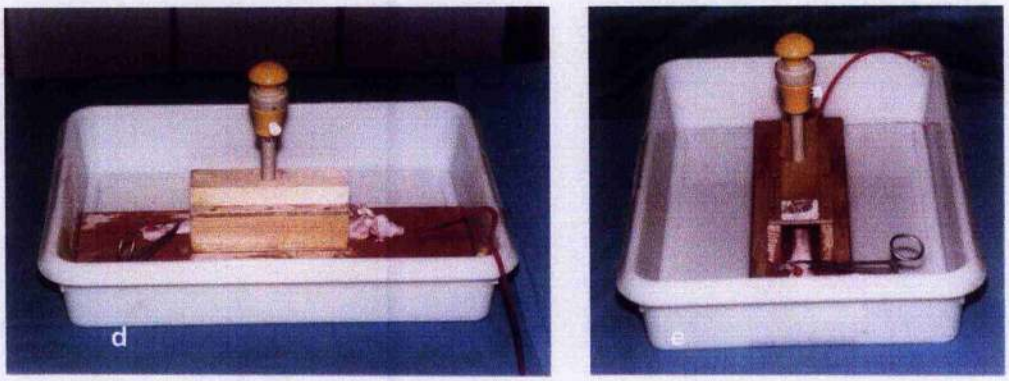


Figure 5.2(d,e) The snug fit of the cannula within the device ensured perpendicular placement with every insertion.

5.3.4 End-points

Each trocar was inserted, by hand, a total of ten times and was pushed through until the resistance of the back wall of the jig was felt. The trocar was left in position until the aorta had been inspected for evidence of deflection. The aorta was then removed from the device and was examined for injury to the adventitia and any fluid leak. The specimen was then opened to evaluate the intimal aspects of both the anterior and posterior walls. The maximum width of the injury was measured with a dial calliper gauge, accurate to 0.1mm (Squires Model and Craft Tools, Bognor Regis, West Sussex, England).

5.3.5 Statistics

5.3.5.1 Selection of Sample Size

No literature or prior experience was available to assist in the calculation of a suitable sample size. It was therefore elected to introduce each trocar ten times during this pilot study.

5.3.5.2 Methods of Analysis

All data were analysed on SPSS (Statistical Package for Social Sciences v 9.0, SSPS UK Ltd, Woking, Surrey, UK). The Kruskal-Wallis test was used to compare continuous data among all of the groups and the Mann-Whitney test for direct comparisons of two selected groups. The Wilcoxon signed ranks test was utilised for analysis of paired continuous data and

Fisher's exact test was used for comparisons of nominal data. Results were considered significant at the 5% level (i.e. $p < 0.05$).

5.4 Results

5.4.1 The incidence of deflection

None of the aortas impinged by a trocar with a pyramidal tip or sharp conical tip deflected. However, three of the aortas deflected upon contact with the blunted conical trocar and eight on contact with the Hasson trocar. Deflection occurred more frequently when a non-sharp tipped trocar (Hasson and blunt conical) was used rather than a sharp tipped trocar (pyramidal and sharp conical) (Fisher's exact test, $p<0.001$). There was a tendency for deflection to occur more often in the Hasson group than in the blunt conical group, although this was not statistically significant ($p=0.07$, Fisher's exact test).

5.4.2 The incidence of injury and relation to tip profile

All ten aortas in the pyramidal and sharp conical groups were injured by the trocars. Seven aortas in the blunt conical group and three in the Hasson trocar group were injured during the process of trocar insertion. The tips were re-categorised by profile to sharp and blunt and analysis demonstrated a difference in the incidence of injury ($p<0.001$, Fisher's exact test). There was no statistically significant difference in the injury rate between Hasson and blunt conical trocars ($p=0.179$, Fisher's exact test).

5.4.3 Type of leakage

It became obvious that the trocar injuries resulted in two patterns of leakage. The first and most common ($n=22$) was a brisk, "spurting" leak, which occurred in all aortas that were impinged by the pyramidal and sharp conical trocars and in two aortas that were injured by the blunt conical tip (Figure 5.3). The second type ($n=8$) was a contained "haematoma" (essentially a pseudoaneurysm) that limited the loss of fluid in the tissues around the aorta (Figure 5.4). This occurred with five aortas in the blunt conical group and three aortas in the

Hasson group. This difference in the pattern of haemorrhage was statistically significant when the blunt conical trocar was compared with the pyramidal or sharp conical trocars (p=0.003, Fisher's exact test) and when the Hasson trocar was compared with the pyramidal or sharp conical trocars (p=0.003, Fisher's exact test) (Figure 5.5). There was no statistically significant difference in the incidence of the "contained" leak between the groups that were injured by the Hasson trocar and blunt conical trocar (p=1.000, Fisher's exact test).

Figure 5.3 The aorta has been removed from the device to demonstrate the spurting jet of fluid that occurred after injury with a pyramidal trocar. Note the "haematoma" due to the injury of the posterior wall. The clipped vessel to the right is the superior mesenteric artery (SMA).

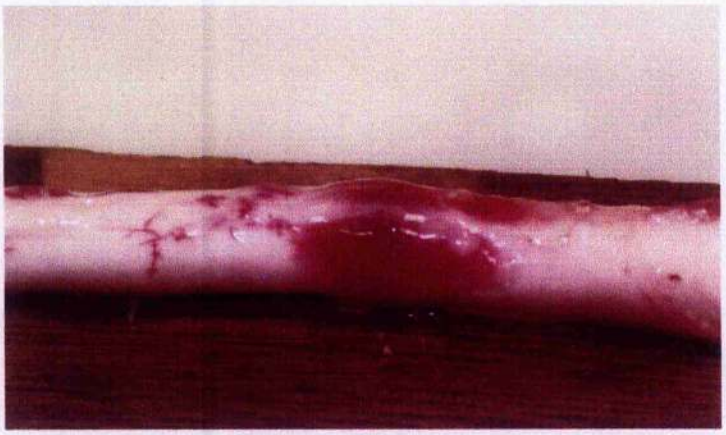


Figure 5.4 This specimen demonstrates a contained "haematoma," (essentially a pseudo-aneurysm) within the peri-aortic tissue after an injury with a blunted conical trocar.

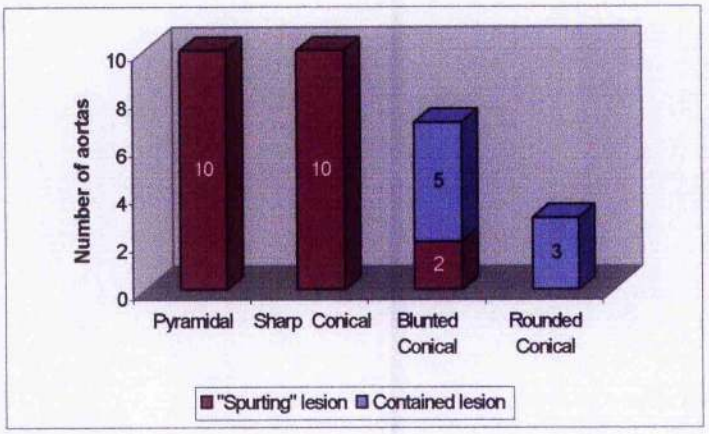


Figure 5.5. Graphical illustration of the incidence of "spurting" leakage and contained "haematoma" caused by the four different trocar tips. Ten aortas were used for each group.

5.4.4 Injuries to the wall of the aorta

There was a statistically significant difference among the groups in the median size of the adventitial defect in the front wall and the back wall ($p<0.001$, anterior wall defect, $p=0.002$, posterior wall defect, Kruskal-Wallis test). There was no statistically significant difference among the groups for the size of the intimal injury ($p=0.296$, anterior wall defect, $p=0.321$, posterior wall defect, Kruskal-Wallis test) (Table 5.1 and Figure 5.6).

		Pyramidal	Conical sharp	Conical blunted	Hasson
Adventitial defect (cm)	**Anterior**	**3.1** (2.5 – 4.22)	**1.75** (1.15 – 2.75)	**0** (0 – 1.28)	**0** (0 – 0.98)
	Posterior	**1.5** (1.28 – 1.85)	**0.6** (0.38 – 0.8)	**0** (0 – 1.1)	**0** (0 – 0.4)
Intimal defect (cm)	**Anterior**	**5.15** (3.15 – 7.3)	**4.95** (3.7 – 5.75)	**5.8** (0 – 6.55)	**0** (0 – 7.12)
	Posterior	**2.65** (1.28 – 1.85)	**1.95** (1.0 – 2.48)	**2.5** (0 – 3.35)	**0** (0 – 5.42)

Table 5.1 The median size of the injury created by the four types of trocar on the anterior and posterior adventitial and intimal walls of the aorta. The interquartile range is quoted in parenthesis.

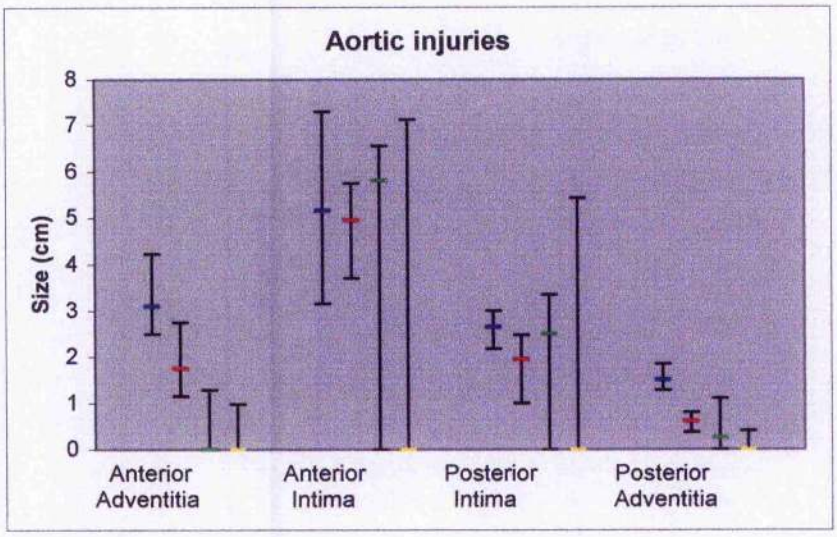


Figure 5.6 The median size of the defects in the aortic wall after injury by pyramidal (blue), conical sharp (red), conical blunt (green) and Hasson (yellow) trocars. The error bars represent the interquartile ranges.

5.4.5 Injuries to the anterior adventitia

The pyramidal trocar caused a larger defect than the sharp conical, blunt conical and Hasson trocars. The sharp conical trocar created a wider injury than the blunt conical or Hasson trocars. There was no statistically significant difference in the size of injury created by the blunted conical or Hasson trocars (Table 5.2).

	Hasson	**Blunt Conical**	**Sharp Conical**
Pyramidal	0.001	0.002	0.007
Sharp Conical	0.021	0.025	
Blunt Conical	0.657		

Table 5.2 Probability values for comparisons of the size of the trocar induced injuries of the adventitia of the anterior wall of the aorta, derived with the Mann-Whitney test. For the median wound sizes and interquartile ranges, see Table 5.1.

5.4.6 Injuries to the posterior adventitia

The pyramidal trocar caused a significantly larger defect than the sharp conical, blunt conical and Hasson trocars. The sharp conical trocar created an injury that was statistically larger than the Hasson trocar but was the same as that caused by the conical blunt trocar. There was no statistically significant difference in the size of injury created by the blunted conical or Hasson trocars (Table 5.3).

	Hasson	Blunt Conical	Sharp Conical
Pyramidal	0.01	0.001	0.001
Sharp Conical	0.039	0.618	
Blunt Conical	0.375		

Table 5.3 Probability values for comparisons of the size of the trocar induced injuries of the adventitia of the posterior wall of the aorta, derived with the Mann-Whitney test. For the median wound sizes and interquartile ranges, see Table 5.1.

5.4.7 Injuries to the anterior and posterior intima

There were no statistically significant differences in the sizes of the intimal wounds of the anterior or posterior walls, although the difference between wounds created by the sharp tipped trocars and the Hasson trocars were approaching significance in the anterior wall (Tables 5.4 and 5.5). Although there were less injuries among the aortas impaled by the blunted conical and Hasson trocars, the ranges of the size of the injuries when they occurred were of similar magnitude (Figure 5.6). The shape of the intimal injuries varied with the type of trocar. Most of the wounds caused by pyramidal trocars were tri-radiate and the wounds created by the conical and Hasson trocars were typically linear (Figures 5.7 to 5.9).

	Hasson	Blunt Conical	Sharp Conical
Pyramidal	0.053	0.677	0.677
Sharp Conical	0.089	0.596	
Blunt Conical	0.353		

Table 5.4 Probability values for comparisons of the size of the trocar induced injuries of the intima of the anterior wall of the aorta, derived with the Mann-Whitney test.

For the median wound sizes and interquartile ranges, see Table 5.1.

	Hasson	Blunt Conical	Sharp Conical
Pyramidal	0.122	0.939	0.096
Sharp Conical	0.122	0.448	
Blunt Conical	0.443		

Table 5.5 Probability values for comparisons of the size of the trocar induced injuries of the intima of the posterior wall of the aorta, derived with the Mann-Whitney test.

For the median wound sizes and interquartile ranges, see Table 5.1.

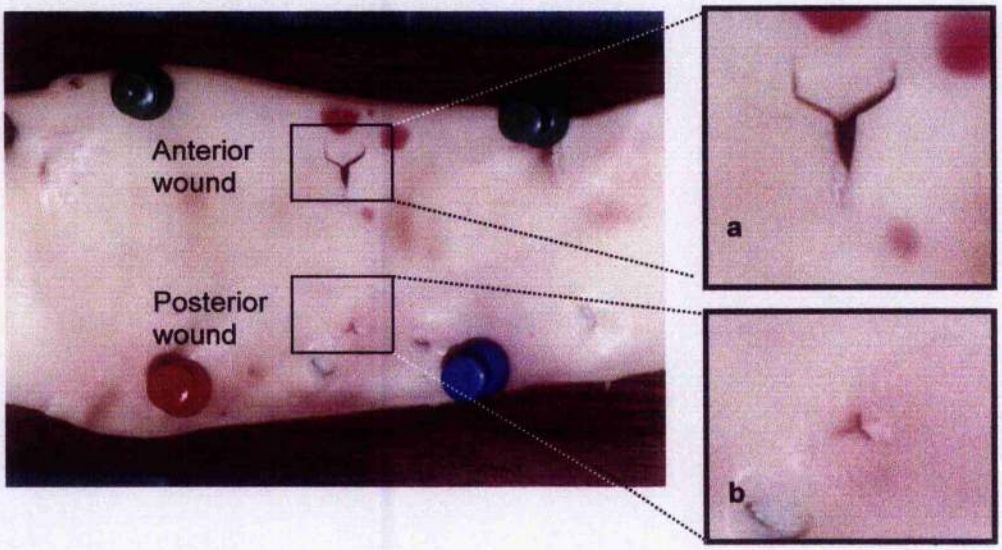


Figure 5.7 The aorta has been opened longitudinally to display the wound in the intimal surface. In this specimen, a pyramidal trocar created the injury and left a characteristic tri-radiate wound in the anterior (a) and posterior walls (b).

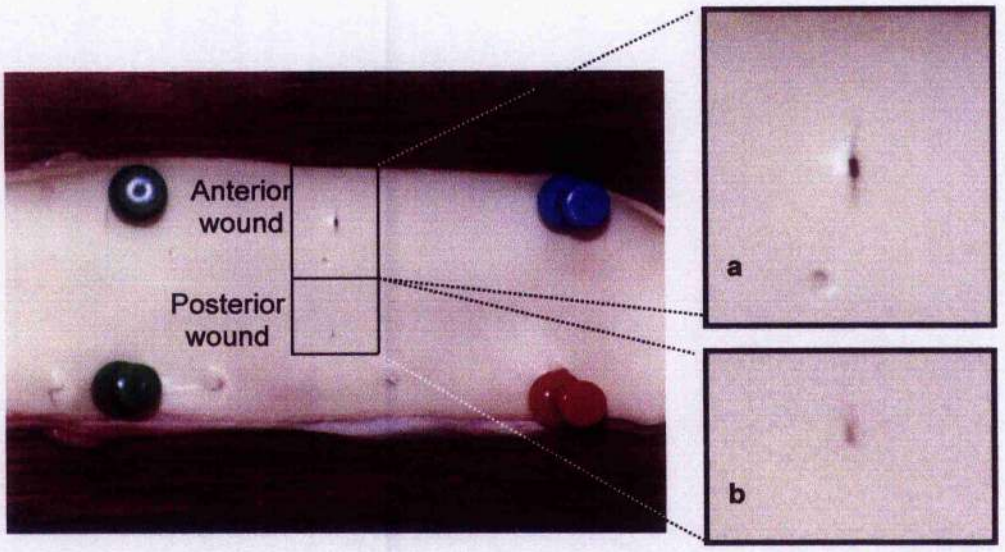


Figure 5.8. On this occasion, a sharp, conical trocar was used. Note the small, central, round defect with a linear transverse wound in the intima of the anterior wall (a). Although the wound in the posterior wall is much smaller, it is longer in the transverse diameter (b).

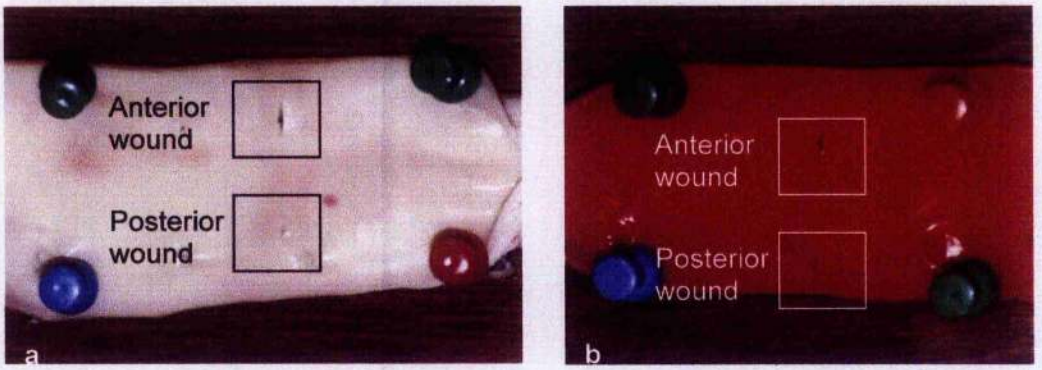


Figure 5.9. Injury with a blunted conical trocar (a) and a Hasson trocar (b) produce a similar pattern and size of wound when viewed from the intimal surface. Specimen (b) has stained strongly with the colouring in the saline. The reason for this is unclear as the specimen was obtained from the same batch of aortas and there was no change in the concentration of the dye in the saline used for this specimen.

5.4.8 Comparison of the size of the adventitial and intimal wounds within groups

Injuries to the adventitia, caused by sharp tipped trocars were significantly smaller in the back wall compared with the front wall (pyramidal trocars, $p=0.005$ and sharp conical trocars, $p=0.012$, Wilcoxon signed ranks test). When an injury was caused by a blunt tipped

trocar, there was no statistically significant difference in size between the anterior and posterior defects (blunt conical trocar, p= 0.916 and Hasson trocar p=0.593, Wilcoxon signed ranks test). However, due to the small number of injuries in these latter groups, the results have to be treated with caution.

Wounds in the intima, caused by the sharp tipped trocars and the blunted conical trocar were smaller in the posterior wall compared with the anterior wall (pyramidal trocar, p= 0.005, sharp conical trocar, p= 0.005, blunt conical trocar, p=0.18, Wilcoxon signed ranks test). There was a similar tendency for the Hasson trocar (p=0.109, Wilcoxon signed ranks test) but due to the small number of injuries, no firm conclusion can be drawn from the result. Injuries in the adventitia of the anterior and posterior walls of the aorta, created by pyramidal, sharp conical and blunt conical trocars, were typically smaller than the corresponding wound in the intima. A similar trend was observed for the Hasson trocar but due to the smaller number of total injuries observed in this group, it was not statistically significant (Table 5.6).

Trocar type	Anterior wall Adventitial vs Intimal wound	Posterior wall Adventitial vs Intimal wound
Pyramidal	0.022	0.007
Conical (Sharp)	0.005	0.007
Conical (Blunt)	0.018	0.018
Hasson	0.109	0.109

Table 5.6 p-values, derived by comparison of the adventitial and intimal wound measurements with the Wilcoxon Signed Ranks test. For the median wound sizes and interquartile ranges, see Table 5.1.

5.5 Discussion

It is quite clear from the data, that a trocar with a sharp tip, regardless of whether it has a pyramidal or conical profile, readily impales the aorta upon contact as all aortas in these

groups were injured and "bled." A trocar with a blunt tip is more likely to deflect the aorta and reduce the incidence of injury although it does not completely abolish the risk. Logically, the relative "bluntness" might increase the deflection rate and decrease the likelihood of an injury. However, comparison of the data derived in this experiment for blunt conical and Hasson trocars does not support this theory but as the numbers involved in this study were small, caution has to be exercised in the interpretation of this statistical comparison.

These results cast some light on the theories previously discussed in the introduction and demonstrate that the sharpness of the tip can obviate the benefit of a conical tip. The theory that trocars with a conical profile "should be preferred" because they deflect vessels is correct (Böhm *et al,* 1998; Hurd *et al,* 1995; Semm, 1995) but only as long as the tip is blunt. However, it has been demonstrated in this study that a blunt tip does not completely obviate the risk of injury and caution should be exercised during the insertion of any type of trocar. A sharp tip may increase the ease with which the trocar is inserted but this does not automatically translate into a lower rate of visceral injury as previously suggested, since contact with the viscera will inevitably result in injury (Corson *et al,* 1989; Nezhat *et al,* 1991). This current study confirms earlier assertions that these authors drew conclusions that were not supported by their data (cf. section 1.8.5).

Although the size of the adventitial wound was related to the profile of the trocar tip, the size of the corresponding wound in the intima was relatively uniform in all groups. This is in contrast to the pattern found in the anterior abdominal wall where the conical tip creates a smaller wound. As regards the shape, the majority of the wounds created by the pyramidal trocar were tri-radiate, yet all the intimal wounds, created by conical trocars, were orientated in a transverse direction and were linear. Examination of the structure of the aorta may explain these findings.

The aorta consists of three layers -- the tunica adventitia, tunica media and tunica intima. The

adventitia mainly consists of a network of collagenous fibres and some elastic fibres. The tunica media is the thickest of the three aortic layers and consists of concentric lamellae of elastic material with intervening layers of smooth muscle and fibrous tissue. The smooth muscle forms a spiral but as it has a very low pitch, it appears to be arranged circumferentially. The intima consists of an endothelial layer with its basal lamina and a subendothelial layer with smooth muscle cells, collagen and elastic tissue (Ross & Reith, 1985).

The small adventitial wound obtained with the conical trocar indicates that the randomly arranged fibres were displaced by the trocar and subsequently returned to almost their original position. The transverse orientation of the intimal wound suggests that the underlying media (which is attached to the intima) split along the line of the smooth muscle fibres, in a manner analogous to that of the striated muscle of the abdomen (Bhoyrul *et al*, 1996), and resulted in a wound that was longer in the transverse dimension. It is not clear, from the available data, whether or not a similar mechanism occurred with the blunted trocars, as both the blunt conical and Hasson trocars lack a sharp tip to initially penetrate the tissue. Conceivably though, the pressure effect could actually split apart the smooth muscle fibres and allow passage of the trocar. The mechanism of injury for the pyramidal trocar was obvious - as previously seen in the abdominal wall model, the pyramidal trocar cut a wound through the tissue regardless of its composition. Histological confirmation would strengthen these conclusions and it is planned to pursue this in future experiments.

It is not clear if one injury pattern is more sinister than the other. A blunt tip and a conical profile may result in deflection of the aorta, but the trocar can still cause an injury that will compromise the integrity of the vessel. However, the relatively small adventitial wound in the blunted trocar groups was accompanied by a small defect in the peri-aortic tissue that effectively resealed the wound and created a pseudo-aneurysm.

