Extraperitoneal Approach Reduces Neutrophil Activation, Systemic Inflammatory Response and Organ Dysfunction in Aortic Aneurysm Surgery*

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Objectives: to compare the effects of transperitoneal and extraperitoneal approaches on systemic inflammatory response, neutrophil activation and organ dysfunction in elective abdominal aortic aneurysm (AAA) repair.

Patients and methods: twenty patients admitted for elective infrarenal AAA repair were prospectively randomised into transperitoneal (n=10) or extraperitoneal (n=10) groups. Neutrophil activation was assessed by measuring the plasma levels of neutrophil elastase/z-anti-trypsin complexes before surgery, intraoperatively and at 6 h, 12 h, 24 h and then daily after surgery. Venous blood samples for estimation of liver function tests, full blood counts, urea and electrolytes and arterial samples for blood gas analysis were taken daily from preoperatively to day 5 after surgery. Multiple organ dysfunction (MOD) and systemic inflammatory response (SIR) scores were calculated daily.

Results: the concentrations of neutrophil elastase/z-anti-trypsin complexes were significantly higher in the transperitoneal group at 6 h after surgery compared to the extraperitoneal group (799(455–921) ng/ml (median(i.q.r.)) vs 307(171–395) ng/ml, p<0.005), and at 12 h (397(364–936) ng/ml vs 319(134–352) ng/ml, p<0.05). The MOD scores were significantly higher in the transperitoneal group in comparison to the extraperitoneal group at day 1 (2.5(2–3.3) vs 1(0–1), p<0.001) and day 2 (2.5(2–3.3) vs 1(0–1), p<0.001). The SIR scores were also significantly higher at day 1 (1(0–2) vs 0, p<0.01), day 2 (1.5(0–2.3) vs 0, p<0.01), and day 3 (1(0–1) vs 0, p<0.05).

Conclusions: neutrophil activation, systemic inflammatory response and organ dysfunction are increased in elective AAA repair when a transperitoneal approach is used. This may be related to intestinal manipulation and mesenteric traction which are reduced in the extraperitoneal approach.

Key Words: Abdominal aortic aneurysm; Neutrophil activation; Organ dysfunction.

Introduction

Multiple organ dysfunction syndrome (MODS) is a common cause of late death following repair of ruptured abdominal aortic aneurysms (AAAs). Although the 30-day mortality rate in elective AAA repair is much lower at around 5%, MODS contributes to a significant proportion of the overall deaths. Single organ dysfunction is not uncommon and may pose an additional strain on other organs and systems particularly those which have been previously compromised. Cardiac, respiratory and renal complications account for the majority of morbidity following AAA surgery and contribute significantly to the mortality.

Intestinal mucosal barrier dysfunction, systemic inflammatory response syndrome (SIRS), neutrophil recruitment and activation have been demonstrated in patients undergoing AAA surgery and may play an important role in the aetiology of MODS. Intestinal manipulation and ischaemia-reperfusion injury to the gut and lower limbs secondary to clamping and unclamping of the aorta or hypovolaemia are factors that may lead to intestinal mucosal barrier dysfunction, which may in turn lead to bacterial translocation and endotoxaemia. This induces a systemic inflammatory response characterised by an increased production of pro-inflammatory cytokines which can trigger other inflammatory cascades such as the complement, coagulation and kinin systems. They also activate polymorphonuclear neutrophils with further production.

*Presented at the XIVth Annual ESVS Meeting, London 2000. † Please address all correspondence to: L. L. Lau, Vascular Surgery Unit, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, Northern Ireland.
of inflammatory and toxic mediators resulting in microvascular damage and remote organ injury. A significant correlation was found between endotoxaemia, cytokine production and organ dysfunction following open AAA repair.10,16

Surgical repair of AAAs is undergoing continuous refinements and the results of elective conventional open repair have greatly improved. The development of a variety of alternative approaches and techniques have facilitated the operative management of complex aneurysmal disease and reduced the physiological stresses of these major procedures, especially in high-risk patients. The transperitoneal approach is the most widely used method of aneurysm exposure but recently there has been a resurgence of interest in the extraperitoneal approach. Some surgeons maintain that the extraperitoneal technique offers technical and physiological advantages over the conventional transperitoneal route.17,18 This may be related to the non-violation of the peritoneal cavity and avoidance of intestinal manipulation as compared to the transperitoneal route. Significant haemodynamic changes have been demonstrated during transperitoneal exposure of aorta which correlates in time and magnitude with the release of vasoactive agents.19,20 These haemodynamic alterations may compromise splanchnic perfusion and lead to intestinal mucosal barrier dysfunction. An increase in intestinal permeability, greater degree of endotoxaemia and higher interleukin-6 production has previously been demonstrated in patients undergoing transperitoneal AAA repair as compared to the extraperitoneal route.14,21

The aim of this study is to investigate the effects of transperitoneal and extraperitoneal approaches on systemic inflammatory response, neutrophil activation and organ dysfunction in elective AAA repair.

**Patients and Methods**

Patients undergoing elective infrarenal abdominal aortic aneurysm repair were prospectively randomised, using a sealed envelope system, into either the transperitoneal (TP) or extraperitoneal (EP) approach after informed written consent. Patients were excluded from the study if they had previous history of abdominal or aortic surgery, inflammatory bowel disease, gastrointestinal malignancy or chronic inflammatory disorders. Patients with diabetes mellitus, renal impairment (serum creatinine >140 mmol/l), poor ventricular function on echocardiogram (ejection fraction <50%) or any condition that favoured one or the other approach were also excluded. This study was approved by the Research Ethics Committee of the Queen’s University of Belfast.

All patients received general anaesthesia with propofol (AstraZeneca, Cheshire, U.K.). Prophylactic antibiotics were given intravenously during anaesthetic induction (1.5 g Cefuroxime, GlaxoWellcome, Middlesex, U.K.). Central venous and arterial catheters were inserted into internal jugular vein and radial artery respectively for haemodynamic monitoring. All patients received 70 IU/kg of heparin prior to aortic cross-clamping. Perioperative epidural analgesia with fentanyl and bupivacaine (AstraZeneca, Cheshire, U.K.) was used in all patients.

In the transperitoneal approach a midline abdominal incision was used. After general laparotomy, the small intestine was placed in a plastic gut bag and the bag was tightened just enough to retain but not strangulate the small intestine. This was then exteriorised and retracted to the right side of the abdominal wound before aortic dissection. In the extraperitoneal group a left subcostal transverse incision was used. After dividing the respective muscle layers, the peritoneum was dissected free from the posterior abdominal wall and the left kidney