Initial logic would suggest that a spurting vessel is a more serious injury because it can result in a rapid loss of blood into the peritoneal cavity. However, this type of injury should be obvious and readily recognised in most cases, prompting conversion to laparotomy. An injury that results in intimal disruption and a contained leak, with minimal or slow blood loss, could afford slightly more time for control and repair. In the operative setting though, it may pass unnoticed, as bowel and omentum overlying the retroperitoneum may obscure the damage. The consequences of a missed injury are delayed haemorrhage or even distal ischaemia (as a result of embolic phenomena) (Hannay *et al,* 1995). Extreme caution and a high index of suspicion are mandatory.

There are some potential weaknesses of this study.

Firstly, it did not use human tissue. However, porcine tissue is an acceptable alternative to human tissue (Bhoyrul *et al,* 1996; Böhm *et al,* 1998), which would be difficult to obtain in the climate of current public opinion over the use of cadaveric tissue. The fluid within the pressure system was crystalloid, which is less viscous than blood and this could conceivably influence the pattern of leakage through the wound. The influence of clotting and the natural history of a "contained" leak were not followed. In addition, while the pressure wave in the abdominal aorta in vivo is dynamic, the experiments were performed on a static model. A pump mechanism could recreate this but the changing intra-aortic pressure would introduce another variable of pressure at the time of injury. This would require the development of a mechanism to coordinate trocar insertion and pressure.

Blinding of the investigator was not possible. However, the device to standardise the position of the aorta, the angle and initial point of contact between the trocar and the aorta, ensured that these factors were not influenced by observer bias. The only aspect that was not standardised was the rate of insertion, which could conceivably influence the injury rate and pattern.

Although differences were detected between blunt tipped and sharp tipped trocars, it must be conceded that this study was underpowered. The absence of a statistically significant result for the comparison of deflection and injury rates between the two groups of blunt trocars (i.e. blunt conical and Hasson trocars) requires cautious interpretation due to the low injury rates. There were only seven injuries in the blunt conical group and three injuries in the Hasson group, which makes a type 2 error a real possibility. Further investigation is indicated and planned.

CHAPTER 6

OVERVIEW OF THE THESIS

6.1 Summary

The advantages of laparoscopic cholecystectomy over open cholecystectomy are now well established. These include lower release of cytokines, less impairment of cell-mediated immunity, less pain, better pulmonary function, faster postoperative recovery, fewer complications and improved cosmetic appearance. Nevertheless, it has been shown by several authors that small changes in technique and careful attention to detail can further reduce aspects of the physiological insult of laparoscopic surgery and result in improvements in outcome for the patient (cf. section 1.6). The aim of this thesis was to take this concept and apply it to trocars and cannulae and the process of access. Although the trocar and cannula system is central to laparoscopic surgery and numerous theories abound over its use (cf. section 1.8), there are relatively little prospective data in the literature concerning the impact of size (cf. section 1.7) and the pattern of visceral and vascular injury related to the profile of the tip (cf. section 1.8).

In chapter 2, the impact of a reduction in the size of the trocars, cannulae and instruments was addressed in a clinical study. Smaller instruments are now freely available and there have been a number of reports that have described their use for diagnostic and therapeutic purposes. Data from these reports have been used to suggest that smaller wounds may result in up to 70% less pain and analgesic consumption, a faster recovery and virtually invisible wounds (cf. section 1.7.2). However, uncertainty remains over the value of the technique due to reductions in the image quality, the flexibility and resilience of the instruments and the fact that there could be a learning curve, even for experienced laparoscopic surgeons. As the micropuncture technique was already in use in Leeds, it was logical that a randomised controlled trial should be performed to address these questions.

The study was designed to address several issues, namely clinical outcome for the patient, the

effect on respiratory physiology and the stress response and thirdly, the feasibility of the procedure. The procedures and the anaesthetics were carefully standardised to ensure that the only variable that differed between groups was the size of the cannulae and much effort was exerted to ensure that the protocol was not significantly breached during the study

The most important issue for patients is clinical outcome as that is what they can see and perceive. The patients who agreed to participate were invited to provide objective information that covered their pain experience, presence of nausea and vomiting, use of analgesia and quality of life. Analysis of the data collected, suggested that after the micropuncture technique, although less parenteral analgesia was required, there was no significant reductions in pain scores. Nausea and vomiting were not a major feature after either technique of cholecystectomy and quality of life scores were similar throughout the study. Interestingly, quality of life was significantly better for both techniques at four weeks after surgery when compared to preoperative values.

Physiological and biochemical measurements of pulmonary function and the stress response failed to reveal any significant differences between the two techniques and would suggest that the reduction in size of the incisions is too small to have much impact on these parameters. It is worth noting that to date, no other study has addressed the impact on the stress response.

Rather than try to assess the surgeons' subjective perceptions of the level of difficulty of MPLC compared to CLC, operative times were measured. The rationale behind this was that any potential difficulties that arose from the use of the smaller laparoscope or instruments would be manifest as an increase in operative times that could be objectively compared. Furthermore, a breakdown of the procedure would highlight any particular aspect that was most affected by the new technique. It was demonstrated that it took longer to clip and divide the cystic duct and artery (probably due to the change to a 3mm laparoscope during the manoeuvre) but this did not significantly increase overall operative times. In support of the

concept that the micropuncture technique was no more technically demanding was the fact that none of the procedures were converted to a conventional laparoscopic cholecystectomy.

The remaining experiments in chapters 3 to 5, were devoted to examination of the influence of the tip of the trocar on its passage through the abdominal wall and its effects should it come into contact with bowel or a major blood vessel. The facts that have been established in the literature are that conical trocars require a higher force of entry but cause smaller wounds and are less likely to injure small vessels that they encounter during the insertion process. Cutting trocars slice through tissue, create a wound of the same diameter and are more likely to injure small blood vessels (cf. section 1.8.6).

It has been assumed that the high entry force associated with a conical or blunt trocar results in less control and that the deeper incursion into the abdominal cavity combined with an increased risk of "overshoot," results in higher rates of visceral or vascular injury. However, some authors have contended that while a conical trocar requires a higher insertion force, it pushes aside viscera upon contact and is less likely to cause major vascular trauma. No data have been reported that support these claims (cf. section 1.8.5).

Investigation of these aspects proved somewhat of a challenge. A clinical study of bowel and major vascular injuries was not possible due to the infrequent nature of the events. Likewise, it was difficult to envisage how the point at which a trocar and cannula assembly penetrated the peritoneum could be measured in the clinical setting. The conditions found in-vivo though would be difficult to replicate in the laboratory.

The experiment in chapter 3 was designed so that the depth at which the trocar and cannula penetrated the abdomen could be seen and measured. The investigations in chapters 4 and 5 concentrated on the injury pattern of the trocar tips on bowel and aorta and were designed so that the specimens could be deliberately targeted in a standardised fashion. Although the

experiments that were performed represent pilot studies on which future work will be based, some interesting findings emerged.

The first experiment demonstrated that the conical trocar depressed the abdominal wall to a greater extent than the pyramidal trocar before it penetrated the peritoneum and facilitated entry of the cannula. This is in keeping with the assumptions in the literature (cf. section 1.8.5). However, this study also suggested that the sharpness of the leading point of the conical trocar and the profile of the remainder of the tip both exerted an influence on the passage of the trocar and cannula through the abdominal wall. Although the tip of the sharp conical trocar penetrated the peritoneum with less displacement of the abdominal wall than the blunt conical trocar, the final depth of incursion into the abdomen was similar for both blunt and sharp, conical trocars. The subsequent studies suggest that there are potentially serious sequelae to this observation.

Sharp tipped trocars (both pyramidal and conical) resulted in penetrating injuries upon contact with the bowel or aorta in all cases. Presumably, the sharp tip caught the serosa or adventitia and prevented lateral movement so that the bowel or aorta could not deflect. The implications of this are that any contact with abdominal viscera is potentially serious and that sharp conical trocars, which are introduced further into the abdominal cavity than pyramidal trocars before the cannula is completely inserted, will be more likely to come into contact with the viscera and cause injury.

The blunted conical trocars however, only caused a small depression in the bowel wall that did not penetrate the serosa, that could not be seen on the posterior wall in up to 40% of cases and vanished within a couple of minutes. Also, deflection occurred in most instances of "off-centre" contact. This implies that in relation to bowel, although the blunt conical trocar may penetrate further into the abdomen than the pyramidal trocar to achieve complete insertion of the cannula, it is unlikely to result in injury.

In the aortic model, deflection was more likely to occur and injuries, less likely to occur with blunt trocars than with sharp trocars. When the blunt trocars did cause an injury, the intimal wound was similar in size to the sharp trocars but the "bleed" was usually contained in a pseudo-aneurysm. There was a trend for the Hasson trocar to cause more deflections and fewer injuries but this did not reach statistical significance, presumably because the number of injuries was relatively low (n= 3). It is probable that these finding could improve the clinical outcome in the event of vascular trauma during insertion of a blunted trocar.

6.2 Conclusions

6.2.1 The influence of diameter

Cholecystectomy using smaller trocars, cannulae and instruments is widely applicable to elective cholecystectomy in a westernised population. Although the change from a 10mm to a 3mm laparoscope increased the time to clip and divide the cystic duct and artery, this had no impact on the overall time of the procedure. Despite a reduction in the consumption of parenteral analgesia among the patients in the micropuncture group, there was no corresponding reduction in pain scores. Overall, this study found no evidence that fine calibre instruments conferred any obvious major clinical benefits to the patients.

6.2.2 The influence of profile of the trocar tip

Pyramidal trocars encroach less into the abdominal cavity during the process of insertion, but will injure bowel or aorta upon contact. Sharp conical trocars depress the abdominal wall to a greater extent before they facilitate entry of the cannula and will injure bowel or aorta upon contact. Blunt conical trocars require to be inserted to the same depth as sharp conical trocars but are extremely unlikely to traumatise bowel. They can deflect aorta and are less likely to cause injury than sharp tipped trocars.

It is not possible from these data to quantify the risk of injury from a pyramidal trocar that facilitates entry of the cannula with less depression of the abdominal wall or a blunt conical

trocar that encroaches further into the abdomen but is less likely than a sharp trocar to cause injury should it contact bowel or aorta. However, it can be deduced that a blunt conical trocar is unlikely to cause injury if bowel is inadvertently contacted during open or closed access and that trocars with a sharp tip should probably be avoided.

6.3 Future Work

There are a number of questions that have arisen from the work presented in this thesis.

In relation to the size of the trocars, the impact on ambulatory cholecystectomy remains unknown. As 75% of day cases in the unit are discharged on the same day, a much larger study will be required to assess whether the reduction in parenteral analgesia improves same-day discharge rates. Due to the volume of work, the expertise and the organisation of the unit, this should be a feasible project. It would also allow an opportunity to collect visual analogue pain scores to assess whether or not the study was underpowered (as suggested by the retrospective analysis of the power of the data) or there is indeed no difference in pain scores.

Future experiments emanating from the work on profile of the trocar tip will include evaluation, with larger groups, of the influence of the diameter of the trocar, the shielded trocar and the relative "bluntness" of the tip. Some of this work is already underway using a modification of the apparatus described in chapter 3. Confirmation by histology of the mechanism of the injury sustained by the individual components of the aortic wall will also be performed. The injury pattern sustained by large veins (i.e. the vena cava) requires evaluation and it is also necessary to quantify the distance between the peritoneal surface of the abdominal wall and the viscera in an attempt to establish the relative safety of the pyramidal and blunt conical trocars.

The modified "Laparolift"™ device that was employed in chapters 3 and 4 promoted discussions with a local instrument manufacturer to create a device that will not only give

variable control over the rate of insertion but will also measure the force generated through a load cell within the system and store the information on computer. In addition, a device to standardise the tension of the abdominal wall specimen has been designed to circumvent the lack of pressure from the pneumoperitoneum. This has taken much longer than anticipated but has now become available.

Looking beyond the laboratory, a randomised clinical trial of conical and pyramidal trocars has been proposed and granted ethical approval. Intraoperatively, this will examine the peak forces generated during insertion of the trocar and removal of the cannula using the above device. The number of cannula displacement episodes and the incidence of gas leak will be assessed to determine if the smaller wound created by a conical trocar reduces the incidence of these irritating problems. Postoperatively, wound related complications will be recorded. The two main difficulties in commencing this trial however, have been firstly the design of a robust device for the insertion and removal of the trocars / cannulae that will incorporate a load cell but can still be sterilised and secondly, the development of a computer program that will record the information. It is anticipated that these difficulties should be overcome now that an instrument manufacturer has expressed an interest in providing technical assistance in the development of the equipment for the project.

6.4 Publications and presentations

6.4.1 Publication

Micropuncture Cholecystectomy: A randomised controlled trial.

Ainslie WG, Catton JA, Davides D, Dexter S, Gibson J, Larvin M, McMahon MJ, Moore M, Smith S, Vezakis A.

Surgical Endoscopy 2003;17(5):766-772

6.4.2 Oral Presentations

Micropuncture Cholecystectomy: A randomised controlled trial.

Ainslie WG, Catton JA, Davides D, Dexter S, Gibson J, Larvin M, McMahon MJ, Moore M, Smith S, Vezakis A.

8th World Congress of Endoscopic Surgery hosted by SAGES. New York

13th March 2002.

Prize paper, also presented as poster under presentation regulations.

Less Invasive Instruments.

Ainslie WG, Larvin M, McMahon MJ.

Invited presentation.

What's new, what's true? The Leeds Gastro-intestinal Course. 3rd June 1999

Micropuncture Laparoscopic Cholecystectomy.

Ainslie WG, Larvin M, McMahon MJ.

Invited presentation.

The Livingstone Surgical Travelling Club, Leeds. 14th May 1999

6.4.3 Poster presentation

Micropuncture Cholecystectomy: A randomised controlled trial.

Ainslie WG, Catton JA, Davides D, Dexter S, Gibson J, Larvin M, McMahon MJ, Moore M, Smith S, Vezakis A.

Association of Endoscopic Surgeons of Great Britain and Ireland, Dublin. 24th May 2002

APPENDIX 1

Anaesthetic regime for the randomised trial of conventional laparoscopic and micropuncture laparoscopic cholecystectomy.

Preop Patients ASA I or II (see below).

No premed

Drip - Hartmann's 1000mls all patients, but extra fluids as clinically required.

Induction Propofol + lignocaine

Atracurium

Diamorphine 5 mg (for patients 50-90 kg: reduce/ increase if light/heavy)

Droperidol 2 mg

Atropine 0.3 mg

Diclofenac 100 mg PR after induction

Orogastric tube

Maintenance Atracurium (PRN)

Nitrous oxide 70% : oxygen 30% + isoflurane to c. 1 MAC on CAPNOMAC (modify isoflurane according to blood pressure if necessary) and $EtCO_2$ maintained @ 4.5%. Record maximum MAC value used.

Reversal Neostigmine + glycopyrrolate : O_2 in recovery.

Post-op Anti-emetic requirements - to be scored : Cyclizine 50 mg 6 hrly as required.

Analgesic requirements - to be scored : Cocodamol $^{30}/_{500}$ 4-6 hrly as required.

Physical Status Scale: American Society of Anesthesiologists (ASA)

ASA	Physical Status
1	A normally healthy individual. No organic, physiological, biochemical or psychiatric disturbance.
2	A patient with mild to moderate systemic disease. This may or may not be related to the disorder requiring surgical treatment e.g. diabetes mellitus, hypertension.
3	A patient with severe systemic disease which is not incapacitating e.g. heart disease with limited exercise tolerance, uncontrolled hypertension or diabetes.
4	A patient with incapacitating systemic disease that is a constant threat to life with or without surgery e.g. congestive cardiac failure, severe and persistent angina.
5	A moribund patient who is not expected to live and where surgery is performed as a last resort e.g. ruptured aortic aneurysm.
E	A patient who requires an emergency operation.

APPENDIX 2

Leeds Institute For Minimally Invasive Therapy (LIMIT)

Pain and Sickness Scores

We would like to know how much pain or discomfort you might feel after your operation. You can show us by drawing a small cross on the lines as shown here.

For example,

If you have very little discomfort then you might mark it like this:-

No pain ——×—————————————— **Worst pain**

However, if you feel you have just about the worst pain you can imagine, you might mark it like this :-

No pain ——————————————×— **Worst pain**

If your pain was somewhere in between, then you might do this:-

No pain ————×———————————— **Worst pain**

There is also a space to write in how many painkillers you take each day and where you feel any pains. If you feel sick then you can tell us about it by circling a number using the system:-

0 - I do not feel sick at all
1 - I feel sick but am not vomiting
2 - I am retching
3 - I am vomiting

Please add any comments you wish to make about the operation at the end of the sheet. These would be most welcome. Please remember to bring this completed sheet with you to the outpatient clinic.

Thank you for your help.

The LIMIT team.

8 hours post-op

No pain ——————————————————— **Worst pain**

Pain location	-				
Number of tablets	-				
Sickness score	-	0	1	2	3

12 hours post-op

No pain ——————————————————— **Worst pain**

Pain location	-				
Number of tablets	-				
Sickness score	-	0	1	2	3

Day 1

No pain ——————————————————— **Worst pain**

Pain location -
Number of tablets -
Sickness score - 0 1 2 3

Day 2

No pain ——————————————————— **Worst pain**

Pain location -
Number of tablets -
Sickness score - 0 1 2 3

Day 3

No pain ——————————————————— **Worst pain**

Pain location -
Number of tablets -
Sickness score - 0 1 2 3

Day 4

No pain ——————————————— **Worst pain**

Pain location -
Number of tablets -
Sickness score - 0 1 2 3

Day 5

No pain ——————————————— **Worst pain**

Pain location -
Number of tablets -
Sickness score - 0 1 2 3

Day 6

No pain ——————————————— **Worst pain**

Pain location -
Number of tablets -
Sickness score - 0 1 2 3

Day 7

No pain ——————————————————— **Worst pain**

Pain location	-				
Number of tablets	-				
Sickness score	-	0	1	2	3

Comments?

APPENDIX 3

Interleukin-6 and ACTH assay methods

Interleukin-6 - This was measured using a quantitative sandwich enzyme-linked immunosorbent assay kits (ELISA). Each plate contained 96 wells, pre-coated with a murine monoclonal antibody, highly specific for human IL-6. The minimum detectable concentration of the kit was 0.7pg/ml, with an intra-assay sensitivity of 2.6% and inter-assay sensitivity of 4.5% (Quantikine Human IL-6 immunoassay, R&D Systems Inc, Minneapolis, USA).

IL-6 standard was reconstituted with 5ml of calibrator diluent to produce a stock solution at 300pg/ml and gently agitated for 15 minutes. 333µL of solution was mixed with a further 667µL of diluent to produce a standard of 100pg/ml. 500µL of this new standard was mixed with 500µL of diluent to produce a standard of 50pg/ml. This process was repeated until standards of 25pg/ml, 12.5 pg/ml, 6.25pg/ml and 3.12pg/ml were obtained. Pure diluent was used as a standard of 0pg/ml.

Buffered surfactant wash solution was supplied as 21 ml of concentrate that was diluted with distilled water to a volume of 500ml.

Substrate solution was produced by mixing 12.5 ml of stabilised hydrogen peroxide with 12.5 ml of tetramethylbenzidine, 15 minutes prior to use.

Procedure - All samples and standards were plated in duplicate. 100µL of assay diluent (buffered protein) was inserted into each well, to which 100µL of sample or standard were added and incubated at room temperature for 2 hours. Each well was aspirated and washed three times (400µL of wash buffer per rinse) and after the last wash, the plate was blotted against clean towelling paper. 200µL of IL-6 conjugate (polyclonal antibody against IL-6,

conjugated to horseradish peroxidase) was added to each well and incubated for a further 2 hours at room temperature. After a further wash, 200µL aliquots of substrate solution were added and incubated in the dark for 20 minutes. Stop solution (50µL of 2N sulphuric acid) was added to each well.

A Labsystems Multiskan RC micro plate reader and Genesis v3.00, PC based software (Life Sciences International (UK) Limited, Basingstoke, Hampshire, UK) measured the optical density at a wavelength of 450nm, with correction set for 540nm. A standard curve was generated for each set of samples and values for the duplicate specimens were averaged by the PC software package.

ACTH - This was measured using a quantitative sandwich ELISA kit Each plate contained 96 wells and was pre-coated with streptavidin. The minimum detectable concentration of the kit is 0.46pg/ml, with an intra-assay sensitivity of 3.6% and inter-assay sensitivity of 6.0% (ACTH ELISA #SDX018, Sangui BioTech Inc, California, USA).

ACTH standards A-F (Table app3.1) were reconstituted with 2ml of distilled water and after standing for 10 minutes, were gently inverted.

Procedure - All samples and standards were plated in duplicate. 200µL of sample or standard was pipetted into each well after which, 25µL of biotinylated antibody, followed by 25µL of enzyme labelled antibody were added. The microplate was covered with aluminium foil to protect it from light and then placed on an orbital shaker set at 170 rpm for 4 hours at room temperature. Each well was aspirated and washed five times with 350µL of the wash solution, then lotted dry. 150µL of tetramethylbenzidine substrate was dispensed into each well. Once again, the plates were covered in foil and placed on the orbital shaker for 30 minutes. 100µL of 1N sulphuric acid was added as a stop solution.

Buffered surfactant wash solution was supplied as 30ml of concentrate that was diluted with distilled water to a volume of 600ml.

Standard	Concentration of ACTH (pg/ml)
A	0
B	4.3
C	15.3
D	47
E	140
F	425

Table A3.1 Concentration of ACTH standards

A Labsystems Multiskan RC micro plate reader and Genesis v3.00, PC based software (Life Sciences International (UK) Limited, Basingstoke, Hampshire, UK) measured the optical density at a wavelength of 450nm, then at 405nm and a standard curve was generated for each microplate. Sample values below 150pg/ml were interpolated from the calibration curve generated at a wavelength of 450nm and those greater than 150pg/ml, from the curve generated at 405nm. Values of the duplicate specimens were averaged.

Official use only	99/1
ID	
State	
Thermometer	211
Score	
Date	

Health Questionnaire

EQ 5D

EQ-5D

An Instrument to Value Health

Describing your own health today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

Self-Care

I have no problems with self-care

I have some problems washing or dressing myself

I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities

I have some problems with performing my usual activities

I am unable to perform my usual activities

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety/Depression

I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

It will help us to understand your answers better if you complete the following questions.

1. **What is your age in years?** ☐

2. **Are you:**

male	**female**	Please tick appropriate box
☐ 1	☐ 2	

3. **Are you:**

a current smoker	☐ 1	Please tick appropriate box
an ex-smoker	☐ 2	
a never smoker	☐ 3	

4. **Which of the following best describes your main activity?**

in employment or self employment	☐ 1	Please tick appropriate box
retired	☐ 2	
housework	☐ 3	
student	☐ 4	
seeking work	☐ 5	
other (please specify)	☐ 6	

5. **Did your education continue after the minimum school leaving age?**

yes	**no**	Please tick appropriate box
☐ 1	☐ 2	

6. **Do you have a degree or equivalent professional qualification?**

yes	**no**	Please tick appropriate box
☐ 1	☐ 2	

7. **If you know your post code would you please write it here** ☐

Thank you for taking the time to complete this questionnaire.

APPENDIX 5

Randomised Trial of Standard and Micropuncture Laparoscopic Cholecystectomy.

Patient Information Sheet.

This is an invitation to participate in a research study.

You are going to have your gallbladder removed by laparoscopic surgery ("keyhole" surgery.) We have recently developed a modification of the keyhole technique using thinner instruments. This may reduce discomfort caused by the operation but it is not known for certain. We think that both variants of the operation are equally safe.

We invite you to join a study to compare the two types of "keyhole" operation.

If you agree to take part, you will be allocated at random to one or other type of operation once you have been anaesthetised. This means the type of operation would be determined by chance, like tossing a coin. You would therefore have an equal chance of having either operation. This is the fairest and most exact way of finding out if one kind of surgery is better. Neither you nor the nursing staff will be aware of the variant of the operation which you have received - but the information would be available if needed for your care.

After the operation we will ask you to record your level of discomfort and perform some basic functional tests such as getting out of bed, getting out of your chair and moving small objects. We will also take five blood samples and perform some simple breathing tests. In all other respects, your treatment will be routine.

After leaving the hospital, we will review your progress one week and then four weeks later in the outpatient clinic.

Participation in this research is **entirely voluntary** and you can decline to take part or withdraw at any time without affecting your care.

All information collected about you will be kept confidential and it will not be possible for anyone else to identify you from it. The findings of the study will be published in the medical research literature and as part of an MD thesis.

In the unlikely event that you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

If you have any queries, you can contact Mr W Ainslie at LIMIT (Leeds Institute for Minimally Invasive Therapy) at 0113 392 3466 or the address overleaf.

Leeds Institute For Minimally Invasive Therapy
LIMIT

Patient Consent Form

A randomised comparison of postoperative pain and recovery after standard laparoscopic cholecystectomy and micropuncture laparoscopic cholecystectomy.

	Please delete as applicable
1. I have read the Patient Information Sheet.	Yes/No
2. I have had the opportunity to ask questions and discuss the research study.	Yes/No
3. I am satisfied with the answers to my questions.	Yes/No
4. I have received enough information about this study.	Yes/No
5. I have spoken to Prof/Mr/Ms	Yes/No
6. I understand that I am free to withdraw from the study at any time without giving a reason and that it will not affect my future care.	Yes/No
7. I agree to take part in this research study.	Yes/No

Signature..... Date.....

Name.....

Signature of witness..... Date.....

Name.....

APPENDIX 6: DATA

CHAPTER 1

Introduction

	% reduction in FVC	
	OC	**LC**
Randomised studies		
Frazee *et al*, 1991	48	27
McMahon *et al*, 1994	46	35
Coelho *et al*, 1993	40	26
Putensen-Himmer *et al*, 1992	43	30
Cohort studies		
Joris *et al*, 1992	41	15
Mealy *et al*, 1992	48	22
Peters *et al*, 1993	35	23
Rademaker *et al*, 1992	71	42
Schauer *et al*, 1993	51	21

Values for the percentage reduction in forced vital capacity after open cholecystectomy and laparoscopic cholecystectomy as reported in the literature (Figure 1.3).

CHAPTER 2

Micropuncture Results

Patient Characteristics (Table 2.2)

Patient	Group	Age (years)	Sex	Height (m)	Weight (kg)	BMI (kg/m^2)	Symptom time (months)	Waiting list time (months)	ASA
MP001	MPLC	40	Female	1.66	76.3	27.7	19	7.5	2
MP002	LC	49	Female	1.67	61	21.9	19	12.8	1
MP003	LC	53	Male	1.88	107.5	30.4	10	7.0	1
MP004	MPLC	39	Female	1.55	58.1	24.2	36	10.3	1
MP005	LC	63	Female	1.64	72.8	27.1	12	4.2	2
MP006	MPLC	61	Female	1.64	62.2	23.1	12	7.0	2
MP007	LC	48	Female	1.69	88.2	30.9	37	4.0	1
MP008	MPLC	74	Male	1.71	64.5	22.1	3	0.7	1
MP010	MPLC	52	Female	1.69	92.2	32.3	30	7.2	1
MP011	MPLC	61	Female	1.56	85.3	35.1	10	5.9	1
MP012	LC	39	Male	1.74	79.4	26.2	8	7.5	1
MP014	MPLC	42	Female	1.56	89.8	36.9	58	6.9	1
MP015	MPLC	58	Female	1.55	60.9	25.3	10	1.9	1
MP016	LC	47	Female	1.58	74	29.6	10	5.0	1
MP017	MPLC	62	Female	1.58	52	20.8	18	2.1	2
MP018	MPLC	60	Female	1.57	57.4	23.3	60	9.4	1
MP019	LC	47	Female	1.69	72.7	25.5	0	9.0	1
MP020	MPLC	64	Female	1.58	57	22.8	24	12.2	1
MP021	MPLC	29	Female	1.63	86.5	32.6	1	0.2	1
MP022	LC	48	Female	1.63	82.2	30.9	6	1.5	1

Patient Characteristics (Table 2.2) continued

Patient	Group	Age (years)	Sex	Height (m)	Weight (kg)	BMI (kg/m^2)	Symptom time (months)	Waiting list time (months)	ASA
MP023	LC	58	Female	1.46	71.5	33.5	36	3.5	1
MP024	LC	52	Female	1.54	73	30.8	20	0.7	2
MP026	MPLC	71	Female	1.54	56.8	24.0	4	2.2	1
MP027	MPLC	47	Female	1.61	68.2	26.3	14	2.8	1
MP028	LC	53	Female	1.56	67.3	27.7	13	11.3	1
MP029	LC	29	Female	1.66	54	19.6	21	13.2	1
MP030	MPLC	68	Female	1.59	83.2	32.9	24	1.6	1
MP031	MPLC	46	Female	1.67	68.4	24.5	19	11.5	1
MP032	LC	29	Female	1.59	68.95	27.3	25	16.2	1
MP033	LC	53	Female	1.62	80.8	30.8	2	5.0	2
MP034	LC	48	Female	1.59	62.2	24.6	13	12.0	2
MP035	LC	43	Male	1.75	90.7	29.6	10	2.7	1
MP036	MPLC	70	Female	1.64	61	22.7	420	15.5	1
MP037	MPLC	53	Female	1.75	98.5	34.3	4	2.8	2
MP038	LC	71	Female	1.45	48.6	23.1	18	12.3	2
MP039	MPLC	63	Female	1.68	69.2	24.5	0	2.0	1
MP041	LC	54	Female	1.59	77.6	30.7	32	30.2	2
MP042	MPLC	52	Female	1.65	79	29.0	13	7.8	2
MP043	LC	55	Male	1.7	70.75	24.5	10	1.0	1
MP044	MPLC	34	Female	1.61	61	23.5	39	21.3	2

Extent of Biliary Disease (Table 2.3)

Patient	Group	Emergency admissions	Calculi	Size (cm)	Polyp	Contracted	Thickened	Adhesions	CBD dilated
MP001	MPLC	No	Yes	1	No	No	Yes	No	No
MP002	LC	No	Yes	2	No	No	No	No	No
MP003	LC	No	Yes	1.6	No	No	Yes	No	No
MP004	MPLC	No	Yes	2	No	No	No	No	No
MP005	LC	BC	Yes	0.5	No	No	Yes	Yes	Yes
MP006	MPLC	No	Yes	4	No	No	Yes	Yes	No
MP007	LC	AC	Yes	2	No	No	Yes	No	No
MP008	MPLC	BC	Yes	0.5	No	No	Yes	Yes	No
MP010	MPLC	No	Yes	0.2	No	No	Yes	No	No
MP011	MPLC	No	Yes	2	No	No	Yes	Yes	No
MP012	LC	AC	Yes	2	No	No	Yes	Yes	No
MP014	MPLC	No	Yes	1.5	No	No	Yes	Yes	No
MP015	MPLC	BC	Yes	0.25	No	No	Yes	No	No
MP016	LC	No	No	0	No	No	Yes	No	No
MP017	MPLC	No	Yes	1	No	No	Yes	Yes	No
MP018	MPLC	No	No	0	No	No	No	Yes	No
MP019	LC	No	Yes	0.5	No	No	Yes	No	No
MP020	MPLC	No	Yes	1	No	No	No	No	No
MP021	MPLC	No	Yes	0.25	No	No	No	No	No
MP022	LC	BC	Yes	0.5	No	No	No	Yes	No

CBD - common bile duct

AC - acute cholecystitis, **BC** - biliary colic

Extent of Biliary Disease (Table 2.3) continued

Patient	Group	Emergency admissions	Calculi	Size (cm)	Polyp	Contracted	Thickened	Adhesions	CBD dilated
MP023	LC	No	Yes	0.5	No	No	No	No	No
MP024	LC	No	Yes	0.5	No	No	Yes	Yes	No
MP026	MPLC	No	Yes	0.5	No	No	No	No	No
MP027	MPLC	No	Yes	3	No	Yes	No	Yes	No
MP028	LC	BC	Yes	0.25	No	No	No	No	No
MP029	LC	No	Yes	0.5	No	No	No	Yes	No
MP030	MPLC	No	Yes	2	No	No	Yes	Yes	No
MP031	MPLC	No	Yes	0.5	No	No	No	No	No
MP032	LC	No	Yes	0.4	No	Yes	Yes	Yes	No
MP033	LC	No	Yes	1	Yes	No	No	Yes	No
MP034	LC	No	Yes	0.5	No	No	Yes	Yes	No
MP035	LC	BC	Yes	0.4	No	Yes	Yes	Yes	No
MP036	MPLC	No	Yes	1	No	No	Yes	No	Yes
MP037	MPLC	No	Yes	2	No	Yes	Yes	No	No
MP038	LC	No	Yes	0.1	No	No	Yes	No	No
MP039	MPLC	No	No	0.1	Yes	No	No	Yes	No
MP041	LC	No	Yes	1.5	No	Yes	Yes	Yes	No
MP042	MPLC	No	Yes	1	No	No	No	Yes	No
MP043	LC	No	Yes	0.25	No	No	Yes	No	No
MP044	MPLC	No	Yes	0.25	No	No	Yes	Yes	No

CBD - common bile duct

AC - acute cholecystitis, **BC** - biliary colic

Operative Details (Table 2.4)

Patient	Group	Operator	Number of cannulae	Pressure (mmHg)	Max Pressure (mmHg)	CO_2 (litres)	IOC	Complications
MP001	MPLC	Consultant	4	7	7	71.3	No	Readmission - pain
MP002	LC	Consultant	4	7	7	-	Yes	
MP003	LC	Trainee	4	7	7	486	Yes	
MP004	MPLC	Consultant	4	7	7	102	Yes	
MP005	LC	Consultant	4	7	7	-	Yes	
MP006	MPLC	Consultant	4	7	7	120	Yes	Diarrhoea
MP007	LC	Consultant	4	15	15	131	No	
MP008	MPLC	Consultant	4	7	7	-	Yes	
MP010	MPLC	Trainee	5	10	10	222	Yes	
MP011	MPLC	Trainee	4	7	15	194	Yes	
MP012	LC	Consultant	4	7	10	143	No	
MP014	MPLC	Consultant	5	7	9	-	Yes	
MP015	MPLC	Consultant	4	8	8	-	No	
MP016	LC	Consultant	4	7	7	79.4	Yes	Haematoma - umbilicus
MP017	MPLC	Consultant	4	7	7	56.4	No	
MP018	MPLC	Consultant	4	7	7	140	No	
MP019	LC	Consultant	4	7	7	62.4	Yes	Haematoma - umbilicus
MP020	MPLC	Consultant	4	7	7	26.8	Yes	
MP021	MPLC	Consultant	5	7	7	40.3	Yes	
MP022	LC	Consultant	4	7	7	51.6	Yes	Haematoma - umbilicus

IOC - intraoperative cholangiogram

Operative Details (Table 2.4) continued

Patient	Group	Operator	Number of cannulae	Pressure (mmHg)	Max Pressure (mmHg)	CO_2 (litres)	IOC	Complications
MP023	LC	Consultant	4	7	10	125	Yes	
MP024	LC	Consultant	5	7	7	87.9	Yes	
MP026	MPLC	Consultant	4	7	7	69	Yes	
MP027	MPLC	Consultant	4	7	15	89.9	Yes	
MP028	LC	Consultant	5	7	7	51.9	Yes	Bile leak
MP029	LC	Trainee	4	7	7	92.3	Yes	
MP030	MPLC	Consultant	5	7	7	120	Yes	
MP031	MPLC	Trainee	4	7	7	140	Yes	
MP032	LC	Consultant	4	7	7	99.3	Yes	Stitch granuloma
MP033	LC	Consultant	5	7	7	53.6	Yes	Infection 5th port
MP034	LC	Trainee	4	7	7	92.3	Yes	
MP035	LC	Consultant	4	7	15	128	Yes	
MP036	MPLC	Consultant	4	7	7	67.5	Yes	
MP037	MPLC	Consultant	5	7	7	81.1	No*	
MP038	LC	Consultant	4	7	12	84.3	No	
MP039	MPLC	Consultant	4	7	7	33.6	No	
MP041	LC	Consultant	6	7	10	276	No	
MP042	MPLC	Trainee	4	7	7	62.5	Yes	
MP043	LC	Consultant	5	7	7	-	Yes	
MP044	MPLC	Consultant	4	7	7	60.3	Yes	

IOC - intraoperative cholangiogram

* - iodine allergy

Operative Times (Table 2.5)

Patient	Group	Cannulae inserted	Calot's Δ dissected	Cholan-giogram	Duct and artery divided	GB off liver	GB placed in bag	Total operative time
MP001	MPLC	-	-	-	-	-	-	1:14:00
MP002	LC	-	-	-	-	-	-	1:25:00
MP003	LC	-	-	-	-	-	-	2:20:00
MP004	MPLC	-	-	-	-	-	-	1:04:00
MP005	LC	-	-	-	-	-	-	1:21:00
MP006	MPLC	0:02:42	0:37:18	0:07:25	0:04:13	0:08:12	0:01:32	1:29:48
MP007	LC	0:06:58	0:37:02	0:02:00	0:00:30	0:10:56	0:01:11	1:26:30
MP008	MPLC	0:07:38	0:41:29	0:03:53	0:06:49	-	0:01:57	1:23:08
MP010	MPLC	0:06:24	1:05:36	0:08:30	0:04:29	-	0:02:23	1:42:47
MP011	MPLC	0:06:34	0:20:13	0:07:58	0:03:09	0:26:21	0:01:13	1:50:20
MP012	LC	0:03:30	0:27:10	-	-	0:13:48	-	1:11:06
MP014	MPLC	0:19:35	1:15:33	0:02:27	0:02:51	0:01:16	0:00:54	2:00:30
MP015	MPLC	0:02:00	0:26:07	0:07:03	0:00:51	0:06:49	0:02:02	0:59:32
MP016	LC	0:01:42	0:16:50	0:05:33	0:02:50	-	0:01:19	0:46:18
MP017	MPLC	0:06:03	0:37:45	0:07:33	0:12:23	0:03:14	0:02:22	1:40:27
MP018	MPLC	0:05:57	0:32:12	0:04:33	0:04:56	0:04:14	0:02:05	1:12:50
MP019	LC	0:05:55	0:11:18	0:10:33	0:00:54	0:06:55	0:02:12	1:04:02
MP020	MPLC	0:09:58	0:07:19	0:08:08	0:03:15	0:06:14	0:01:58	0:44:40
MP021	MPLC	0:10:15	0:13:43	0:06:11	0:05:20	0:03:44	0:00:38	0:51:45
MP022	LC	0:06:15	0:06:30	0:08:34	0:01:30	0:04:54	0:00:50	0:47:45

Quoted times are **hours:minutes:seconds**. For the first five procedures, only total operative times were collected. For a complete explanation of the timed segments of the procedures, see section 2.3.5

(-) – missing data.

Operative Times (Table 2.5) continued

Patient	Group	Cannulae inserted	Calot's A dissected	Cholan-giogram	Duct and artery divided	GB off liver	GB placed in bag	Total operative time
MP023	LC	0:05:57	0:17:03	0:06:04	0:00:19	0:04:15	-	1:02:59
MP024	LC	0:04:33	0:26:50	0:05:42	0:01:22	0:01:36	0:04:12	0:54:49
MP026	MPLC	0:10:23	0:17:19	0:08:01	0:10:58	0:15:35	-	1:16:52
MP027	MPLC	0:07:59	0:14:37	0:15:39	0:01:01	0:14:59	0:02:20	1:22:55
MP028	LC	0:05:07	0:15:15	0:05:38	0:00:30	0:03:34	0:01:31	0:38:27
MP029	LC	0:06:45	0:19:36	0:07:39	0:01:40	0:04:28	0:01:02	1:08:02
MP030	MPLC	0:10:40	0:22:42	0:20:58	0:10:49	0:01:01	0:05:36	1:27:08
MP031	MPLC	0:05:10	0:27:00	0:10:02	0:10:50	0:22:06	0:02:07	1:40:05
MP032	LC	0:09:35	0:34:42	0:23:47	0:03:31	0:08:35	0:01:31	1:39:10
MP033	LC	0:01:53	0:23:57	0:08:38	0:01:05	-	0:01:42	0:52:42
MP034	LC	0:01:52	0:26:08	0:03:50	0:01:01	0:04:49	0:01:00	0:56:06
MP035	LC	0:04:50	0:27:38	0:06:37	0:00:50	-	0:01:00	0:52:23
MP036	MPLC	0:06:36	0:14:54	0:21:20	0:02:23	0:04:38	0:02:43	1:02:50
MP037	MPLC	0:11:00	0:08:12	-	-	0:13:37	0:01:28	0:56:00
MP038	LC	0:08:56	0:09:33	-	-	0:07:16	0:00:52	1:03:54
MP039	MPLC	0:03:00	0:11:00	0:09:45	0:02:27	0:09:33	0:06:21	0:50:00
MP041	LC	0:06:12	0:08:48	-	-	0:03:06	0:01:16	0:54:12
MP042	MPLC	0:08:05	0:19:05	0:11:22	0:01:54	0:13:14	0:01:50	1:03:10
MP043	LC	0:05:29	0:19:23	0:05:14	0:01:24	0:02:44	0:03:21	0:45:43
MP044	MPLC	0:10:07	0:15:08	0:13:18	0:03:17	-	0:00:55	0:50:00

Quoted times are **hours:minutes:seconds**. For the first five procedures, only total operative times were collected. For a complete explanation of the timed segments of the procedures, see section 2.3.5.

(-) – missing data.

Visual Analogue Pain Scale Scores (Figure 2.7, Table 2.6)

Patient	Group	8 hrs	12 hrs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
MP001	MPLC	21	14	53	45	42	52	57	9	8
MP002	CLC	16	12	34	12	0	0	0	0	0
MP003	CLC	31	30	23	16	12	15	14	12	10
MP004	MPLC	5	7	64	35	60	28	13	3	2
MP005	CLC	13	13	14	38	23	21	24	24	27
MP006	MPLC	13	19	43	33	15	7	18	13	7
MP007	CLC	13	38	44	46	36	28	25	24	19
MP008	MPLC	10	10	14	6	6	8	7	5	8
MP010	MPLC	28	30	30	45	12	8	4	0	0
MP011	MPLC	20	38	36	39	18	38	6	3	2
MP012	CLC	49	46	44	48	47	43	36	30	40
MP014	MPLC	64	50	64	58	51	48	36	55	55
MP015	MPLC	29	22	23	15	15	18	13	9	8
MP016	CLC	26	48	45	27	14	11	15	3	38
MP017	MPLC	29	19	15	15	12	4	4	3	4
MP018	MPLC	21	22	21	19	9	6	7	42	16
MP019	CLC	10	48	47	34	22	17	11	6	7
MP020	MPLC	37	28	33	29	26	30	26	24	25
MP021	MPLC	40	37	39	31	27	24	10	4	4
MP022	CLC	37	41	37	33	29	14	12	9	13

Visual Analogue Pain Scale Scores (Figure 2.7, Table 2.6) continued

Patient	Group	8 hrs	12 hrs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
MP023	CLC	36	37	41	34	39	42	37	35	72
MP024	CLC	7	6	37	31	37	3	2	2	0
MP026	MPLC	21	16	12	25	0	10	5	3	2
MP027	MPLC	50	67	80	65	26	18	6	6	5
MP028	CLC	29	25	34	22	15	6	7	5	6
MP029	CLC	10	3	10	19	6	10	3	2	2
MP030	MPLC	78	22	35	24	7	0	5	3	1
MP031	MPLC	-	-	-	-	-	-	-	-	-
MP032	CLC	47	36	54	40	28	12	15	14	10
MP033	CLC	51	68	69	70	50	42	22	12	12
MP034	CLC	24	21	26	24	29	21	14	6	4
MP035	CLC	42	0	38	41	41	15	2	2	1
MP036	MPLC	20	20	18	14	13	10	7	4	2
MP037	MPLC	19	13	24	14	12	11	7	5	5
MP038	CLC	65	-	72	64	58	42	67	67	60
MP039	MPLC	4	12	20	22	23	4	8	5	1
MP041	CLC	31	51	54	66	59	35	20	20	13
MP042	MPLC	12	-	32	71	12	14	20	13	7
MP043	CLC	34	20	18	13	7	5	3	3	2
MP044	MPLC	79	57	32	34	40	40	43	44	24

Analgesia (Tables 2.7 and 2.8)

Patient	Group	Total* 24 hrs	Total* 1 wk	Parent-eral†	Oral 24 hrs	Oral 1 wk
MP001	MPLC	22	73	0	12	63
MP002	LC	22	28	0	12	18
MP003	LC	20	38	10	0	18
MP004	MPLC	22	52	0	12	42
MP005	LC	16	64	0	6	54
MP006	MPLC	16	40	0	6	30
MP007	LC	22	34	0	12	24
MP008	MPLC	10	10	0	0	0
MP010	MPLC	22	40	0	12	30
MP011	MPLC	34	85	0	24	75
MP012	LC	32	134	10	12	114
MP014	MPLC	28	142	0	18	132
MP015	MPLC	22	46	0	12	36
MP016	LC	28	67	0	18	57
MP017	MPLC	16	34	0	6	24
MP018	MPLC	28	58	0	18	48
MP019	LC	28	94	0	18	84
MP020	MPLC	10	19	0	0	9
MP021	MPLC	28	136	0	18	126
MP022	LC	22	91	0	12	81

All values are expressed as equivalents of morphine (mg). For conversion values, see table 2.1

* - Total quantity of intra-operative and post-operative doses (parenteral and oral)

† - Postoperative only

Analgesia (Tables 2.7 and 2.8) continued

Patient	Group	Total* 24 hrs	Total* 1 wk	Parent-eral†	Oral 24 hrs	Oral 1 wk
MP023	LC	34	79	0	24	69
MP024	LC	22	40	0	12	30
MP026	MPLC	16	22	0	6	12
MP027	MPLC	14	20	0	4	10
MP028	LC	16	40	0	6	30
MP029	LC	42	108	20	12	78
MP030	MPLC	22	28	0	12	18
MP031	MPLC	34	-	0	24	-
MP032	LC	38	110	10	18	90
MP033	LC	22	22	0	12	12
MP034	LC	32	56	10	12	36
MP035	LC	22	100	0	12	90
MP036	MPLC	16	22	0	6	12
MP037	MPLC	16	34	0	6	24
MP038‡	LC	33	135	10	18	120
MP039	MPLC	10	34	0	0	24
MP041	LC	22	76	0	12	66
MP042	MPLC	28	115	0	18	105
MP043	LC	22	22	0	12	12
MP044	MPLC	64	160	30	24	120

All values are expressed as equivalents of morphine (mg). For conversion values, see table 2.1

* - Total quantity of intra-operative and post-operative doses (parenteral and oral)

† - Postoperative only

‡ - Reduced intraoperative diamorphine (weight < 50 kg)

(-) - Missing data (not supplied by patient)

Nausea and vomiting (Table 2.9)

Patient	Group	8 hrs	12 hrs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Anti-emetic requested
MP001	MPLC	0	0	1	0	1	1	1	0	0	Yes
MP002	LC	0	0	0	0	1	0	0	0	0	No
MP003	LC	2	3	0	0	0	0	2	0	0	Yes
MP004	MPLC	0	0	0	0	0	0	0	0	0	No
MP005	LC	0	0	0	1	0	0	0	0	0	No
MP006	MPLC	0	0	0	0	0	0	0	0	0	No
MP007	LC	0	0	0	0	0	1	0	0	0	No
MP008	MPLC	0	0	0	0	0	0	0	0	0	No
MP010	MPLC	2	1	0	0	0	0	0	0	0	Yes
MP011	MPLC	1	0	0	0	0	0	0	0	0	No
MP012	LC	0	0	0	0	0	0	0	0	0	No
MP014	MPLC	2	1	1	1	1	1	1	1	1	Yes
MP015	MPLC	0	0	0	0	1	0	0	1	0	No
MP016	LC	3	1	3	0	0	0	1	0	0	Yes
MP017	MPLC	3	0	1	0	0	0	0	0	0	No
MP018	MPLC	0	0	0	0	0	0	0	0	0	No
MP019	LC	1	0	0	0	0	0	0	0	0	No
MP020	MPLC	1	0	0	0	0	0	0	0	0	Yes
MP021	MPLC	0	1	0	0	0	0	0	0	0	No
MP022	LC	1	0	1	1	0	0	0	0	0	No

0 – no nausea or vomiting

1 – nausea only

2 – retching, no vomiting

3 – vomiting

(-) – missing data

Nausea and vomiting (Table 2.9) continued

Patient	Group	8 hrs	12 hrs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Anti-emetic requested
MP023	LC	0	0	0	0	0	0	0	0	2	No
MP024	LC	0	0	0	0	1	0	0	0	0	Yes
MP026	MPLC	0	0	0	0	0	0	0	0	0	No
MP027	MPLC	2	0	0	0	0	0	0	0	0	Yes
MP028	LC	0	3	0	0	0	0	0	0	0	No
MP029	LC	0	0	2	3	1	0	1	0	0	Yes
MP030	MPLC	0	0	2	0	0	0	0	0	0	No
MP031	MPLC	-	-	-	-	-	-	-	-	-	Yes
MP032	LC	0	0	3	0	0	0	0	0	0	Yes
MP033	LC	1	2	3	1	0	0	0	0	0	No
MP034	LC	3	0	0	0	0	0	0	0	0	No
MP035	LC	1	0	1	1	1	0	0	0	0	No
MP036	MPLC	0	1	0	0	0	1	0	0	0	No
MP037	MPLC	3	1	0	0	0	0	0	0	0	No
MP038	LC	0	-	0	0	1	0	0	0	0	No
MP039	MPLC	1	0	0	1	0	0	0	0	0	No
MP041	LC	3	2	1	1	3	3	3	1	1	No
MP042	MPLC	3	-	0	0	0	0	0	0	0	Yes
MP043	LC	0	0	0	0	0	0	0	0	0	No
MP044	MPLC	2	0	0	0	0	0	0	0	0	Yes

0 – no nausea or vomiting

1 – nausea only

2 – retching, no vomiting

3 – vomiting

(-) – missing data

Summary of nausea and vomiting scores for the first postoperative week (cf. section 2.4.5)

Time	Group	Number with a score of:				Total number
		0	1	2	3	
8 hours	CLC	11	4	1	3	19
	MPLC	10	3	4	3	20
12 hours	CLC	13	1	2	2	18
	MPLC	14	5	0	0	19
Day 1	CLC	12	3	1	3	19
	MPLC	16	3	1	0	20
Day 2	CLC	13	5	0	1	19
	MPLC	18	2	0	0	20
Day3	CLC	13	5	0	1	19
	MPLC	17	3	0	0	20
Day4	CLC	17	1	0	1	19
	MPLC	17	3	0	0	20
Day5	CLC	15	2	1	1	19
	MPLC	18	2	0	0	20
Day6	CLC	18	1	0	0	19
	MPLC	18	2	0	0	20
Day7	CLC	17	1	1	0	19
	MPLC	19	1	0	0	20

Peak Expiratory Flow Rate (Figure 2.8, Table 2.10)

Patient	Group	PEFR 1	PEFR 2	PEFR 3	PEFR 4	PEFR 5
MP001	MPLC	397.08	343.2	343.62	411.54	-
MP002	LC	342.84	314.16	314.94	367.02	366.12
MP003	LC	616.2	601.92	589.38	715.12	-
MP004	MPLC	435	337.62	355.68	424.5	-
MP005	LC	450.9	410.22	382.26	487.5	418.8
MP006	MPLC	413.22	386.04	393.12	401.4	341.52
MP007	LC	402.6	183.72	283.98	316.38	369.96
MP008	MPLC	653.58	617.4	562.68	549.6	465.6
MP010	MPLC	488.46	316.74	368.22	470.82	500.4
MP011	MPLC	284.46	-	315.72	359.94	330.48
MP012	LC	612.9	225.54	432.9	589.38	605.7
MP014	MPLC	279.72	130.8	67.08	287.58	311.22
MP015	MPLC	349.14	151.8	226.44	298.98	331.8
MP016	LC	421.26	361.56	384.6	397.2	442.98
MP017	MPLC	323.82	223.14	229.8	286.5	289.38
MP018	MPLC	398.46	271.74	312.06	376.2	422.82
MP019	LC	387.12	323.34	338.1	373.74	364.44
MP020	MPLC	298.62	162.66	229.02	294.84	272.46
MP021	MPLC	401.4	318.72	291.06	438.3	434.58
MP022	LC	381.3	168.12	208.86	336.36	394.74

PEFR – Peak Expiratory Flow Rate (litres/second)

Time 1 – Preoperatively

Time 2 – 8 hours postoperatively

Time 3 – 24 hours postoperatively

Time 4 – 1 week postoperatively

Time 5 – 4 weeks postoperatively

(-) – missing data (non-attendance or declined test)

Peak Expiratory Flow Rate (Figure 2.8, Table 2.10) continued

Patient	Group	PEFR *1*	PEFR 2	PEFR 3	PEFR *4*	PEFR 5
MP023	LC	252.48	208.86	225.6	225.24	243.78
MP024	LC	274.74	304.92	278.94	357.36	330.84
MP026	MPLC	291.48	248.28	232.8	269.1	253.26
MP027	MPLC	481.86	241.26	215.64	372.78	410.34
MP028	LC	326.76	290.22	288.54	345.36	380.4
MP029	LC	344.58	214.32	155.04	253.74	311.52
MP030	MPLC	435.78	226.02	205.08	285.54	331.92
MP031	MPLC	265.44	232.32	212.64	301.14	295.5
MP032	LC	475.74	255.66	382.14	500.94	470.04
MP033	LC	364.38	201.42	237.42	382.98	317.7
MP034	LC	288.12	168.48	135.54	280.38	233.76
MP035	LC	565.92	292.92	335.34	436.62	434.1
MP036	MPLC	305.88	152.04	228.3	283.8	305.94
MP037	MPLC	435.9	326.28	346.62	431.64	370.26
MP038	LC	190.74	93.48	94.26	116.82	173.22
MP039	MPLC	438.78	325.62	-	445.44	437.88
MP041	LC	350.64	151.92	203.28	277.14	281.76
MP042	MPLC	406.98	-	246.24	-	-
MP043	LC	554.4	452.1	409.98	450.84	439.56
MP044	MPLC	337.68	245.88	232.92	251.22	249.6

PEFR – Peak Expiratory Flow Rate (litres/second)

Time 1 – Preoperatively

Time 2 – 8 hours postoperatively

Time 3 – 24 hours postoperatively

Time 4 – 1 week postoperatively

Time 5 – 4 weeks postoperatively

(-) – missing data (non-attendance or declined test)

Forced Vital Capacaity (Figure 2.8, Table 2.10)

Patient	Group	FVC 1	FVC 2	FVC 3	FVC 4	FVC 5
MP001	MPLC	3.39	2.94	3.3	3.55	-
MP002	LC	2.85	2.5	2.55	2.54	2.64
MP003	LC	4.91	5.12	5.05	5.32	-
MP004	MPLC	3.15	3.16	3.08	3.1	-
MP005	LC	3.35	2.12	2.32	2.49	2.58
MP006	MPLC	3.5	3.58	3.22	3.49	3.55
MP007	LC	2.78	1.8	2.03	2.88	2.78
MP008	MPLC	4.09	3.94	4.33	4.5	4.34
MP010	MPLC	4.16	2.76	2.83	3.83	3.95
MP011	MPLC	2.75	-	2.54	2.71	2.6
MP012	LC	5.31	2.48	3.81	4.73	5.13
MP014	MPLC	2.99	0.85	0.67	2.8	2.94
MP015	MPLC	3.55	2.34	2.94	3.14	3.21
MP016	LC	3.88	3.01	3.24	3.92	4.03
MP017	MPLC	2.57	2.33	2.27	2.45	2.42
MP018	MPLC	2.83	2.47	2.7	2.64	2.75
MP019	LC	4.23	2.79	3.6	3.96	4.06
MP020	MPLC	1.72	1.45	1.47	1.62	1.58
MP021	MPLC	3.5	1.58	3.14	3.47	3.38
MP022	LC	3.5	1.64	2.35	3.3	3.16

FVC – Forced Vital Capacity (litres)

Time 1 – Preoperatively

Time 2 – 8 hours postoperatively

Time 3 – 24 hours postoperatively

Time 4 – 1 week postoperatively

Time 5 – 4 weeks postoperatively

(-) – missing data (non-attendance or declined test)

Forced Vital Capacaity (Figure 2.8, Table 2.10) continued

Patient	Group	FVC 1	FVC 2	FVC 3	FVC 4	FVC 5
MP023	LC	1.71	1.39	1.45	1.55	1.65
MP024	LC	2.78	2.45	2.38	2.5	2.39
MP026	MPLC	1.99	1.61	1.53	1.93	1.87
MP027	MPLC	3.72	2.91	2.19	3.35	3.52
MP028	LC	2.84	2.91	2.5	2.79	2.93
MP029	LC	3.98	3.45	3.54	3.94	4.05
MP030	MPLC	3.05	2.37	2.35	2.64	2.94
MP031	MPLC	3.71	2.76	2.39	3.48	3.58
MP032	LC	3.4	2.57	2.09	3.4	3.19
MP033	LC	3.04	1.47	2.5	3.01	3
MP034	LC	3.03	2.63	2.73	2.8	2.4
MP035	LC	4.71	3.15	3.77	4.37	4.24
MP036	MPLC	2.55	1.71	2.2	2.37	2.42
MP037	MPLC	3.3	3.07	3.13	3.43	3.22
MP038	LC	1.43	0.89	0.89	1.49	1.58
MP039	MPLC	3.06	2.67	-	3.08	3.21
MP041	LC	2.67	1.64	1.87	2.66	2.12
MP042	MPLC	3.48	-	2.72	-	-
MP043	LC	4.03	3.7	3.85	3.98	4.2
MP044	MPLC	3.27	2.2	2.45	2.93	2.95

FVC – Forced Vital Capacity (litres)

Time 1 – Preoperatively

Time 2 – 8 hours postoperatively

Time 3 – 24 hours postoperatively

Time 4 – 1 week postoperatively

Time 5 – 4 weeks postoperatively

(-) – missing data (non-attendance or declined test)

Forced Expiratory Volume in 1 second (Figure 2.8, Table 2.10)

Patient	Group	FEV_1 1	FEV_1 2	FEV_1 3	FEV_1 4	FEV_1 5
MP001	MPLC	2.95	2.68	2.72	3	-
MP002	LC	2.24	2.19	2.25	2.13	2.19
MP003	LC	3.9	4.23	4.08	4.19	-
MP004	MPLC	2.93	2.78	2.69	2.73	-
MP005	LC	2.13	1.92	2.06	2.32	2.27
MP006	MPLC	2.69	2.74	2.67	2.82	2.65
MP007	LC	2.54	1.57	1.85	2.46	2.4
MP008	MPLC	3.57	3.49	3.52	3.56	3.53
MP010	MPLC	3.41	2.45	2.4	3.12	3.27
MP011	MPLC	2.12	-	2.03	2.13	2.04
MP012	LC	4.39	2.15	3.17	4.01	4.44
MP014	MPLC	2.28	0.81	0.42	2.27	2.31
MP015	MPLC	2.69	1.74	2.31	2.47	2.5
MP016	LC	2.83	2.33	2.36	2.9	3.05
MP017	MPLC	2.04	1.88	1.86	1.95	2.01
MP018	MPLC	2.46	1.97	2.26	2.26	2.37
MP019	LC	3.3	2.37	2.94	3.1	3.18
MP020	MPLC	1.41	1.23	1.27	1.4	1.38
MP021	MPLC	3.07	-	2.77	3.13	2.98
MP022	LC	2.98	1.32	1.96	2.79	2.83

FEV_1 – Forced Expiratory Volume in 1 second (litres)

Time 1 – Preoperatively

Time 2 – 8 hours postoperatively

Time 3 – 24 hours postoperatively

Time 4 – 1 week postoperatively

Time 5 – 4 weeks postoperatively

(-) – missing data (non-attendance or declined test)

Forced Expiratory Volume in 1 second (Figure 2.8, Table 2.10) continued

Patient	Group	FEV_1 1	FEV_1 2	FEV_1 3	FEV_1 4	FEV_1 5
MP023	LC	1.48	1.34	1.36	1.47	1.4
MP024	LC	2.34	2.15	2.04	2.04	2
MP026	MPLC	1.68	1.41	1.29	1.56	1.58
MP027	MPLC	2.82	2.31	1.78	2.57	2.66
MP028	LC	2.44	2.45	2.15	2.35	2.45
MP029	LC	3.3	2.8	2.24	2.95	2.76
MP030	MPLC	2.55	1.99	2.03	2.24	2.56
MP031	MPLC	2.69	2.41	1.89	2.62	2.69
MP032	LC	3.08	2.39	2.94	3.12	2.93
MP033	LC	2.61	1.38	2.19	2.66	2.48
MP034	LC	2.55	1.92	2.07	2.38	2.08
MP035	LC	4	2.71	3.24	3.74	3.61
MP036	MPLC	2.16	1.3	1.81	1.91	1.99
MP037	MPLC	2.66	2.43	2.5	2.79	2.63
MP038	LC	1.06	0.7	0.73	1.1	1.12
MP039	MPLC	2.24	2.15	-	2.24	2.31
MP041	LC	2.31	1.46	1.59	2.14	1.81
MP042	MPLC	2.85	-	2.33	-	-
MP043	LC	3.45	3.29	3.28	3.43	3.58
MP044	MPLC	2.71	2.05	2.14	2.5	2.48

FEV_1 – Forced Expiratory Volume in 1 second (litres)

Time 1 – Preoperatively

Time 2 – 8 hours postoperatively

Time 3 – 24 hours postoperatively

Time 4 – 1 week postoperatively

Time 5 – 4 weeks postoperatively

(-) – missing data (non-attendance or declined test)

EuroQoL EQ-5D Dimension Responses (Figure 2.9, Table 2.11)

Patient	Group	M1	M2	M3	M4	M5	C1	C2	C3	C4	C5	A1	A2	A3	A4	A5
MP001	MPLC	2	2	2	1	-	1	1	2	1	-	2	2	2	2	-
MP002	LC	1	2	1	1	-	1	1	1	1	-	1	2	2	2	-
MP003	LC	1	2	1	1	-	1	1	1	1	-	1	2	2	1	-
MP004	MPLC	1	1	1	1	-	1	1	1	1	-	1	1	1	2	-
MP005	LC	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1
MP006	MPLC	1	1	2	1	1	1	1	1	1	1	1	-	2	2	1
MP007	LC	1	1	1	1	1	1	1	1	1	1	2	3	3	2	1
MP008	MPLC	1	1	1	1	1	1	1	1	1	1	1	2	2	1	1
MP010	MPLC	1	2	1	1	1	1	2	1	1	1	1	2	1	1	1
MP011	MPLC	1	3	1	1	1	1	2	1	1	1	1	2	3	1	1
MP012	LC	1	2	2	2	1	1	2	1	2	1	1	3	2	3	2
MP014	MPLC	1	2	2	2	2	1	3	2	2	2	1	3	2	2	2
MP015	MPLC	1	3	2	1	1	1	2	2	1	1	1	3	2	2	1
MP016	LC	1	1	1	1	1	1	1	1	1	1	1	2	2	1	1
MP017	MPLC	1	1	1	1	1	1	1	1	1	1	1	2	2	2	1
MP018	MPLC	1	2	1	1	1	1	1	1	1	1	1	2	1	1	1
MP019	LC	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
MP020	MPLC	1	2	1	1	1	1	2	1	1	1	1	2	2	2	2
MP021	MPLC	1	2	2	1	1	1	2	2	1	1	1	2	2	2	1
MP022	LC	2	2	2	1	1	1	2	2	1	1	2	3	2	2	1

Responses to each of the EQ-5D dimensions at time points 1 (preop), **2** (8 hours), **3** (24 hours), **4** (1 week), **5** (4 weeks). For EQ-5D questionnaire, refer to appendix 4

Dimensions **M** - Mobility
C - Self-care
A - Activities

Responses **1** - No problems
2 - Some problems
3 - Unable to
(-) - Missing value

EuroQoL EQ-5D Dimension Responses (Figure 2.9, Table 2.11) continued

Patient	Group	M1	M2	M3	M4	M5	C1	C2	C3	C4	C5	A1	A2	A3	A4	A5
MP023	LC	1	2	1	2	1	1	2	1	1	1	1	3	2	2	2
MP024	LC	1	2	1	1	1	1	1	1	1	1	1	2	2	2	1
MP026	MPLC	1	1	1	1	1	1	1	1	1	1	2	1	2	2	1
MP027	MPLC	1	1	2	1	1	1	2	2	1	1	1	3	3	2	1
MP028	LC	1	2	2	1	1	1	2	1	1	1	1	2	2	1	1
MP029	LC	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
MP030	MPLC	1	2	1	1	1	1	1	1	1	1	1	3	1	1	1
MP031	MPLC	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1
MP032	LC	1	3	1	1	1	1	3	1	1	1	1	2	1	1	1
MP033	LC	-	1	1	1	1	-	1	1	1	1	-	1	1	1	1
MP034	LC	1	2	2	1	1	1	2	2	1	1	1	2	2	1	1
MP035	LC	1	2	2	1	1	1	2	2	1	1	1	3	3	2	1
MP036	MPLC	1	2	2	1	1	1	1	2	1	1	1	2	2	1	1
MP037	MPLC	1	2	2	1	1	1	2	1	1	1	1	2	2	1	1
MP038	LC	1	3	1	1	1	1	1	1	1	1	2	2	2	2	1
MP039	MPLC	1	1	1	1	1	1	1	1	1	1	1	1	3	2	1
MP041	LC	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1
MP042	MPLC	1	2	1	1	1	1	1	1	1	1	1	2	1	1	1
MP043	LC	1	2	1	1	1	1	1	1	1	1	1	2	1	1	1
MP044	MPLC	2	3	2	2	2	2	3	3	2	2	2	3	3	2	2

Responses to each of the EQ-5D dimensions at time points **1** (preop), **2** (8 hours), **3** (24 hours), **4** (1 week), **5** (4 weeks). For EQ-5D questionnaire, refer to appendix 4

Dimensions **M** - Mobility
C - Self-care
A - Activities

Responses **1** - No problems
2 - Some problems
3 - Unable to
(-) - Missing value

EuroQoL EQ-5D Dimension Responses (Figure 2.9, Table 2.11) continued

Patient	Group	P1	P2	P3	P4	P5	AD1	AD2	AD3	AD4	AD5
MP001	MPLC	2	2	2	2	-	2	1	1	1	-
MP002	LC	1	2	1	1	-	1	1	1	1	-
MP003	LC	1	2	2	1	-	1	1	1	1	-
MP004	MPLC	1	1	2	2	-	2	1	1	1	-
MP005	LC	2	2	2	2	2	1	1	1	1	1
MP006	MPLC	1	2	2	2	1	1	1	1	1	1
MP007	LC	2	2	2	2	1	2	1	1	1	1
MP008	MPLC	1	2	2	1	1	1	1	1	1	1
MP010	MPLC	1	2	2	1	1	1	1	1	1	1
MP011	MPLC	1	2	2	2	1	2	1	1	1	1
MP012	LC	1	2	2	2	2	1	1	1	1	1
MP014	MPLC	1	3	2	2	2	2	2	2	2	2
MP015	MPLC	1	2	2	2	1	2	2	2	2	2
MP016	LC	1	2	2	2	1	1	1	1	1	1
MP017	MPLC	1	2	2	1	1	1	1	1	1	1
MP018	MPLC	2	2	2	1	1	2	1	1	1	1
MP019	LC	1	2	2	2	2	1	1	1	1	1
MP020	MPLC	1	2	2	2	1	1	1	1	1	1
MP021	MPLC	1	2	2	2	2	1	1	1	1	1
MP022	LC	2	2	2	2	2	1	1	1	1	1

Responses to each of the EQ-5D dimensions at time points **1** (preop), **2** (8 hours), **3** (24 hours), **4** (1 week), **5** (4 weeks). For EQ-5D questionnaire, refer to appendix 4

Dimensions **P** - Pain
AD - Anxiety/ Depression

Responses **1** - None
2 - Some
3 - Severe
(-) - Missing value

EuroQoL EQ-5D Dimension Responses (Figure 2.9, Table 2.11) continued

Patient	Group	P1	P2	P3	P4	P5	AD1	AD2	AD3	AD4	AD5
MP023	LC	2	2	2	3	2	1	1	1	1	1
MP024	LC	1	2	2	1	1	2	1	1	1	1
MP026	MPLC	2	2	2	2	1	1	1	1	1	1
MP027	MPLC	1	2	2	2	1	1	1	1	1	1
MP028	LC	2	2	2	1	1	1	1	1	1	1
MP029	LC	1	1	1	2	2	1	1	1	1	1
MP030	MPLC	2	2	1	2	1	1	1	1	1	1
MP031	MPLC	1	2	2	1	1	1	1	1	1	1
MP032	LC	1	2	2	1	1	1	1	1	1	1
MP033	LC	-	2	2	2	1	-	1	1	1	1
MP034	LC	1	2	2	1	1	1	2	1	1	1
MP035	LC	1	2	2	1	2	1	1	1	1	1
MP036	MPLC	1	2	2	1	2	1	1	1	1	1
MP037	MPLC	1	2	2	1	1	1	1	1	1	1
MP038	LC	2	2	2	2	2	2	2	2	1	1
MP039	MPLC	1	2	2	1	1	1	1	1	1	1
MP041	LC	1	2	2	2	1	1	1	1	1	1
MP042	MPLC	1	2	2	2	2	1	1	1	1	1
MP043	LC	2	2	1	1	1	1	1	1	1	1
MP044	MPLC	2	3	2	2	2	2	2	2	2	2

Responses to each of the EQ-5D dimensions at time points **1** (preop), **2** (8 hours), **3** (24 hours), **4** (1 week), **5** (4 weeks). For EQ-5D questionnaire, refer to appendix 4

Dimensions **P** - Pain
AD - Anxiety/ Depression

Responses **1** - None
2 - Some
3 - Severe
(-) - Missing value

Summary of the responses to the EuroQoL dimensions (Figure 2.9, Table 2.11)

Mobility

Time	Group	Number with a score of:		
		1	2	3
Preop	CLC	17	1	0
	MPLC	19	2	0
8 hours	CLC	7	10	2
	MPLC	8	10	3
24 hours	CLC	14	5	0
	MPLC	12	9	0
1 week	CLC	17	2	0
	MPLC	19	2	0
4 weeks	CLC	17	0	0
	MPLC	17	2	0

Self-care

Time	Group	Number with a score of:		
		1	2	3
Preop	CLC	18	0	0
	MPLC	20	1	0
8 hours	CLC	12	6	1
	MPLC	12	7	2
24 hours	CLC	16	3	0
	MPLC	14	6	1
1 week	CLC	18	1	0
	MPLC	19	2	0
4 weeks	CLC	17	0	0
	MPLC	17	2	0

Usual activities

Time	Group	Number with a score of:		
		1	2	3
Preop	CLC	15	3	0
	MPLC	18	3	0
8 hours	CLC	5	9	5
	MPLC	4	11	5
24 hours	CLC	7	10	2
	MPLC	6	11	4
1 week	CLC	9	9	1
	MPLC	8	13	0
4 weeks	CLC	15	2	0
	MPLC	16	3	0

Pain

Time	Group	Number with a score of:		
		1	2	3
Preop	CLC	11	7	0
	MPLC	16	5	0
8 hours	CLC	1	18	0
	MPLC	1	18	2
24 hours	CLC	3	16	0
	MPLC	1	20	0
1 week	CLC	8	10	1
	MPLC	8	13	0
4 weeks	CLC	9	8	0
	MPLC	14	5	0

Summary of the responses to the EuroQoL dimensions (Figure 2.9, Table 2.11) continued

Anxiety and depression

Time	Group	Number with a score of:		
		1	2	3
Preop	CLC	15	3	0
	MPLC	14	7	0
8 hours	CLC	17	2	0
	MPLC	18	3	0
24 hours	CLC	18	1	0
	MPLC	18	3	0
1 week	CLC	19	0	0
	MPLC	18	3	0
4 weeks	CLC	17	0	0
	MPLC	16	3	0

EuroQoL EQ-5D Scores (Figure 2.10-11, Table 2.12)

Patient	Group	Th 1	Th 2	Th 3	Th 4	Th 5	WI 1	WI 2	WI 3	WI 4	WI 5
MP001	MPLC	70	80	65	90	-	0.62	0.69	0.59	0.76	-
MP002	LC	85	55	75	89	-	1	0.69	0.88	0.88	-
MP003	LC	90	75	80	90	-	1	0.69	0.76	1	-
MP004	MPLC	84	85	65	75	-	0.85	1	0.8	0.76	-
MP005	LC	80	80	85	90	90	0.8	0.8	0.8	0.76	0.8
MP006	MPLC	80	70	66	60	80	1	-	0.69	0.76	1
MP007	LC	73	71	73	79	97	0.69	0.43	0.43	0.76	1
MP008	MPLC	89	85	88	98	99	1	0.76	0.76	1	1
MP010	MPLC	90	75	87	91	97	1	0.59	0.8	1	1
MP011	MPLC	50	63	77	75	88	0.85	0.07	0.43	0.8	1
MP012	LC	98	50	81	70	98	1	0.26	0.69	0.26	0.76
MP014	MPLC	95	20	30	80	85	0.85	-0.18	0.52	0.52	0.52
MP015	MPLC	84	44	80	79	95	0.85	-0.06	0.52	0.69	0.85
MP016	LC	85	80	75	85	99	1	0.76	0.76	0.8	1
MP017	MPLC	90	78	88	91	99	1	0.76	0.76	0.88	1
MP018	MPLC	60	39	50	65	79	0.73	0.69	0.8	1	1
MP019	LC	90	50	60	80	80	1	0.8	0.8	0.8	0.8
MP020	MPLC	80	55	65	70	90	1	0.59	0.76	0.76	0.88
MP021	MPLC	90	75	85	90	98	1	0.59	0.59	0.76	0.8
MP022	LC	85	45	60	85	90	0.69	0.26	0.59	0.76	0.8

Scores for the EQ-5D questionnaires at time points **1** (preop), **2** (8 hours), **3** (24 hours), **4** (1 week), **5** (4 weeks). For EQ-5D questionnaire, refer to appendix x

Th – Health Thermometer Scores

WI – Weighted Index Scores

(-) – Missing values

EuroQoL EQ-5D Scores (Figure 2.10-11, Table 2.12) continued

Patient	Group	Th 1	Th 2	Th 3	Th 4	Th 5	WI 1	WI 2	WI 3	WI 4	WI 5
MP023	LC	67	76	70	61	70	0.8	0.26	0.76	0.16	0.76
MP024	LC	90	90	99	99	100	0.85	0.69	0.76	0.88	1
MP026	MPLC	80	80	83	79	90	0.76	0.8	0.76	0.76	1
MP027	MPLC	95	30	25	81	100	1	0.33	0.26	0.76	1
MP028	LC	80	60	70	90	100	0.8	0.59	0.69	1	1
MP029	LC	50	40	55	98	30	1	1	1	0.8	0.8
MP030	MPLC	75	55	95	98	100	0.8	0.36	1	0.8	1
MP031	MPLC	95	88	90	96	96	1	0.8	0.8	0.88	1
MP032	LC	93	50	50	100	99	1	-0.04	0.8	1	1
MP033	LC	-	50	45	70	85	-	0.8	0.8	0.8	1
MP034	LC	89	49	79	95	95	1	0.52	0.59	1	1
MP035	LC	94	60	60	95	95	1	0.26	0.26	0.88	0.8
MP036	MPLC	84	63	70	76	78	1	0.69	0.59	1	0.8
MP037	MPLC	80	45	44	88	98	1	0.59	0.69	1	1
MP038	LC	60	51	60	65	65	0.69	0.11	0.69	0.76	0.8
MP039	MPLC	98	88	89	96	99	1	0.8	0.43	0.88	1
MP041	LC	78	74	76	94	98	1	0.8	0.8	0.76	1
MP042	MPLC	85	51	60	98	98	1	0.69	0.8	0.8	0.8
MP043	LC	80	70	80	89	94	0.8	0.69	1	1	1
MP044	MPLC	31	22	30	40	35	0.52	-0.43	0.08	0.52	0.52

Scores for the EQ-5D questionnaires at time points **1** (preop), **2** (8 hours), **3** (24 hours), **4** (1 week), **5** (4 weeks). For EQ-5D questionnaire, refer to appendix x

Th – Health Thermometer Scores

WI – Weighted Index Scores

(-) – Missing values

Interleukin-6 (Figure 2.12, Table 2.13)

Patient	Group	Sample1	Sample2	Sample3	Sample4	Sample5
MP001	MPLC	2.2	1	1.2	13.2	0.8
MP002	LC	0.2	0.1	2.2	16.4	2
MP003	LC	0.7	1.4	11.1	4.3	10.1
MP004	MPLC	0.3	7.9	15.8	35.6	4.6
MP005	LC	1.7	0	1	111.3	20.4
MP006	MPLC	3.3	2	2.9	19.1	14.6
MP007	LC	0.9	1.6	14.8	19.4	14.7
MP008	MPLC	1.9	0.6	3.6	8	2
MP010	MPLC	3.5	2	6.8	19.1	59
MP011	MPLC	1.3	0.5	4.5	20.6	7.7
MP012	LC	1.2	1.2	2.4	4	11.7
MP014	MPLC	4.2	2.3	7.5	32.5	2.8
MP015	MPLC	0.1	0	1.3	9.4	6
MP016	LC	0.8	0.9	7.2	2.9	5.8
MP017	MPLC	0.7	5.6	2.1	2.4	1.7
MP018	MPLC	0	0	1.8	4.6	27.9
MP019	LC	0.6	1.1	36.8	6.9	8.2
MP020	MPLC	0	0.7	7.5	4.4	4.9
MP021	MPLC	2.2	1.6	7.1	5.8	15.6
MP022	LC	1.6	2.9	8.8	18.5	7.4

Sample times are defined in section 2.3.9.Results are expressed in pg/ml.

Interleukin-6 (Figure 2.12, Table 2.13) continued

Patient	Group	Sample1	Sample2	Sample3	Sample4	Sample5
MP023	LC	3	3.7	9.6	15.4	-
MP024	LC	0.9	0.6	17.2	7.4	2.4
MP026	MPLC	1.5	1.7	2.2	48.7	11.1
MP027	MPLC	1.7	1.2	8.7	25.7	28.4
MP028	LC	1.8	0.5	7.9	6	7.6
MP029	LC	1.8	0.3	4	4.4	4.8
MP030	MPLC	22.8	26.1	43	179.24	130.28
MP031	MPLC	0.4	0.7	5.4	7.7	6.1
MP032	LC	0.1	1.1	3.8	17.5	13.6
MP033	LC	1.6	0.6	4.8	5.9	9.5
MP034	LC	0.3	0.1	4.4	4.8	5.7
MP035	LC	0.9	3	3.6	5	6.2
MP036	MPLC	3.8	3.1	30.4	20.4	45
MP037	MPLC	2.2	3.4	19.5	52.6	38.8
MP038	LC	3.2	3.2	20.1	36.8	27.2
MP039	MPLC	1.7	1.6	10.9	423.94	73.9
MP041	LC	2.2	1.7	15.1	40	92.2
MP042	MPLC	1.1	1.7	18.7	5.9	10.9
MP043	LC	1.7	0.4	24.5	9	18
MP044	MPLC	1.1	0.2	21.8	19.9	25

Sample times are defined in section 2.3.9.Results are expressed in pg/ml.

Adrenocorticotrophic Hormone (Figure 2.13, Table 2.14)

Patient	Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
MP001	MPLC	28.2	14.4	31.9	11.5	29.4
MP002	LC	16.2	12.5	37.4	9.3	6.3
MP003	LC	25.1	19	370.06	85.4	15.4
MP004	MPLC	11.7	106.5	104	33.2	5.6
MP005	LC	6.6	7	16.1	6.6	4.5
MP006	MPLC	52.1	34.7	25.7	35	31.1
MP007	LC	17.5	51.7	335.56	15.6	11.3
MP008	MPLC	25.6	33	136.4	35.2	33.2
MP010	MPLC	13.8	25.4	172.6	38.3	4.1
MP011	MPLC	23.2	163	314.4	31.8	6.7
MP012	LC	29.4	25.1	110.2	16.5	10.3
MP014	MPLC	14.5	14.6	302.3	32.4	33.7
MP015	MPLC	88.1	68.2	40.3	13.5	8.1
MP016	LC	34.8	28.3	686.3	28.2	10.8
MP017	MPLC	25.5	72.4	45.6	192.57	8.4
MP018	MPLC	34.4	40	22.7	13.6	5.7
MP019	LC	10.7	10.1	105.6	166.3	7
MP020	MPLC	29.9	22.6	63.3	8.1	9.7
MP021	MPLC	14.3	16	10.2	10.7	9.4
MP022	LC	35.7	70.3	181.3	47.4	10.8

Sample times are defined in section 2.3.9. Results are expressed in pg/ml.

Adrenocorticotrophic Hormone (Figure 2.13, Table 2.14) continued

Patient	Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
MP023	LC	10.5	20.4	110.8	10.6	-
MP024	LC	50.4	54	123	7.5	6.9
MP026	MPLC	21.2	17.2	13.9	155.5	7.7
MP027	MPLC	32.7	32	360.3	297.7	30.9
MP028	LC	15	12.6	10	133.2	12.8
MP029	LC	9.5	24	29.7	26.2	4.1
MP030	MPLC	28.8	27.2	211.5	6.7	6.1
MP031	MPLC	23.4	49.6	61	16.7	9.2
MP032	LC	18.6	120.9	118	10.4	10
MP033	LC	71.7	84.3	382.9	31.6	7.8
MP034	LC	29.8	63.2	49.8	309.4	6.1
MP035	LC	18.7	19.3	171.1	56	13
MP036	MPLC	18.8	26.1	196.4	24.8	14.3
MP037	MPLC	33.8	28.7	24.4	7	15.4
MP038	LC	32.4	36.1	42	15.5	9.6
MP039	MPLC	21.8	27.7	19.3	227.9	14.8
MP041	LC	41.9	50.3	162.8	34.6	15.2
MP042	MPLC	15.7	27	32.5	13.2	12.9
MP043	LC	46.7	28.9	14.4	18.7	13.5
MP044	MPLC	8.9	8	264.7	303.2	7.6

Sample times are defined in section 2.3.9. Results are expressed in pg/ml.

Vasopressin (Figure 2.14, Table 2,15)

Patient	Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
MP001	MPLC	1.95	1.75	1.65	2.25	1.85
MP002	LC	1.95	1.7	2.25	3.75	2
MP003	LC	1.15	1.25	11.55	14.5	1.7
MP004	MPLC	2.4	5.6	26.45	17.45	1.9
MP005	LC	2.55	1.4	2.35	8.75	4.05
MP006	MPLC	2.45	2	2.7	2.3	3
MP007	LC	1.8	2.35	31.15	4.65	2.35
MP008	MPLC	1.95	2	3.95	1.9	1.75
MP010	MPLC	2	1.95	34.4	28.55	2.2
MP011	MPLC	2.15	2.15	4.1	3.2	2.05
MP012	LC	1.95	2.45	2.45	1.75	4.15
MP014	MPLC	2.55	1.95	14.15	18.5	2.65
MP015	MPLC	1.5	2	3.3	2.4	2.1
MP016	LC	2.1	1.55	19.55	2.9	2.05
MP017	MPLC	11.6	5.2	26.55	78.05	3.35
MP018	MPLC	1.5	2.3	3.55	8.25	2.15
MP019	LC	3.55	2.3	32.2	2.7	32.9
MP020	MPLC	2.55	2.3	2.15	16.14	2.39
MP021	MPLC	3.21	1.85	4.94	5.31	4.75
MP022	LC	1.6	2.3	25.4	7.05	2.2

Sample times are defined in section section 2.3.9. Results are expressed in pg/ml.

Vasopressin (Figure 2.14, Table 2,15) continued

Patient	Group	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
MP023	LC	1.75	7.19	3.61	2	-
MP024	LC	3.05	12.86	4.71	4.33	2.3
MP026	MPLC	0.85	0.95	7.75	9.7	2.25
MP027	MPLC	2.08	3.6	51.88	24.17	7
MP028	LC	2.25	2.55	3.55	14.44	2.75
MP029	LC	3.06	7.94	2.85	2.4	3.75
MP030	MPLC	5.25	1.1	20.8	5.56	5.63
MP031	MPLC	4.94	4.4	7.15	2.85	3
MP032	LC	2.22	13.45	2.86	8.86	6.71
MP033	LC	4.55	6.05	27.17	10.35	4.5
MP034	LC	1.21	1.25	14.55	11.14	1.38
MP035	LC	1.31	0.5	27.1	11.38	2.25
MP036	MPLC	1.21	0.78	16.64	12.08	0.88
MP037	MPLC	1.25	1	3.6	2.38	1.64
MP038	LC	0.86	1.7	3.61	1.43	0.81
MP039	MPLC	1.31	0.55	1.13	11.19	2.13
MP041	LC	1.5	1	25.2	17.9	5.1
MP042	MPLC	1.6	0.95	3	1.6	1.5
MP043	LC	5.38	4.25	4.38	2.7	4.75
MP044	MPLC	2.33	1.15	16.25	39.92	1.17

Sample times are defined in section section 2.3.9. Results are expressed in pg/ml.

Mobility Data (Figure 2.15-19, Tables 2.16 – 20)

Patient	Group	Time to rise from bed					Time to rise from chair					Time to walk 20m				
		Pre -op	8 hrs	24 hrs	1 wk	4 wks	Pre -op	8 hrs	24 hrs	1 wk	4 wks	Pre -op	8 hrs	24 hrs	1 wk	4 wks
MP001	MPLC	4.3	5.9	6.4	3	-	2.4	3	4.2	1.3	-	15.6	20.3	22	13.3	-
MP002	LC	3.9	5.9	4.4	2.6	2.8	1.4	2.5	2.3	1.2	1.2	17	28.2	21.3	15.8	15.5
MP003	LC	2.3	5.3	5.4	2.3	-	1.3	1.4	1.2	0.9	-	13.3	15.5	13.8	11.5	-
MP004	MPLC	3.5	2.7	2.8	2.7	-	1.3	1.4	1.4	1.4	-	16.6	16.5	17	14.2	-
MP005	LC	3.1	4	4.1	2.7	2.8	1	1.2	1.2	1.1	1.1	16.1	17.2	17.6	14.4	14.5
MP006	MPLC	2.6	4.6	6.1	3.2	2.9	1.2	1.5	1.5	1.5	1.3	14.8	15.7	17.4	15.7	15.1
MP007	LC	2.6	5.8	5.7	4	2.1	1.3	2	1.5	1.8	1	14.4	17.5	15.5	14.4	14.7
MP008	MPLC	2	4.2	3.2	2.1	2.5	1.1	1.8	1.2	1	1.1	15.4	15.4	13.5	12.5	12.8
MP010	MPLC	3.2	9.1	5.1	3	2.5	1.5	2.5	1.6	1.3	1.2	16.9	31.9	20.2	15.6	15.6
MP011	MPLC	5.6	R	6.4	4.2	4.1	1.7	R	1.8	1.3	1.1	20.5	R	31.2	20.1	18.5
MP012	LC	3.2	8.2	3.8	3.9	2.6	1.4	2.7	1.6	1.4	1.1	17.4	28.9	21.1	19.3	15.3
MP014	MPLC	4.2	R	29.4	5.6	3.2	1.3	R	3.6	1.8	1.2	18.2	R	33.4	21.5	17.6
MP015	MPLC	2.7	14.4	5.6	2.8	2.5	1	2.6	1.7	0.9	0.8	18	36.6	26.7	18.6	15.6
MP016	LC	3.6	4.8	4.4	2.7	2.4	1.7	1.2	1.3	1.3	0.8	17.5	22.9	20	17.3	15.6
MP017	MPLC	2.3	5.2	3.5	2.2	1.9	1.1	1.4	1.1	1	1.1	15	19.3	18.6	16.5	15.4
MP018	MPLC	3	6.4	3.1	1.9	1.7	1	2.2	1.2	0.9	0.9	15.5	25.2	18.7	14.7	14
MP019	LC	2.1	4.4	2.8	2.4	2.3	1	1	1	0.9	1	14.6	21.8	17	15.1	15
MP020	MPLC	3.5	8.9	5.1	3.8	3.1	1.4	3.4	1.6	1.6	1.6	19.3	37.2	24.9	21.7	21.2
MP021	MPLC	3	20.4	11.6	5.7	3.9	0.9	7.9	3.6	1.4	1.4	16.4	38.6	29.3	16	15.2
MP022	LC	3.2	16.5	5.4	5.6	3.8	1.3	3.3	1.9	1.4	1.3	18.3	44.9	30.7	19.8	16.8

For an explanation of the tests, see section 2.3.10. All times are in seconds.

(-) - missing data – patients did not return for follow-up

R - patients declined to mobilise.

Mobility Data (Figure 2.15-19, Tables 2.16 – 20) continued

Patient	Group	Time to rise from bed					Time to rise from chair					Time to walk 20m				
		Pre -op	8 hrs	24 hrs	1 wk	4 wks	Pre -op	8 hrs	24 hrs	1 wk	4 wks	Pre -op	8 hrs	24 hrs	1 wk	4 wks
MP023	LC	6	13.2	16.5	4.3	4.2	1.6	2.9	2.5	1.6	1.4	21.8	57.3	27.8	24	20
MP024	LC	2.9	11.3	4.7	3.4	2.7	1.2	3.7	1.5	1.3	1.2	17.3	62	25	18	16.2
MP026	MPLC	3	4.8	3.8	3.3	2.8	1.4	1.3	1.2	1.3	0.9	17.1	22.4	19.6	16.1	16
MP027	MPLC	2.9	8.3	15.3	3.2	2.6	1.3	2.4	3.4	1.5	1.4	17.3	28.5	27.4	16.8	16.2
MP028	LC	2.4	9.2	6.9	3.1	2.6	1	2	2.3	1.3	1.3	16.7	39.9	36.2	14.6	14.8
MP029	LC	3	4.5	3.1	2.5	2.5	1	1.3	1.3	1.1	1.1	16.6	20	17.9	14.4	13
MP030	MPLC	4.3	8.2	6.2	3.2	5	1.9	2.2	1.9	1.6	1.7	19.2	24.3	19.2	18.3	20.2
MP031	MPLC	2.9	5.4	4.8	3	2.7	1	1.2	1.2	1	1.1	16.8	21.8	17.3	15.9	15.7
MP032	LC	3.3	12.4	5.4	2.4	3.2	1.1	3.9	2.8	1.2	1	17.8	36.2	32.4	17.9	17
MP033	LC	3.2	6.6	5.3	2.3	2.8	1.2	1.7	1.4	1	1.1	18.7	23.3	20.9	15.9	15.8
MP034	LC	3.1	6.7	5.8	2.7	2.6	1.1	2.5	2.1	1.3	1.1	18.2	37.7	26.8	16.3	16.1
MP035	LC	3.8	6.4	6.3	4.1	2.9	1.7	2.8	2	1.8	1.5	18.2	29.9	20.5	16.8	15.8
MP036	MPLC	4.2	9.9	9.3	3.6	3.6	2.3	2.1	2.5	1.7	1.7	19	33.9	22.9	18	16.7
MP037	MPLC	3.6	4.9	4.1	3.5	3	1.5	1.3	1.4	1.3	1.2	15.1	18.3	18.6	15.4	15.3
MP038	LC	6.7	R	9.4	4.8	4.9	2.7	R	4.2	1.9	2.5	27.2	R	44.2	22.3	20.9
MP039	MPLC	4.1	5.1	5	2.5	3	1.2	1.6	1.8	1.1	1.2	16.4	27.1	30	15.3	15.6
MP041	LC	2.6	6.3	3.9	4.1	3	0.8	2.4	1.5	1.4	1.2	16.8	30.2	20.8	18.4	15.7
MP042	MPLC	2.5	R	7.4	2.8	2.7	0.8	R	2.1	0.8	0.9	17.1	R	27.9	14.2	15.7
MP043	LC	3.6	4.9	2.6	2.3	2.4	1.5	1.9	1.3	1.3	1.3	20.8	25.1	17.6	17.1	16.1
MP044	MPLC	3.4	R	13.8	6.4	6.5	1.2	R	3.2	2.9	1.8	23.4	R	35.7	26.6	21.8

For an explanation of the tests, see section 2.3.10. All times are in seconds.

(-) - missing data – patients did not return for follow-up

R - patients declined to mobilise.

Mobility Data (Figure 2.15-19, Tables 2.16 – 20) continued

Patient	Group	Time to move objects left					Time to move objects right				
		Pre-op	8 hrs	24 hrs	1 wk	4 wk	Pre-op	8 hrs	24 hrs	1 wk	4 wks
MP001	MPLC	13.5	17	18.2	15.2	-	14	18.2	15.2	12.4	-
MP002	LC	15.3	20.3	18.5	16.8	15.5	13.2	21.4	18.6	15.8	14.1
MP003	LC	11.9	14.8	12.3	10.9	-	12.1	14.2	12.2	11.5	-
MP004	MPLC	17.7	15.4	14.1	12.9	-	17.7	15.4	14.1	13.7	-
MP005	LC	14.5	14.7	13.9	11.6	13	13.4	13.9	13.5	11.8	12.3
MP006	MPLC	10.9	13.7	13.4	12.9	11.5	12.2	15.1	13.9	12.5	12.6
MP007	LC	14.5	15.6	13.9	14.9	14.7	15.3	17.7	15	15.7	14.1
MP008	MPLC	13.7	11.1	11	9.7	11.4	11.5	11.2	9.7	9.2	10
MP010	MPLC	18.6	28.6	18.3	17.6	14.5	17.2	23.6	18.4	14.6	13.5
MP011	MPLC	18.1	R	23.6	18.8	18.3	18	R	21.9	18.7	17.3
MP012	LC	17	20.9	19	20.4	18.7	18.6	23.7	19.8	19	17.3
MP014	MPLC	23.8	R	32.6	23.9	20.6	19.8	R	27.8	22.4	19.5
MP015	MPLC	14.7	27.7	21.8	18.9	16.8	14.2	29.6	21.9	21.1	13.5
MP016	LC	15.1	17.4	15.8	14.4	14.6	15	16.7	18	13.7	13.8
MP017	MPLC	14.9	18.5	15.8	14.5	13	13.4	16	14.2	13.8	11.8
MP018	MPLC	15.9	21.8	17.5	14.2	15.2	16.1	22.3	17.5	14.2	14.5
MP019	LC	13.6	14	13.5	12.3	11.7	11.9	14.9	12.2	12.2	11.4
MP020	MPLC	18.9	23.4	20.1	18.5	18.9	19.3	25	18.5	19.1	17.9
MP021	MPLC	13.3	20.4	18.7	11.5	11.6	11.2	22.5	18.6	12	11.1
MP022	LC	18.8	27.7	22.8	18	17.4	18	33.3	21.7	17.7	16.4

For an explanation of the tests, see section 2.3.10. All times are in seconds.

(-) - missing data – patients did not return for follow-up

R - patients declined to mobilise.

Mobility Data (Figure 2.15-19, Tables 2.16 – 20) continued

Patient	Group	Time to move objects left					Time to move objects right				
		Pre-op	8 hrs	24 hrs	1 wk	4 wk	Pre-op	8 hrs	24 hrs	1 wk	4 wks
MP023	LC	22.9	25.9	23.8	22.9	19.9	21.6	24.8	21.3	23	18.6
MP024	LC	14.4	18.9	13	14	12.7	14.7	19	12.1	13.2	12.5
MP026	MPLC	20.4	26	20.2	18.5	18	20.4	24.9	19.7	17.9	17.1
MP027	MPLC	21.5	32.9	25.8	20	18.4	21.8	30.1	26.3	19.8	18
MP028	LC	16.8	19.9	19.7	15.2	13.7	15.1	18.3	18.9	14.9	14.1
MP029	LC	14.4	15.3	14.7	13.2	13.8	13.7	15.3	15.2	13	13.7
MP030	MPLC	15.9	25.3	20.6	16.1	12	14.8	22.1	19.2	15.1	13.7
MP031	MPLC	17.1	18.4	17.4	15.9	14.2	14.7	19.7	17.4	15.1	13.5
MP032	LC	18	25.1	20.6	15.1	14.9	16.9	24.1	20.2	16	13.7
MP033	LC	18.5	20.5	17.9	12.5	12	14.4	18.8	16.3	13.2	10.9
MP034	LC	18.6	21	18.7	16.1	16.4	16.1	20.6	20.9	16.4	15.1
MP035	LC	21.9	24.3	25	21.8	21.7	20.6	23.5	21.9	20.1	19.3
MP036	MPLC	22.8	29.4	22.4	22.8	18.5	22.1	22.2	22.3	21.8	19
MP037	MPLC	16.3	18.8	17.9	15.3	15.5	16	17.4	17.7	15.4	14.3
MP038	LC	24.7	R	21.2	21.4	21.5	28	R	27.8	27.5	20.9
MP039	MPLC	13.9	16.5	21.4	13.6	13.3	13.8	15.6	18.2	13.8	12
MP041	LC	16	17.9	18.2	16.4	13.7	17.3	17.8	17.2	16.7	13.7
MP042	MPLC	13.3	R	26.4	14	14.3	15.8	R	20.3	13.8	13
MP043	LC	15.4	16.7	13.2	13.6	13.2	14.5	16.9	14.8	14	13.9
MP044	MPLC	17.3	R	26.4	18.5	20.9	17.8	R	27.5	20.3	21.3

For an explanation of the tests, see section 2.3.10. All times are in seconds.

(-) - missing data – patients did not return for follow-up

R - patients declined to mobilise.

CHAPTER 3. Manual insertion of trocars

Trocar	D1	D2	D3	Distance	D1(calc)	D2(calc)	D3(calc)
Pyramidal	16	40	58	180	15.0	37.6	54.5
Pyramidal	17	41	54	180	16.0	38.5	50.8
Pyramidal	24	43	60	120	23.0	41.3	57.6
Pyramidal	16	40	55	90	15.5	38.8	53.4
Pyramidal	27	48	61	165	25.5	45.4	57.6
Pyramidal	27	48	61	165	25.5	45.4	57.6
Pyramidal	33	65	66	135	31.5	62.1	63.0
Pyramidal	26	48	58	105	25.1	46.3	56.0
Pyramidal	20	42	53	150	19.0	39.9	50.4
Pyramidal	19	41	51	120	18.2	39.4	49.0
Conical sharp	28	56	66	180	26.3	52.6	62.0
Conical sharp	42	68	80	150	39.9	64.6	76.0
Conical sharp	36	61	73	150	34.2	58.0	69.4
Conical sharp	28	60	67	90	27.2	58.2	65.0
Conical sharp	40	65	81	165	37.8	61.4	76.5
Conical sharp	42	67	76	135	40.1	64.0	72.6
Conical sharp	44	73	81	135	42.0	69.7	77.4
Conical sharp	45	72	81	105	43.4	69.5	78.2
Conical sharp	38	63	72	150	36.1	59.9	68.4
Conical sharp	34	60	68	120	32.6	57.6	65.3
Conical blunt	37	56	66	180	34.8	52.6	62.0
Conical blunt	45	63	71	150	42.8	59.9	67.5
Conical blunt	58	72	81	120	55.7	69.1	77.8
Conical blunt	41	60	73	120	39.4	57.6	70.1
Conical blunt	43	68	75	165	40.6	64.3	70.9
Conical blunt	42	59	70	105	40.5	56.9	67.6
Conical blunt	59	76	85	135	56.3	72.6	81.2
Conical blunt	52	71	79	105	50.2	68.5	76.2
Conical blunt	41	59	71	150	39.0	56.1	67.5
Conical blunt	36	51	63	120	34.6	49.0	60.5

D1 – distance at stage 1, **D2** – distance at stage 2, **D3** – distance at stage 3

The measurements are in millimetres.

The last three columns on the right are the calculated distances using the formula **D(calc)=D(3000–distance)/3000**. For explanation, see section 3.3.3.2

CHAPTER 3. Insertion of trocars by mechanical device

Type	D1	D2	D3	Distance	D1(calc)	D2(calc)	D3(calc)
Pyramidal	14	39	52	180	13.2	36.7	48.9
Pyramidal	16	38	46	180	15.0	35.7	43.2
Pyramidal	21	42	55	150	20.0	39.9	52.3
Pyramidal	23	45	58	150	21.9	42.8	55.1
Pyramidal	24	44	55	120	23.0	42.2	52.8
Pyramidal	27	50	60	120	25.9	48.0	57.6
Pyramidal	21	45	58	180	19.7	42.3	54.5
Pyramidal	20	40	55	180	18.8	37.6	51.7
Pyramidal	28	52	66	150	26.6	49.4	62.7
Pyramidal	22	46	59	120	21.1	44.2	56.6
Conical sharp	27	49	55	180	25.4	46.1	51.7
Conical sharp	30	51	60	180	28.2	47.9	56.4
Conical sharp	29	61	66	150	27.6	58.0	62.7
Conical sharp	38	56	65	150	36.1	53.2	61.8
Conical sharp	34	61	68	120	32.6	58.6	65.3
Conical sharp	36	63	71	120	34.6	60.5	68.2
Conical sharp	43	73	80	180	40.4	68.6	75.2
Conical sharp	38	68	75	150	36.1	64.6	71.3
Conical sharp	40	62	71	180	37.6	58.3	66.7
Conical sharp	36	70	80	120	34.6	67.2	76.8
Conical blunt	32	50	54	180	30.1	47.0	50.8
Conical blunt	31	48	55	180	29.1	45.1	51.7
Conical blunt	39	58	63	150	37.1	55.1	59.9
Conical blunt	41	58	63	150	39.0	55.1	59.9
Conical blunt	42	62	68	120	40.3	59.5	65.3
Conical blunt	40	53	63	120	38.4	50.9	60.5
Conical blunt	42	-	-	180	39.5	-	-
Conical blunt	45	66	76	150	42.8	62.7	72.2
Conical blunt	56	70	80	150	53.2	66.5	76.0
Conical blunt	46	-	-	120	44.2	-	-

D1 – distance at stage 1, **D2** - distance at stage 2, **D3** – distance at stage 3

The measurements are in millimetres.

The last three columns on the right are the calculated distances using the formula **D(calc)=D(3000–distance)/3000**. For explanation, see section 3.3.3.2

CHAPTER 4. Central injuries of the bowel

Trocar	Deflection	Shape of Injury*	Side
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Pyramidal	No	Stellate	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical sharp	No	Puncture	Anterior/posterior
Conical blunt	Yes	Crush	Anterior
Conical blunt	No	Crush	Anterior
Conical blunt	No	Crush	Anterior
Conical blunt	No	Crush	Anterior/posterior
Conical blunt	No	Crush	Anterior/posterior
Conical blunt	No	Crush	Anterior/posterior
Conical blunt	No	Crush	Anterior/posterior
Conical blunt	No	Crush	Anterior/posterior
Conical blunt	No	Crush	Anterior
Conical blunt	No	Crush	Anterior/posterior

* Stellate wound – tri-radiate incision through bowel wall

Puncture wound – pin-point defect through bowel wall

Crush wound – circular crush injury, no penetration of the bowel wall

CHAPTER 4. "Off-centre" injuries of the bowel

Trocar	Deflection	Shape of Injury*	Side
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Puncture	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Puncture	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Pyramidal	No	Stellate	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical sharp	No	Puncture	Anterior/Posterior
Conical blunt	Yes	Crush	Anterior/Posterior
Conical blunt	No	Crush	Anterior/Posterior
Conical blunt	Yes	Crush	Anterior/Posterior
Conical blunt	Yes	Crush	Anterior/Posterior
Conical blunt	Yes	Crush	Anterior/Posterior
Conical blunt	Yes	Crush	Anterior/Posterior
Conical blunt	Yes	Crush	Anterior
Conical blunt	Yes	Crush	Anterior/Posterior
Conical blunt	No	Crush	Anterior
Conical blunt	No	Crush	Anterior/Posterior

* Stellate wound – tri-radiate incision through bowel wall
Puncture wound – pin-point defect through bowel wall
Crush wound – circular crush injury, no penetration of the bowel wall

CHAPTER 5. Effect of trocar tip profile on aortic injuries

Trocar profile	Front Adv	Front Int	Shape front	Back Int	Back Adv	Shape back	Deflect	Leakage
Pyramidal	3	7.3	Stellate	3.2	2.2	Stellate	No	Spurter
Pyramidal	7	10.4	Stellate	3	2	Stellate	No	Spurter
Pyramidal	2.5	7.3	Linear	3	1.5	Stellate	No	Spurter
Pyramidal	4.3	3.2	Stellate	2.3	1.5	Stellate	No	Spurter
Pyramidal	4.2	6.2	Linear	2.8	1.5	Stellate	No	Spurter
Pyramidal	2.8	4.7	Linear	2.8	1.8	Linear	No	Spurter
Pyramidal	3.2	5.2	Linear	1.3	1.3	Linear	No	Spurter
Pyramidal	2.3	5.1	Linear	1.8	0.7	Stellate	No	Spurter
Pyramidal	3.8	3	Stellate	2.5	1.5	Stellate	No	Spurter
Pyramidal	2.5	3	Stellate	2.3	1.2	Stellate	No	Spurter
Conical sharp	3.5	7.8	Linear	2.7	0.3	Linear	No	Spurter
Conical sharp	3.2	5.9	Linear	2	0.5	Linear	No	Spurter
Conical sharp	2.2	5.5	Linear	3.7	0.7	Linear	No	Spurter
Conical sharp	0	4	Linear	2.4	0	Linear	No	Spurter
Conical sharp	1	2.9	Linear	0.6	0.8	Linear	No	Spurter
Conical sharp	1.4	3.4	Linear	1.1	0.8	Linear	No	Spurter
Conical sharp	2	4.8	Linear	1.7	0.4	Linear	No	Spurter
Conical sharp	2.6	5.1	Linear	0.7	0.4	Linear	No	Spurter
Conical sharp	1.2	5.7	Linear	1.9	0.7	Linear	No	Spurter
Conical sharp	1.5	3.8	Linear	2.4	1.5	Linear	No	Spurter

Front adv – adventitial wound, front wall
Front int – intimal wound, front wall
Shape - wound shape
Measurements are in millimetres

Back adv – adventitial wound, back wall
Back int – intimal wound, back wall

Effect of trocar tip profile on aortic injuries (continued)

Trocar profile	Front Adv	Front Int	Shape front	Back Int	Back Adv	Shape back	Deflect	Leakage
Conical blunt	0.7	8	Linear	2.5	1.1	Linear	No	Contained
Conical blunt	4.5	6	Linear	2.5	1	Linear	No	Spurter
Conical blunt	1.1	6.5	Linear	3.3	1.5	Linear	No	Contained
Conical blunt	0	5.9	Linear	4.1	1.1	Linear	No	Contained
Conical blunt	0	6.7	Linear	2.4	0.5	Linear	No	Contained
Conical blunt	0	0	-	0	0	-	Yes	-
Conical blunt	0	0	-	0	0	-	Yes	-
Conical blunt	0	5.7	Linear	3	0	Linear	No	Contained
Conical blunt	0	0	-	0	0	-	Yes	-
Conical blunt	1.8	4.7	Linear	3.5	0	Linear	No	Spurter
Hasson	0	0	-	0	0	-	Yes	-
Hasson	0	0	-	0	0	-	Yes	-
Hasson	0	0	-	0	0	-	Yes	-
Hasson	0	0	-	0	0	-	Yes	-
Hasson	2.1	7	Linear	5.1	3.7	Linear	No	Contained
Hasson	0	0	-	0	0	-	Yes	-
Hasson	0	0	-	0	0	-	Yes	-
Hasson	0	0	-	0	0	-	Yes	-
Hasson	4.1	8.2	Linear	6.9	1.6	Linear	Yes	Contained
Hasson	0.6	7.5	Linear	6.4	0	Linear	No	Contained

Front adv – adventitial wound, front wall
Front int – intimal wound, front wall
Shape - wound shape
Measurements are in millimetres

Back adv – adventitial wound, back wall
Back int – intimal wound, back wall

REFERENCES

- Agnifili A, Ibi I, Verzaro R, Colangeli A, De Bernardinis G (1993) Peri-operative pulmonary function, pain and stress response after cholecystectomy performed via laparotomy or laparoscopy: Comparison between laparoscopy and laparotomy. Min Inv Ther 2:283-288
- Aitola P, Airo I, Kaukinen S, Ylitalo P (1998) Comparison of N_2O and CO_2 pneumoperitoneums during laparoscopic cholecystectomy with special reference to postoperative pain. Surg Laparosc Endosc 2:140-144
- Aktan AÖ, Büyükgebiz O, Yeğen C, Yalin R (1994) How minimally invasive is laparoscopic cholecystectomy? Surg Laparosc Endosc 4:18-21
- Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL (1985) Rapid dissolution of gallstones by methyl tert-butyl ether. Preliminary observations. New Engl J Med 312:217-220
- Aoki T, Tanii M, Takahashi K, Tateda T, Miyazawa A (1994) Cardiovascular changes and plasma catecholamine levels during laparoscopic cholecystectomy. Anesth Analg 78:S8
- Azurin DJ, Go LS, Arroyo LR, Kirkland ML (1995) Trocar site herniation following laparoscopic cholecystectomy and the significance of an incidental pre-existing umbilical hernia. Am Surg 61:718-720
- Badia JM, Whawell SA, Scott-Coombes DM, Abel PD, Williamson RCN, Thompson JN (1996) The peritoneal and systemic cytokine response to laparotomy. Br J Surg 83:347-348
- Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ (1992) Systemic cytokine response after major surgery. Br J Surg 79:757-760
- Baraka A, Jabbour S, Hammoud R, Aouad M, Najjar F, Khoury G, Sibai A (1994) End-tidal carbon dioxide tension during laparoscopic cholecystectomy. Anaesthesia 49:304-306

- Barkun JS, Barkun AN, Sampalis JS, Fried G, Taylor B, Wexler MJ, Goresky CA, Meakins JL (1992) Randomised controlled trial of laparoscopic versus mini cholecystectomy. Lancet 340:1116-1119
- Basso L, McCollum PT, Darling MRN, Tocchi A, Tanner WA (1992) A descriptive study of pregnant women with gallstones. Relation to dietary and social habits, education, physical activity, height and weight. Eur J Epidem 8:629-633
- Bellón JM, Manzano L, Bernados L, Ga-Honduvila N, Buján J, Alvarez-Mon M (1997) Cytokine levels after open and laparoscopic cholecystectomy. Eur Surg Res 29:27-34
- Berci G (1998) Laparoscopic cholecystectomy using fine-caliber instruments. Smaller is not necessarily better. Surg Endosc 12:197
- Berggren U, Gordh T, Grama D, Haglund U, Rastad J, Arvidsson D (1994) Laparoscopic versus open cholecystectomy: Hospitalisation, sick leave, analgesia and trauma responses. Br J Surg 81:1362-1365
- Bessell JR, Karatassas A, Jamieson GG, Maddern GJ (1995) Hypothermia induced by laparoscopic insufflation: A randomized study in a pig model. Surg Endosc 9:791-795
- Bhoyrul S, Mori T, Way LW (1996) Radially expanding dilatation. A superior method of laparoscopic trocar access. Surg Endosc 10:775-778
- Bisgaard T, Klarskov B, Trap R, Kehlet H, Rosenberg J (2000) Pain after microlaparoscopic cholecystectomy. Surg Endosc 14:340-344
- Bisgaard T, Klarskov B, Trap R, Kehlet H, Rosenberg J (2002) Microlaparoscopic vs conventional laparoscopic cholecystectomy. A prospective randomised double-blind trial. Surg Endosc 16:458-464
- Böhm B, Knigge M, Kraft M, Gründel K, Boenick U (1998) Influence of different trocar tips on abdominal wall penetration during laparoscopy. Surg Endosc 12:1434-1438
- Bougard FS, Pianim NA, Leighton TA, Dubecz S, Davis IP, Lippmann M, Klein S, Liu S (1993) Helium insufflation for laparoscopic operation. Surg Gynecol Obstet 177:140-146

- Bonjer HJ, Hazebroek EJ, Kazemier G, Giuffrida MC, Meijer WS, Lange JF (1997) Open versus closed establishment of pneumoperitoneum in laparoscopic surgery. Br J Surg 84:599-602
- Borgatta L, Gruss L, Barad D, Kaali SG (1990) Direct trocar insertion versus Veress needle use for laparoscopic sterilization. J Reprod Med 35:891-894
- Boswell WC, Odom JW, Rudolph R, Boyd CR (1993) A method for controlling bleeding from abdominal wall puncture site after laparoscopic surgery. Surg Laparosc Endosc 3:47-48
- Bozzini PH (1806) Lichtleiter, eine Erfindung zur Anschauung innerer Theile und Krankheiten nebst der Abbildung. Journal der practischen Arzneykunde und Wundarzneykunst (Berlin) 24:107-124
- Brooks R and the EuroQOL group (1996) EuroQOL: The current state of play. Health Policy 37:53-72
- Carey PD, Wakefield CH, Thayeb A, Monson JRT, Darzi A, Guillou PJ (1994) Effects of minimally invasive surgery on hypochlorous acid production by neutrophils. Br J Surg 81:557-560
- Castell J, Klapproth J, Gross V, Walter E, Andus T, Snyers L, Content J, Heinrich PC (1990) Fate of interleukin-6 in the rat. Eur J Biochem 189:113-118
- Champault G, Cazacu F, Taffinder N (1996) Serious trocar accidents in laparoscopic surgery: A French survey of 103852 operations. Surg Laparosc Endosc 6:367-370
- Chang W. How the medical video camera became the surgeon's tool. In: Arregui ME, Fitzgibbons RJ, Katkhouda N, McKernan JB, Reich H eds. Principles of laparoscopic surgery. Basic and advanced techniques. New York, NY: Springer-Verlag, 1995. pp 777-784.
- Cheah WK, Lenzi JE, So JBY, Kum CK, Goh P (2001) Randomized trial of needlescopic versus laparoscopic cholecystectomy. Br J Surg 88:45-47.

- Chernoff AE, Granowitz EV, Shapiro L, Vannier E, Lonnemann G, Angel JB, Kennedy JS, Rabson AR, Wolff SM, Dinarello CA (1995) A randomized, controlled trial of IL-10 in humans. J Immunol 154:5492-5499
- Chernow B, Alexander R, Smallridge RC, Thompson WR, Cook D, Beardsley D, Fink MP, Lake R, Fletcher JR (1987) Hormonal responses to graded surgical stress. Arch Int Med 147: 1273-1278
- Cheslyn-Curtis S, Hopkins HH. The Hopkins Rod-Lens System. In: Arregui ME, Fitzgibbons RJ, Katkhouda N, McKernan JB, Reich H eds. Principles of laparoscopic surgery. Basic and advanced techniques. New York, NY: Springer-Verlag, 1995. pp 767-770
- Choinière M, Amsel R (1996) A visual analogue thermometer for measuring pain intensity. J Pain Symptom Manage 11:299-311
- Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332:1351-1362
- Cochrane JPS, Forsling ML, Gow NM, Le Quesne L (1981) Arginine vasopressin release following surgical operations. Br J Surg 68:209-213
- Coelho JCU, de Araujo RPM, marchesini JB, Coelho ICMM, Araujo LRR (1993) Pulmonary function after cholecystectomy performed through Kocher's incision, a mini-incision and laparoscopy. World J Surg 17:544-546
- Cohen MM, Young W, Thériault M, Hernandez R (1996) Has laparoscopic cholecystectomy changed patterns of practice and patient outcome in Ontario. Can Med Assoc J 154:491-500
- Collet D (1997) Laparoscopic cholecystectomy in 1994. Results of a prospective survey conducted by the SFCERO on 4624 cases. Surg Endosc 11:56-63
- Collins SL, Moore RA, McQuay HJ (1997) The visual analogue pain intensity scale: What is moderate pain in millimetres? Pain 72:95-97

- Copeland C, Wing R, Hulka JF (1983) Direct trocar insertion at laparoscopy: An evaluation. Obstet Gynecol 62:655-659
- Corson SL, Batzer FR, Gocial B, Maislin G (1989) Measurement of the force necessary for laparoscopic trocar entry. J Reprod Med 34:282-284
- Coventry DM (1995) Anaesthesia for laparoscopic surgery. J R Coll Surg Edinb 40:151-160
- Cowley AW, Liard J-F (1988) Vasopressin and arterial pressure regulation. Hypertension 11(Suppl I):I25-I32
- Cruickshank AM, Fraser WD, Burns HJG, Van Damme J, Shenkin A (1990) Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. Clin Sci 79:161-165
- Cuschieri A, Dubois F, Mouiel J, Mouret P, Becker H, Buess G, Trede M, Troidl H (1991) The European experience with laparoscopic cholecystectomy. Am J Surg 161:385-387
- Da Costa ML, Qureshi MA, Brindley NM, Burke PE, Grace PA, Bouchier-Hayes D (1995) Normal inspiratory muscle strength is restored more rapidly after laparoscopic cholecystectomy. Ann R Coll Surg Engl 77:252-255
- Darzi A, Monson JRT, O'Morain C, Tanner WA, Keane FBV (1989) Extension of selection criteria for extracorporeal shock wave lithotripsy for gallstones. Br Med J 299:302-303
- a) Davides D, Vezakis A, Ye J, Dexter SPL, Martin IG, Larvin M, McMahon MJ (1997) Early experience with micropuncture laparoscopic cholecystectomy. Surg Endosc 11:513 [abstract]
- b) Davides D, Vezakis A, Ye J, Dexter SPL, Martin IG, Larvin M, McMahon MJ (1997) Micropuncture laparoscopic cholecystectomy: The Leeds Technique. Surg Endosc 11:514 [abstract]

- Davides D, Dexter SPL, Vezakis A, Larvin M, Moran P, McMahon MJ (1999) Micropuncture laparoscopic cholecystectomy. Surg Endosc 13:236-8
- Davion T, Tossou H, Delamarre J, Capron JP (1989) Racial differences in gallbladder motor function. Lancet 1:724-725
- Delauney L, Bonnet F, Cherqui D, Rimaniol JM, Dahan E, Atlan G (1995) Laparoscopic cholecystectomy minimally impairs postoperative cardiorespiratory and muscle performance. Br J Surg 82:373-376
- Desormeaux AJ. De l'endoscope et de ses applications au diagnostic et au traitement des affections de l'urèthre et de la vessie. Leçons faites a l'hopital Necker. Paris, France: J.-B. Baillière et fils, 1865
- Deuss U, Dietrich J, Kaulen D, Frey K, Spangenberger W, Allolio B, Matuszczak M, Troidl H, Winkelmann W (1994) The stress response to laparoscopic cholecystectomy: Investigation of endocrine parameters. Endosc 26:235-238
- Dexter SPL, Martin IG, Marton J, McMahon MJ (1997) Long operation and the risk of complications from laparoscopic cholecystectomy. Br J Surg 84:464-466
- Deziel DJ, Millikan KW, Economou SG, Doolas A (1993) Complications of laparoscopic cholecystectomy: A national survey of 4292 hospitals and an analysis of 77604 cases. Am J Surg 165:9-14
- Dinarello CA (1997) Pro-inflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. Chest 112:321S-329S
- Dingfelder JR (1978) Direct laparoscope trocar insertion without prior pneumoperitoneum. J Reprod Med 21:45-47
- Dingfelder JR, Brenner WE (1976) The needlescope and other small diameter laparoscopes for sterilization and diagnostic procedures. Int J Gynaecol Obstet 14:53-58
- Di Padova F, Pozzi C, Tondre MJ, Tritapepe R (1991) Selective and early increase of IL-1 inhibitors, IL-6 and cortisol after elective surgery. Clin Exp Immunol 85:137-142

- Donald RA, Perry EG, Wittert GA, Chapman M, Livesey JH, Ellis MJ, Evans MJ, Yandle T, Espiner EA (1993) The plasma ACTH, AVP, CRH and catecholamine responses to conventional and laparoscopic cholecystectomy. Clin Endocrinology 38:609-615
- Douglas RG, Shaw JHF (1989) Metabolic response to sepsis and trauma. Br J Surg 76:115-122
- a) Drummond GB, Scott DB (1976) Laparoscopy explosion hazards with nitrous oxide. Br Med J 1(6009):586
- b) Drummond GB, Scott DB (1976) Laparoscopy explosion hazards with nitrous oxide. Br Med J 1(6024):1531
- Dubois F, Berthelot G, Levard H (1995) Celioscopic cholecystectomy: Experience with 2006 cases. World J Surg 19:748-752
- Dubois F, Icard P, Berthelot G, Levard H (1990) Celioscopic cholecystectomy. Preliminary report of 36 cases. Ann Surg 211:60-62
- Dunn D, Nair R, Fowler S, McCloy R (1994) Laparoscopic cholecystectomy in England and Wales: Results of an audit by the Royal College of Surgeons of England. Ann R Coll Surg Eng 76:269-275
- Dunn DC, Watson CJE (1992) Disposable guarded trocar and cannula in laparoscopic surgery: A caveat. Br J Surg 79:927
- ECRI (1998) Trocars: Safety and Selection. Health Devices 27:376-399
- Edmondson R, Hale PC (1995) Laparoscopic cholecystectomy in England land and Wales: Results of an audit by the Royal College of Surgeons of England. Ann R Coll Surg Engl 77:69 (Letter)
- Eisenhauer DM, Saunders CJ, Ho HS, Wolfe BM (1994) Hemodynamic effects of argon pneumoperitoneum. Surg Endosc 8:315-321
- Erlinger S, Le Go A, Husson J, Fevery J (1984) Franco-Belgian cooperative study of ursodeoxycholic acid in the medical dissolution of gallstones: A double-blind,

randomized, dose-response study and comparison with chenodeoxycholic acid. Hepatology 4:308-314

- Faber BM, Coddington CC (1997) Microlaparoscopy: A comparative study of diagnostic accuracy. Fertil Steril 67:952-4
- Feig BW, Berger DH, Dougherty TB, Dupuis JF, Johnston DA, Gross RJ, Ota DM (1994) Pulmonary effects of CO_2 abdominal insufflation (CAI) during laparoscopy in high-risk patients. Anesth Analg 78;S108 [Abstract]
- Felber AR, Blobner M, Goegler S, Senekowitsch R, Jelen-Esselbom S (1993) Plasma vasopressin in laparoscopic cholecystectomy. Anesthesiology 79:A32 [Abstract]
- Fernandez E, Towery S (1996) A parsimonious set of verbal descriptors of pain sensation derived from the McGill Pain Questionnaire. Pain 66:31-37
- Fischer E, Marano MA, Van Zee KJ, Rock CS, Hawes AS, Thompson WA, DeForge L, Kenney JS, Remick DG, Bloedow DC, Thompson RC, Lowry SF, Moldawer LL (1992) Interleukin-1 receptor blockade improves survival and haemodynamic performance in Escherichia Coli septic shock, but fails to alter host response to sublethal endotoxaemia. J Clin Invest 89:1551-1557
- Frazee RC, Roberts JW, Okeson GC, Symmonds RE, Snyder SK, Hendricks JC, Smith RW (1991) Open versus laparoscopic cholecystectomy. A comparison of postoperative pulmonary function. Ann Surg 213:651-654
- Fullarton GM, Bell G and the West of Scotland Laparoscopic Cholecystectomy Audit Group (1994) Prospective audit of the introduction of laparoscopic cholecystectomy in the West of Scotland. Gut 35:1121-1126
- Furuya K, Shimizu R, Hirabayashi Y, Ishii R, Fukuda H (1993) Stress hormone responses to major intra-abdominal surgery during and immediately after sevoflurane-nitrous oxide anaesthesia in elderly patients. Can J Anaesth 40:435-439
- Gagner M, Garcia-Ruiz A (1998) Technical aspects of minimally invasive abdominal surgery performed with needlescopic instruments. Surg Endosc Laparosc 8:171-179

- a) Ganong WF. Endocrine functions of the pancreas and the regulation of carbohydrate metabolism. In: Ganong WF ed. Review of Medical Physiology. Norwalk, CT: Appleton and Lange, 1995. pp 306-326
- b) Ganong WF. The adrenal medulla and adrenal cortex. In: Ganong WF ed. Review of Medical Physiology. Norwalk, CT: Appleton and Lange, 1995. pp 327-351
- c) Ganong WF. The heart as a pump. In: Ganong WF ed. Review of Medical Physiology. Norwalk, CT: Appleton and Lange, 1995. pp 514-524
- Garibaldi RA, Cushing D, Lerer T (1991) Risk factors for postoperative infection. Am J Med 91(3B): 158S-163S
- George KA, Chisakatu AM, Gamble JAS, Browne GA (1992) Thoracic epidural infusion for postoperative pain relief following abdominal aortic surgery: Bupivicaine, fentanyl or a mixture of both. Anaesthesia 47:388-394
- Gershenwald JE, Fong Y, Fahey TJ, Calvano SE, Chizzonite R, Kilian PL, Lowry SF, Moldawer LL (1990) Interleukin-1 receptor blockade attenuates the host inflammatory response. Proc Natl Acad Sci USA 87:4966-4970
- Girard RM, Morin M (1993) Open cholecystectomy: Its morbidity and mortality as a reference standard. Can J Surg 36:75-80
- Glaser F, Sannwald GA, Buhr HJ, Kuntz C, Mayer H, Klee F, Herfarth C (1995) General stress response to conventional and laparoscopic cholecystectomy. Ann Surg 221:372-380
- Go PMNYH Schol F, Gouma DJ (1993) Laparoscopic cholecystectomy in the Netherlands. Br J Surg 80:1190-1193
- Goco IR, Chambers LG (1988) Dollars and cents: Minicholecystectomy and early discharge. South Med J 81:162-163
- Goodale RL, Beebe DS, McNevin MP, Boyle M, Letourneau JG, Abrams JH, Cerra FB (1993) Hemodynamic, respiratory and metabolic effects of laparoscopic cholecystectomy. Am J Surg 166:533-537

- Grace PA, Quereshi A, Coleman J, Keane R, McEntee G, Broe P, Osborne H, Bouchier-Hayes D (1991) Reduced postoperative hospitalisation after laparoscopic cholecystectomy. Br J Surg 78:160-162
- Grant PJ, Davies JA, Tate GM, Boothby M, Prentice CRM (1985) Effects of physiological concentrations of vasopressin on haemostatic function in man. Clin Sci 69:471-476
- a) Grant PJ, Hughes JR, Dean HG, Davies JA, Prentice CRM (1986) Vasoopressin and catecholamine secretion during apomorphine-induced nausea mediate acute changes in haemostatic function in man. Clin Sci 71:621-624
- b) Grant PJ, Tate GM, Davies A, Williams NS, Prentice CRM (1986) Intra-operative activation of coagulation – A stimulus to thrombosis mediated by vasopressin? Thrombosis and Haemostasis 55:104-107
- Graves HA, Ballinger JF, Anderson WJ (1991) Appraisal of laparoscopic cholecystectomy. Ann Surg 213:655-664
- Gray AJG, Hoile RW, Ingram GS, Sherry KM. The report of the national confidential enquiry into peri-operative deaths 1996/1997. NCEPOD
- Griffiths JP, Everitt NJ, Lancaster F, Boylston A, Richards SJ, Scott CS, Benson EA, Sue-Ling HM, McMahon MJ (1995) Influence of laparoscopic and conventional cholecystectomy upon cell-mediated immunity. Br J Surg 82:677-680
- Gwosdow AR (1995) Mechanisms of interleukin-1-induced hormone secretion from the rat adrenal gland. Endocrine Research 21:25-37
- Haas M, Glick SM (1978) Radioimmunoassayable plasma vasopressin associated with surgery. Arch Surg 113: 597-600
- Haeusler G, Lehner R, Hanzal E, Kainz C (1996) Diagnostic accuracy of 2mm microlaparoscopy. Acta Obstet Gynecol Scand 75:672-675

- Hampton KK, Grant PJ, Primrose J, Dean HG, Davies JA, Prentice CRM (1991) Haemostatic responses and vasopressin release during colonoscopy in man. Clin Sci 81:257-260
- Hanney RM, Alle KM, Cregan PC (1995) Major vascular injury and laparoscopy. Aust N Z J Surg 65:533-535
- Hashizume M, Sugimachi K, Study Group of Endoscopic Surgery in Kyushu, Japan (1997) Needle and trocar injury during laparoscopic surgery in Japan. Surg Endosc 11:1198-1201
- Hasson HM (1971) A modified instrument and method for laparoscopy. Amer J Obstet Gynec 110:886-887
- Helmreich-Becker I, Meyer zum Bümschenfelde KH, Lohse AW (1998) Safety and feasibility of a new minimally invasive diagnostic laparoscopy technique. Endosc 30:756-762
- Heuer GJ (1934) The factors leading to death in operations upon the gallbladder and bile ducts. Ann Surg 99:881-892
- Hill AG, Finn P, Schroeder D (1993) Postoperative fatigue after laparoscopic surgery. Aust NZJ Surg 63:946-951
- Hill AG, Hill GL (1998) Metabolic response to severe injury. Br J Surg 85:884-890
- Hill AG, Siegel J, Rounds J, Wilmore DW (1997) Metabolic responses to Interleukin-1. Ann Surg 225:246-251
- Horgan PG, Fitzpatrick M, Couse NF, Gorey TF, Fitzpatrick JM (1992) Laparoscopy is less immunotraumatic than laparotomy. Min Inv Ther 1:241-244
- Horgan PG, Rodrick ML, Ellwanger K, Collins KC, Dubravec DB, mannick JA (1988) In vivo effects of an immunosuppressive factor isolated from patients following thermal injury. Surg Forum 39:96-99
- Hunter JG, Staheli J, Oddsdottir M, Trus T (1995) Nitrous oxide pneumoperitoneum revisited. Surg Endosc 9:501-504

- Hunter J (1998) Editorial comment. Am J Surg 176:372
- Hurd WW, Bude RO, DeLancey JOL, Gauvin JM, Aisen AM. (1991) Abdominal wall characterization with magnetic resonance imaging and computed tomography. The effect of obesity on the laparoscopic approach. J Reprod Med 36:473-476
- Hurd WW, Bude RO, DeLancey JOL, Pearl ML (1992) Relationship of the umbilicus to the aortic bifurcation: Implications for laparoscopic technique. Obstet Gynecol 80:48-51
- Hurd WW, Ohl DA (1994) Blunt trocar laparoscopy. Fert Steril 61:1177-1180
- Hurd WW, Randolph JF, Holmberg RA, Pearl ML, Hubbell GP (1994) Open laparoscopy without special instrumentation or sutures. Comparison with a closed technique. J Reprod Med 39:393-397
- Hurd WW, Wang L, Schemmel MT (1995) A comparison of the relative risk of vessel injury with conical versus pyramidal laparoscopic trocars in a rabbit model. Am J Obstet Gynecol 173:1731-1733
- Iwase K, Takenaka H, Yagura A, Ishizaka T, Ohata T, Takagaki M, Oshima S (1992) Hemodynamic changes during laparoscopic cholecystectomy in patients with heart disease. Endoscopy 1992;24:771-773
- Jacobaeus HC (1910) Ueber die Möglichkeit, die Zystoskopie bei Untersuchung seröser Höhlungen anzuwenden. Muenchener Medizinische Wochenschrift 40:2090-2092
- Jakimowicz J, Stultiëns G, Smulders F (1998) Laparoscopic insufflation of the abdomen reduces portal venous flow. Surg Endosc 12:129-132
- Jakeways MSR, Mitchell V, Hashim IA, Chadwick SJD, Shenkin A, Green CJ, Carli F (1994) Metabolic and inflammatory responses after open or laparoscopic cholecystectomy. Br J Surg 81:127-131
- Jarrett JC (1990) Laparoscopy: Direct trocar insertion without pneumoperitoneum. Obstet Gynecol 75:725-727
- Jensen MP, Karoly P, Braver S (1986) The measurement of pain intensity: A comparison of six methods. Pain 27:117-126

- Joris J (1993) Metabolic effects of cholecystectomy. Br J Anaesth 70 (4):493-494
- Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P, Lamy M (1992) Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. Br J Anaesth 69:341-345
- Joris J, Kaba A, Lamy M (1997) Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal procedures. Br J Anaesth 79:422-426
- Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. (1993) Hemodynamic changes during laparoscopic cholecystectomy. Anesth Analg 76:1067-1071
- a) Junghans T, Böhm B, Gründel K, Schwenk W (1997) Effects of pneumoperitoneum with carbon dioxide, argon, or helium on hemodynamic and respiratory function. Arch Surg 132:272-278
- b) Junghans T, Böhm B, Gründel K, Schwenk W, Müller JM (1997) Does pneumoperitoneum with different gases, body positions, and intraperitoneal pressures influence renal and hepatic blood flow? Surgery 121:206-211
- Karayiannakis AJ, Makri GG, Mantzioka A, Karousos D, Karatzas G (1997) Systemic stress response after laparoscopic or open cholecystectomy: A randomised trial. Br J Surg 84:467-471
- Kehlet H (1989) Surgical stress. The role of pain and analgesia. Br J Anaesth 63:189-195
- Kelling G (1902) Ueber Oesophagoskopie, Gastroskopie und Kölioskopie. Muenchener Medicinische Wochenschrift 1:21-24
- Kelling G (1910) Ueber die Möglichkeit, die Zystoskopie bei Untersuchungen seröser Höhlungen anzuwenden. Bemerkungen zu dem Artikel von Jacobäus. Muenchener Medizinische Wochenschrift 45:2358
- Kimura T (1998) Laparoscopic cholecystectomy using fine-caliber instruments. Surg Endosc 12: 1449
- Kimura T, Sakuramachi S, Yoshida M, Kobayashi T, Takeuchi Y (1998) Laparoscopic cholecystectomy using fine-caliber instrument. Surg Endosc 12:283-286

- Kind P, Dolan P, Gudex C, Williams A (1998) Valuations in population health status: Results from a United Kingdom national questionnaire survey. BMJ 316:736-741
- Kishimoto T, Akira S, Narazaki M, Taga T (1995) Interleukin-6 family of cytokines and gp130. Blood 86:1243-1254
- Kloosterman T, von Blomberg ME, Borgstein P, Cuesta MA, Scheper RJ, Meijer S (1994) Unimpaired immune functions after laparoscopic cholecystectomy. Surgery 115:424-428
- Knolmayer TJ, Bowyer MW, Egan JC, Asbun HJ (1998) The effects of pneumoperitoneum on gastric blood flow and traditional hemodynamic measurements. Surg Endosc 12:115-118
- Kobayashi E, Yamauchi H (1997) Interleukin-6 and a delay of neutrophil apoptosis after major surgery. Arch Surg 132:209-210
- a) Koivusalo AM, Kellokumpu I, Lindgren L (1996) Gasless laparoscopic cholecystectomy: Comparison of postoperative recovery with conventional technique. Br J Anaesth 77:576-580
- Koivusalo AM, Kellokumpu I, Ristkari S, Lindgren L (1997) Splanchnic and renal deterioration during and after laparoscopic cholecystectomy: A comparison of the carbon dioxide pneumoperitoneum and the abdominal wall lift method. Anesth Analg 85:886-891
- b) Koivusalo AM, Kellokumpu I, Scheinin M, Tikkanen I, Halme L, Lindgren L (1996) Randomized comparison of the neuroendocrine response to laparoscopic cholecystectomy using either conventional or abdominal wall lift techniques. Br J Surg 83:1532-1536
- Koivusalo AM, Kellokumpu I, Scheinin M, Tikkanen I, Mäkisalo H, Lindgren L (1998) A comparison of gasless mechanical and conventional carbon dioxide pneumo-peritoneum methods for laparoscopic cholecystectomy. Anesth Analg 86:153-158

- Korell M, Schmaus F, Strowitzki T, Schneeweiss SG, Hepp H (1996) Pain intensity following laparoscopy. Surg Laparosc Endosc 6:375-379
- Kovacs GT, Baker G, Dillon M, Peters M (1998) The microlaparoscope soudl be used routinely for diagnostic laparoscopy. Fertil Steril 70:698-701
- Kremer E, Atkinson JH, Ignelzi RJ (1981) Measurement of pain: Patient preference does not confound pain measurement. Pain 10:241-248
- Kum C-K, Eypasch E, Aljaziri A, Troidl H (1996) Randomized comparison of pulmonary function after the "French" and "American" techniques of laparoscopic cholecystectomy. Br J Surg 83:938-941
- Laparolift manual, Origin Medsystems Inc, California, USA. Page 3
- Lazarou SA, Barbul A, Wasserkrug HL, Efron G (1989) The wound is a possible source of posttraumatic immunosuppression. Arch Surg 124:1429-1431
- Lennard TWJ, Shenton BK, Borzotta A, Donnelly PK, White M, Gerrie LM, Proud G, Taylor RM (1985) The influence of surgical operations on components of the human immune system. Br J Surg 72:771-776
- Liem MSL, van der Graaf Y, Zwart RC, Geurts I, van Vroonhoven ThJMV and the Coala trial group (1997) A randomised comparison of physical performance following laparoscopic and open inguinal hernia repair. Br J Surg 84:64-67
- Lindgren L, Koivusalo AM, Kellokumpu I (1995) Conventional pneumoperitoneum compared with abdominal wall lift for laparoscopic cholecystectomy. Br J Anaesth 75:567-572
- Look M, Chew SP, Tan YC, Liew SE, Cheong DMO, Tan JCH, Wee SB, The CH, Low CH (2001) Post-operative pain in needlescopic versus conventional laparoscopic cholecystectomy: A prospective randomised trial. J R Coll Surg Edinb 46:138-142
- MacDonagh RP, Cliff AM, Speakman MJ, O'Boyle PJ, Ewings P, Gudex C (1997) The use of generic measures of health-related quality of life in the assessment of outcome from transurethral resection of the prostate. Br J Urol 79:401-408

- Majeed AW, Troy G, Nicholl JP, Smythe A, Reed MWR, Stoddard CJ, Peacock J, Johnson AG (1996) Randomised, propective, single-blind comparison of laparoscopic versus small incision cholecystectomy. Lancet 347:989-994
- Mantha S, Thisted R, Foss J, Ellis JE, Roizen MF (1993) A proposal to use confidence intervals for visual analogue scale data for pain measurement to determine clinical significance. Anesth Analg 77:1041-1047
- Mar Fan MJ, Chan STF (1998) "Needlescopic" (mini-laparoscopic) surgery: Necessary or unnecessary? Aust NZJ Surg 68:628-629
- a) Marshall RL, Jebson PJR, Davie IT, Scott DB (1972) Circulatory effects of carbon dioxide insufflation of the peritoneal cavity for laparoscopy. Br J Anaesth 44:680-684
- b) Marshall RL, Jebson PJR, Davie IT, Scott DB (1972) Circulatory effects of peritoneal insufflation with nitrous oxide. Br J Anaesth 44:1183-1187
- Martin IG, Dexter SPL, Marton J, Gibson J, Asker J, Firullo A, McMahon MJ (1995) Fundus-first laparoscopic cholecystectomy. Surg Endosc 9:203-206
- Martin IG, Holdsworth PJ, Asker J, Baltas B, Glinatsis MT, Sue-Ling H, Gibson J, Johnston D, McMahon MJ (1992) Laparoscopic cholecystectomy as a routine procedure for gallstones: results of an 'all-comers' policy. Br J Surg 79:807-810
- Maruszynski M, Pojda Z (1995) Interleukin 6 (IL-6) levels in the monitoring of surgical trauma. Surg Endosc 9:882-885
- Matthews JNS, Altman DG, Campbell MJ, Royston P (1990) Analysis of serial measurements in medical research. Br Med J 300:230-235
- Mayol J, Garcia-Aguilar J, Ortiz-Oshiro E, De-Diego Carmona JA, Fernandez-Represa JA (1997) Risks of the minimal access approach for laparoscopic surgery: Multivariate analysis of morbidity related to umbilical trocar insertion. World J Surg 21:529-533
- McClure N, Gallagher AG, McGuigan J (1996) Randomised trial of laparoscopic versus small-incision cholecystectomy. Lancet 347:1623. [Letter]

- McDonald PT, Rich MN, Collins GJ, Andersen CA, Kozloff L (1978) Vascular trauma secondary to diagnostic and therapeutic procedures: Laparoscopy. Am J Surg 135:651-655
- McDougall EM, Figenshau RS, Clayman RV, Monk TG, Smith DS (1994) Laparoscopic pneumoperitoneum: Impact of body habitus. J Laparoendosc Surg 4:385-391
- McGinn FP, Miles AJG, Uglow M, Ozmen M, Terzi C, Humby M. (1995) Randomized trial of laparoscopic cholecystectomy and min-cholecystectomy. Br J Surg 82:1374-1377
- McIntyre RC, Bensard DD, Steigmann GV, Pearlman NW, Durham J (1996) Exposure for laparoscopic cholecystectomy dissection adversely alters biliary ductal anatomy. Surg Endosc 10:41-43
- McKernan JB, Champion JK (1995) Access techniques: Veress needle – initial blind trocar insertion versus open laparoscopy with the Hasson trocar. End Surg 3:35-38
- McLaughlan GJ, MacIntyre IMC (1995) Return to work after laparoscopic cholecystectomy. Br J Surg 82:239-241
- a) McMahon AJ, Baxter JN, Kenny G, O'Dwyer PJ (1993) Ventilatory and blood gas changes during laparoscopic and open cholecystectomy. Br J Surg 80:1252-1254
- a)McMahon AJ, Baxter JN, Murray W, Imrie CW, Kenny G, O'Dwyer PJ (1994) Helium pneumoperitoneum for laparoscopic cholecystectomy: Ventilatory and blood gas changes. Br J Surg 81:1033-1036
- b)McMahon AJ, Baxter JN, O'Dwyer PJ (1993) Preventing complications of laparoscopy. Br J Surg 80:1593-1594
- a)McMahon AJ, Fullarton G, Baxter JN, O'Dwyer (1995) Bile duct injury and bile leakage in laparoscopic cholecystectomy. Br J Surg 82:307-313
- c)McMahon AJ, O'Dwyer PJ, Cruickshank AM, McMillan DC, O'Reilly D St J, Lowe GDO, Rumley A, Logan RW, Baxter JN (1993) Comparison of metabolic responses to laparoscopic and minilaparotomy cholecystectomy. Br J Surg 80:1255-1258

- b)McMahon AJ, Ross S, Baxter JN, Russell IT, Anderson JR, Morran CG, Sunderland GT, Galloway DJ, O'Dwyer PJ (1995) Symptomatic outcome 1 year after laparoscopic and minilaparotomy cholecystectomy: A randomized trial. Br J Surg 82:1378-1382
- b)McMahon AJ, Russell IT, Baxter JN, Anderson JR, Morran CG, Sunderland G, Galloway D, Ramsay G, O'Dwyer PJ (1994) Laparoscopic versus minilaparotomy cholecystectomy: A randomised trial. Lancet 343:135-138
- c)McMahon AJ, Russell IT, Ramsay G, Sunderland G, Baxter JN, Anderson JR, Galloway D, O'Dwyer PJ (1994) Laparoscopic and minilaparotomy cholecystectomy: A randomised trial comparing postoperative pain and pulmonary function. Surgery 115:533-539
- McSherry CK (1989) Cholecystectomy: The gold standard. Am J Surg 158:174-178
- Meakins JL (1988) Host defense mechanisms in surgical patients: Effect of surgery and trauma. Acta Chir Scand Suppl 550:43-53
- Mealy K, Gallagher H, Barry M, Lennon F, Traynor O, Hyland J (1992) Physiological and metabolic responses to open and laparoscopic cholecystectomy. Br J Surg 79:1061-1064
- Melville RJ, Frizis HI, Forsling ML, LeQuesne LP (1985) The stimulus for vasopresiin release during laparoscopy. Surg Gyn Obstet 161:253-256
- Melzack R (1975) The McGill pain questionnaire. Pain 1:277-299
- Melzer A, Weiss U, Roth K, Loefflor M, Buess G (1993) Visually controlled trocar insertion by means of the "optical scalpel." End Surg 1:239-242
- Mikami O, Fujise K, Matsumoto S, Shingu K, Ashida M, Matsuda T (1998) High intra-abdominal pressure increases plasma catecholamines concentrations during pneumoperitoneum for laparoscopic procedures. Arch Surg 133:39-43
- Mikami O, Kawakita S, Fujise K, Shingu K, Takahashi H, Matsuda T (1996) Catecholamine release caused by carbon dioxide insufflation during laparoscopic cholecystectomy. J Urol 155:1368-1371

- Molloy RG, Mannick JA, Rodrick ML (1993) Cytokines, sepsis and immunomodulation. Br J Surg 80:289-297
- Molloy D (1995) The diagnostic accuracy of a microlaparoscope. Journal of the American Association of Gynecologic Laparoscopists 2:203-206
- Monick MM, Aksamit TR, Geist LJ, Hunninghake GW (1994) Dexamethasone inhibits IL-1 and TNF activity in human lung fibroblasts without affecting IL-1 or TNF receptors. Am J Physiol 267:L33-L38
- Moshage H (1997) Cytokines and the hepatic acute phase response. J Path 181:257-266
- Mühe E (1992) Long-term follow-up after laparoscopic cholecystectomy. Endoscopy 24:754-758
- Munck A, Náray-Fejes-Tóth A (1994) Glucocorticoids and stress: Permissive and suppressive actions. Ann NY Acad Sci 746:115-130
- Mutter D, Navez B, Guiy J-F, Guiot P, Russier Y, Vix M, Marescaux J (1998) Value of microlaparoscopy in the diagnosis of right iliac fossa pain. Am J Surg 176:370-372
- Nair RG, Dunn DC, Fowler S, McCloy RF (1997) Progress with cholecystectomy: Improving results in England and Wales. Br J Surg 84:1396-1398
- Naito Y, Fukata J, Tamai S, Seo N, Nakai Y, Mori K, Imura H (1991) Biphasic changes in hypothalamo-pituitary-adrenal function during the early recovery period after major abdominal surgery. J Clin Endocrinol Metab 73:111-117
- Naito Y, Tamai S, Shingu K, Shindo K, Matsui T, Segawa H, Nakai Y, Mori K (1992) Response of plasma adrenocorticotropic hormone, cortisol and cytokines during and after upper abdominal surgery. Anesthesiology 77:426-431
- Nathanson LK (1995) Trocars and other access techniques. End Surg 3:33-34
- Nathanson LK, Shimi S, Cuschieri A (1991) Laparoscopic cholecystectomy: The Dundee technique. Br J Surg 78:155-159

- Naude GP, Ryan MK, Pianim NA, Klein SR, Lippmann M, Bongard FS (1996) Comparative stress hormone changes during helium versus carbon dioxide laparoscopic cholecystectomy. J Laparoendosc Surg 6:93-98
- Nealon WH, Urrutia F, Fleming D, Thompson JC (1991) The economic burden of gallstone lithotripsy. Will cost determine its fate? Ann Surg 213:645-649
- Neuberger TJ, Andrus CH, Wittgen CM, Wade TP, Kaminski DL (1996) Prospective comparison of helium versus carbon dioxide pneumoperitoneum. Gastrointest Endosc 43:38-41
- Neugebauer E, Troidl H, Spangenberger W, Dietrich A, Lefering R and the Cholecystectomy Study Group (1991) Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. Br J Surg 78:150-154
- Newman D (1883) On malpositions of the kidney. Glasgow Med Jour 20:81-139
- Nezhat FR, Silfen SL, Evans D, Nezhat C (1991) Comparison of direct insertion of disposable and standard reusable laparoscopic trocars in previous pneumoperitoneum with Veress needle. Obstet Gynecol 78:148-150
- Ninomiya K, Kitano S, Yoshida T, Bandoh T, Baatar D, Matsumoto T (1998) Comparison of pneumoperitoneum and abdominal wall lifting as to hemodynamics and surgical stress response during laparoscopic cholecystectomy. Surg Endosc 12:124-128
- Nitze M (1879) Eine neue Beobachtungs – und Untersuchungsmethode für Harnröhre, Harnblase und Rectum. Wiener Medizinische Wochenschrift 24:649-652
- Nitze M (1895) Ueber kystoskopische Diagnostik chirurgischer Nierenerkrankungen mit besonderer Berücksichtigung des Harnleiterkatheterismus. Berliner Klinische Wochenschrift 16:350-353
- Nussey SS, Bevan DH, Ang VTY, Jenkins JS (1986) Effects of arginine vasopressin (AVP) infusions on circulating concentrations of platelet AVP, Factor VIII:C and von Willebrand Factor. Thrombosis and Haemostasis 55:34-36

- O'Dwyer PJ, McGregor JR, McDermott EWM, Murphy JJ, O'Higgins NJ (1992) Patient recovery following cholecystectomy through a 6cm or 15cm transverse subcostal incision: A prospective randomized clinical trial. Postgrad Med J 68:817-819
- O'Dwyer PJ. Murphy JJ. O'Higgins NJ (1990) Cholecystectomy through a 5 cm subcostal incision. Br J Surg 77:1189-1190
- Ohzato H, Yoshizaki K, Nishimoto N, Ogata A, Tagoh H, Monden M, Gotoh M, Kishimoto T, Mori T (1992) Interleukin-6 as a new indicator of inflammatory status: Detection of serum levels of Interleukin-6 and C-reactive protein after surgery. Surgery 111:201-209
- O'Leary E, Hubbard K, Tormey W, Cunningham AJ (1996) Laparoscopic cholecystectomy: Haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. Br J Anaesth 76:640-644
- O'Riordain MG, Ross JA, Fearon KCH, Maingay J, Farouk M, Garden J, Carter DC (1995) Insulin and counterregulatory hormones influence acute-phase protein production in human hepatocytes. Am J Physiol 269:E323-E330
- Ortega AE, Peters JH, Incarbone R, Estrada L, Ehsan A, Kwan Y, Spencer CJ, Moore-Jeffries E, Kuchta K, Nicoloff JT (1996) A prospective randomized comparison of the metabolic responses of laparoscopic and open cholecystectomy. J Am Coll Surg 183:249-256
- a) Ott DE (1991) Laparoscopic hypothermia. J Laparoendosc Surg 1:127-131
- b) Ott DE (1991) Correction of laparoscopic insufflation hypothermia. J Laparoendosc Surg 1:183-186
- Payne JH Jr, Grininger LM, Izawa MT, Podoll EF, Lindahl PJ, Balfour J (1994) Laparoscopic or open inguinal herniorrhaphy? Arch Surg 129:973-981
- Penney MD, Hampton D, Oleesky DA, Livingstone C, Mulkerrin E (1992) Radioimmunoassays of arginine vasopressin and atrial natriuretic peptide: Application of

a common protocol for plasma extraction using Sep-Pak C_{18} cartridges. Ann Clin Biochem 29:652-658

- Perissat J, Collet D, Belliard R (1990) Gallstones: Laparoscopic treatment – cholecystectomy, cholecystostomy and lithotripsy. Surg Endosc 4:1-5
- Peters JH, Ortega A, Lehnard SL, Campbell AJ, Schwartz DC, Ellison EC, Innes JT (1993) The physiology of laparoscopic surgery: Pulmonary function after laparoscopic cholecystectomy. Surg Laparosc Endosc 3:370-374
- Plaus WJ (1993) Laparoscopic trocar site hernias. J Laparoendosc Surg 3:567-570
- Pollock RE, Lotzová E, Stanford SD (1991) Mechanism of surgical stress impairment of human Perioperative Natural Killer Cell cytotoxicity. Arch Surg 126:338-342
- Punnonen R, Viinamäki O (1982) Vasopressin release during laparoscopy: Role of increased intra-abdominal pressure. Lancet 1:175-176
- Puri GD, Singh H (1992) Ventilatory effects of laparoscopy under general anaesthesia. Br J Anaesth 68:211-213
- Putensen-Himmer G, Putensen C, Lammer H, Lingnau W, Aigner F, Benzer H (1992) Comparison of post-operative respiratory function after laparoscopy or open laparotomy for cholecystectomy. Anesthesiology 77:675-680
- Puttick MI, Nduka CC, Yong LY, Darzi A (1998) Exposure of peritoneal macrophages to carbon dioxide pneumoperitoneum suppresses function and diminishes anti-tumour cell cytotoxicity. Br J Surg 85:1579 [Abstract]
- Rademaker BM, Ringers J, Odoom JA, de Wit LT, kalkman CJ, Oosting J (1992) Pulmonary function and stress response after laparoscopic cholecystectomy: Comparison with subcostal incision and influence of thoracic epidural analgesia. Anesth Analg 75:381-385
- Raff H (1993) Interactions between neurohypophysial hormones and the ACTH-adrenocortical axis. Ann NY Acad Sci 689:411-425

- Rathert P, Lutzeyer W, Goddwin WE (1974) Phillipp Bozzini (1773-1809) and the Lichtleiter. Urology 3:113-118
- Reddick EJ, Olsen DO (1989) Laparoscopic laser cholecystectomy. A comparison with mini-lap cholecystectomy. Surg Endosc 3:131-133
- Redmond HP, Hofmann K, Shou J, Leon P, Kelly CJ, Daly JM (1992) Effects of laparotomy on systemic macrophage function. Surgery 111:647-655
- Redmond HP, Watson WG, Houghton T, Condron C, Watson RGK, Bouchier-Hayes D (1994) Immune function in patients undergoing open vs laparoscopic cholecystectomy. Arch Surg 129:1240-1246
- Reich H. Laparoscopic surgery for adhesiolysis. In: Arregui ME, Fitzgibbons RJ, Katkhouda N, McKernan JB, Reich H eds. Principles of laparoscopic surgery. Basic and advanced techniques. New York, NY: Springer-Verlag, 1995. pp 283-298
- Reith HB, Kaman S, Mittelkotter O, Kilic Y, Kozuschek W (1997) Cytokine activation in patients undergoing open or laparoscopic cholecystectomy. International Surgery 82:389-393
- Ress AM, Sarr MG, Nagorney DM, Farnell MB, Donohue JH, McIlrath DC (1993) Spectrum and mangement of major complications of laparoscopic cholecystectomy. Am J Surg 165:655-662
- Richardson JD, Trinkle JK (1976) Hemodynamic and respiratory alterations with increased intra-abdominal pressure. J Surg Res 20:401-404
- Richardson MC, Bell G, Fullarton GM, The West of Scotland Laparoscopic Cholecystectomy Audit Group (1996) Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: An audit of 5913 cases. Br J Surg 83:1356-1360
- Riedel HH, Lehmann-Willenbrock E, Conrad P, Semm K (1986) German pelviscopic statistics for the years 1978-1982. Endoscopy 18:219-222

- Robinson JS, Thompson JM, Wood AW (1976) Laparoscopy explosion hazards with nitrous oxide. Br Med J 1(6020):1277
- Roh MS, Drazenovich KA, Barbose JJ, Dinarello CA, Cobb CF (1987) Direct stimulation of the adrenal cortex by interleukin-1. Surgery 102:140-145
- Roslyn JJ, Binns GS, Hughes EFX, Saunders-Kirkwood K, Zinner MJ, Cates JA (1993) Open cholecystectomy: A contemporary analysis of 42474 patients. Ann Surg 218:129-137
- Ross MH, Reith EJ. The cardiovascular system. In Ross MH, Reith EJ eds. Histology. A text and atlas. New York, NY: Harper and Row, 1985. pp 278-301
- Roumen RMH, van Meurs PA, Kuypers HHC, Kraak WAG, Sauerwein RW (1992) Serum interleukin-6 and C reactive protein responses in patients after laparoscopic or conventional cholecystectomy. Eur J Surg 158:541-544
- Russell RCG, Walker CJ, Bloom SR (1975) Hyperglucagonaemia in the surgical patient. Br Med J 1:10-12
- Sackman M, Pauletzki J, Sauerbruch T, Holl J, Schelling G, Paumgartner G (1991) The Munich gallbladder lithotripsy study. Ann Int Med 114:290-296
- Sackman M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G (1990) Early gallstone recurrence rate after successful shock-wave therapy. Gastroenterol 98:392-396
- Salomäki TE, Laitinen JO, Nuutinen LS (1991) A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. Anesthesiology 75:790-795
- Sampliner JE, O'Connell DJ (1968) Biliary surgery in the Southwestern American Indian. Arch Surg 96:1-3
- Schauer PR, Luna J, Ghiatas AA, Glen ME, Warren JM, Sirinek KR (1993) Pulmonary function after laparoscopic cholecystectomy. Surgery 114:389-397
- Schauer SR, Sirinek KR (1995) The laparoscopic approach reduces the endocrine response to elective cholecystectomy. Am Surg 61:106-111

- Schaller G, Kuenkel M, Manegold BC (1995) The optical "Veress-Needle" – initial puncture with a minioptic. End Surg 3:55-57
- Schöb OM, Allen DC, Benzel E, Curet M, Adams MS, Baldwin NG, Largaider F, Zucker KA (1996) A comparison of the pathophysiological effects of carbon dioxide, nitrous oxide, and helium pneumoperitoneum on intracranial pressure. Am J Surg 172:248-253
- Schrenk P, Woisetschläger R, Reiger R, Wayand W (1996) Mechanism, management, and prevention of laparoscopic bowel injuries. Gastrointest Endosc 43:572-574
- Schröder J, Kahlke V, Staubach K, Zabel P, Stüber F (1998) Gender differences in human sepsis. Arch Surg 133:1200-1205
- Schwenk W, Neudecker J, Mall J, Böhm B, Müller JM (2000) Prospective randomised blinded trial of pulmonary function, pain, and cosmetic results after laparoscopic vs microlaparoscopic cholecystectomy. Surg Endosc 14:345-348
- Scott CF (1982) Length of operation and morbidity: Is there a relationship? Plastic and Reconstructive Surgery 69:1017-1021
- Scott J, Huskisson EC (1976) Graphic representation of pain. Pain 2:175-184
- Sculpher M, Dwyer N, Byford S, Stirrat G (1996) Randomised trial comparing hysterectomy and transcervical endometrial resection: Effect on health related quality of life and costs two years after surgery. Br J Obstet Gynaecol 103: 142-194
- Segalas M (1826) Review medicale. Description of an instrument for inspecting the urethra and bladder. Lancet 11:603-604
- Semm K (1995) Cutting versus conical tip designs. End Surg 3:39-47.
- Sheeran P, Hall GM (1997) Cytokines in anaesthesia. Br J Anaesth 78:201-219
- Sherwood R, Berci G, Austin E, Morgenstern L (1980) Minilaparoscopy for blunt abdominal trauma. Arch Surg 115:672-673

- Shigemitsu Y, Saito T, Kinoshita T, Kobayashi M (1992) Influence of surgical stress on bactericidal activity of neutrophils and complications of infection in patients with oesophageal cancer. J Surg Oncol 50:90-97
- Shuto K, Kitano S, Yoshida T, Bandoh T, Mitarai Y, Kobayashi M (1995) Hemodynamic and arterial blood gas changes during carbon dioxide and helium pneumoperitoneum in pigs. Surg Endosc 9:1173-1178
- Sigman HH, Fried GM, Garzon J, Hinchey EJ, Wexler MJ, Meakins JL, Barkun JS (1993) Risks of blind versus open approach to celiotomy for laparoscopic surgery. Surg Laparosc Endosc 3:296-299
- Solis Herruzo JA, Castellano G, Larrodera L, Morillas JD, Moreno Sanchez D, Provencio R, Muñoz-Yagüe MT (1989) Plasma arginine vasopressin concentration during laparoscopy. Hepato-gastroenterol 36:499-503
- Solis Herruzo JA, Moreno D, Gonzalez A, Larrodera L, Castellano G, Gutierrez J, Gozalo A (1991) Effect of intrathoracic pressure on plasma arginine vasopressin levels. Gastroenterol 101:607-617
- Somerville KW, Ellis WR, Whitten BH, Balfour TW, Bell GD (1985) Stones in the common bile duct: Experience with medical dissolution therapy. Postgrad Med J 61:313-316
- Soper NJ, Barteau JA, Clayman RV, Ashley SW, Dunnegan DL (1992) Comparison of early postoperative results for laparoscopic versus standard open cholecystectomy. Surg Gyn Obstet 174:114-118
- Southern Surgeons' Club (1991) A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 324:1073-1078
- Southern Surgeons' Club, Moore MJ, Bennett CL (1995) The learning curve for laparoscopic cholecystectomy. Am J Surg 170:55-59
- Stahl WM (1987) Acute phase protein response to tissue injury. Crit Care Med 15:545-550

- Steiner CA, Bass EB, Talamini MA, Pitt HA, Steinberg EP (1994) Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. N Engl J Med 330:403-408
- Stephan RN, Saizawa M, Conrad PJ, Dean RE, Geha AS, Chaudry IH (1987) Depressed antigen presentation function and membrane interleukin-1 activity of peritoneal macrophages after laparotomy. Surgery 102:147-153
- Steptoe P (1976) Laparoscopy explosion hazards with nitrous oxide. Br Med J 1(6013):833
- Stiff G, Rhodes M, Kelly A, telford KKK, Armstrong CP, Rees BI (1994) Long-term pain: Less common after laparoscopic than open cholecystectomy. Br J Surg 81:1368-1370
- Stouthard JML, Romijn JA, van der Poll T, Endert E, Klein S, Bakker PJM, Veenhof CHN, Sauerwein HP (1995) Endocrinologic and metabolic effects of interleukin-6 in humans. Am J Physiol 268:E813-E819
- Svanvik J (1997) Microlaparoscopic cholecystectomy – the first 20 cases: Is it an alternative to conventional laparoscopic cholecystectomy? Eur J Surg 164:625
- Tait N, Little JM (1995) The treatment of gallstones. Br Med J 311:99-105
- Tan IKS. Metabolic response to illness, injury and infection. In: Oh TE ed. Intensive Care Manual. Oxford: Butterworth-Heinemann, 1997. pp711-715
- Tanaka J, Andoh H, Koyama K (1998) Minimally invasive needlescopic cholecystectomy. Surg Today Jpn J Surg 28:111-113
- Targarona E, Pons MJ, Balagué C, Espert JJ, Moral A, Martínez J, Gaya J, Filella X, Rivera F, Ballesta A, Trías M (1996) Acute phase is the only significantly reduced component of the injury response after laparoscopic cholecystectomy. World J Surg 20:528-534

- Tarnay CM, GlassKB, Munro MG (1999) Entry force and intra-abdominal pressure associated with six laparoscopic trocar-cannula systems: a randomized comparison. Obstet Gynecol 94:83-8
- Tauzin-fin P, Maurette P, Vincon G, Hecquet D, Houdek M, Bonnet F (1992) Clinical and pharmacokinetic aspects of the combination of meperidine and prilocaine for spinal anaesthesia. Can J Anaesthesia 39:655-660
- Tews G, Arzt W, Bohaumilitzky T, Füreder R, Frölich H (1991) Significant reduction of operational risk in laparoscopy through the use of a new blunt trocar. Surg Gyn Obstet 173:67-68
- Thomas WEG and the Basic Surgical Skills Working Party of the Royal College of Surgeons of England (1996) *In* The Royal College of Surgeons of England Basic Surgical Skills: Participants handbook. Edinburgh. George Stewart & Company Ltd.
- Traverso LW, Koo KP, Hargrave K, Unger SW, Roush TS, Swanstrom LL, Woods MS, Donohue JH, Deziel DJ, Simon IB, Froines E, Hunter J, Soper NJ (1997) Standardizing laparoscopic procedure time and determining the effect of patient age/gender and presence or absence of surgical residents during operation. Surg Endosc 11:226-229
- Trede M, Werthmann K, Joswig M, Schwab M (1995) State of the art – 100 years of conventional cholecystectomy. Progress in Surgery 22:32-37
- Turner DJ (1996) A new, radially expanding access system for laparoscopic procedures versus conventional cannulas. J Am Assoc Gynecol Laparosc 3:609-615
- Twycross RG, Wilcock A, Thorp S. Analgesics. In: Twycross RG, Wilcock A, Thorp S eds. Palliative care formulary. Oxford: Radcliffe Medical Press, 1998
- Uco H, Honda M, Adachi M, Inoue H, Nakashima H, Arinaga S, Akiyoshi T (1994) Minimal increase in serum Interleukin-6 levels during laparoscopic cholecystectomy. Am J Surg 168:358-360
- Unger SW, Paramo J, Perez-Izquierdo M (1998) Smaller is better. Surg Endosc 12:1450

- Unger SW, Paramo J, Perez M (2000) Microlaparoscopic cholecystectomy. Surg Endosc 14:336-339
- van der Poll T, Braxton CC, Coyle SM, Barbosa K, Kumar A, Calvano SE, Lowry SF (1995) Effect of epinephrine on cytokine release during human endotoxaemia. Surg Forum 46: 102-103
- van der Poll T, Jansen J, Endert E, Sauerwein HP, van Deventer SJH (1994) Noradrenaline inhibits lipopolysaccharide-induced Tumour Necrosis Factor and Interleukin 6 production in human whole blood. Infect Immun 62: 2046-2050
- Vander Velpen GC, Shimi SM, Cuschieri A (1993) Outcome after cholecystectomy for symptomatic gallstone disease and effect of surgical access: Laparoscopic v open approach. Gut 34:1448-1451
- Vander Velpen GC, Penninckx F, Kerremans R, Van Damme J, Arnout J (1994) Interleukin-6 and coagulation-fibrinolysis fluctuations after laparoscopic and conventional cholecystetomy. Surg Endosc 8:1216-1220
- Van Snick J (1990) Interleukin-6: An overview. Annu Rev Immunol 8:253-278
- Veress J (1938) Neues Instrument zur Ausführung von Brust-oder Bauchpunktionen und Pneumothoraxbehandlung. Deutsche Medizinische Wochenschrift 41:1480-1481
- Vitale GC, Collet D, Larson GM, Cheadle WG, Miller FB, Perissat J (1991) Interruption of professional and home activity after laparoscopic cholecystectomy among American and French patients. Am J Surg 161:396-398
- Voyles CR, Petro AB, Meena AL, Haick AJ, Koury AM (1991) A practical approach to laparoscopic cholecystectomy. Am J Surg 161:365-370
- Wahba RWM, Béïque F, Kleiman SJ (1995) Cardiopulmonary function and laparoscopic cholecystectomy. Can J Anaesth 42:51-63
- Walder AD, Aitkenhead AR (1997) Role of vasopressin in the haemodynamic response to laparoscopic cholecystectomy. Br J Anaesth 78:264-266

- Wallace DH, Serpell MG, Baxter JN, O'Dwyer PJ (1997) Randomized trial of different insufflation pressures for laparoscopic cholecystectomy. Br J Surg 84:455-458
- Watanabe Y, Sato M, Ueda S, Abe Y, Horuichi A, Doi T, Kawachi K (1997) Microlaparoscopic cholecystectomy – the first 20 cases: Is it an alternative to conventional LC? Eur J Surg 164:623-625
- Watson RWG, Redmond HP, McCarthy J, Burke PE, Bouchier-Hayes D (1995) Exposure of the peritoneal cavity to air regulates early inflammatory responses to surgery in a murine model. Br J Surg 82:1060-1065
- Webster EL, Torpy DJ, Elenkov IJ, Chrousos GP (1998) Corticotropin-releasing hormone and inflammation. Ann NY Acad Sci 840:21-32
- Wellwood J (1996) Randomised trial of laparoscopic versus small-incision cholecystectomy. Lancet 347:1622-1623
- West MA, Hackam DJ, Baker J, Rodriguez JL, Bellingham J, Rotstein OD (1997) Mechanism of decreased *in vitro* murine macrophage cytokine release after exposure to carbon dioxide. Ann Surg 226:179-190
- Westerband A, Van De Water JM, Amzallag M, Lebowitz PW, Nwasokwa ON, Chardavoyne R, Abou-Taleb A, Wang X, Wise L. (1992) Cardiovascular changes during laparoscopic cholecystectomy. Surg Gyn Obstet 175:535-538
- Wherry DC, Marohn MR, Malanoski MP, Hetz SP, Rich NM (1996) An external audit of laparoscopic cholecystectomy in the steady state performed in Medical Treatment Facilities of the Department of Defense. Ann Surg 224:145-154
- Wilson RG, Macintyre IMC (1993) Symptomatic outcome after laparoscopic cholecystectomy. Br J Surg 80:439-441
- Wolf JS, Carrier S, Stoller ML (1994) Gas embolism: Helium is more lethal than carbon dioxide. J Laparoendosc Surg 4:173-177

- Wortel CH, van Deventer SJH, Aarden LA, Lygidakis NJ, Büller HR, Hoek FJ, Horikx J, ten Cate JW (1993) Interleukin–6 mediates host defense responses induced by abdominal surgery. Surgery 114:564-570
- Wu W, Zbuzek VK (1982) Vasopressin and anesthesia surgery. Bull N Y Acad Med 58:427-442
- Yee J, Christou NV (1994) The local role of tumour necrosis factor α in the modulation of neutrophil function at sites of inflammation. Arch Surg 129:1249-1255
- Yoshida T, Kobayashi E, Suminaga Y, Yamauchi H, Kai T, Toyama N, Kiyozaki H, Fujimura A, Miyata M (1997) Hormone-cytokine response. Pneumoperitoneum vs abdominal wall-lifting in laparoscopic cholecystectomy. Surg Endosc 11:907-910
- Yuan R, Lee W, Yu S (1997) Mini-laparoscopic cholecystectomy: A cosmetically better, almost scarless procedure. J Laparoendosc Adv Surg Tech 7:205-211
- Zollikofer R (1924) Zur laparoskopie. Schweizerische Medizinische Wochenschrift 11:264-265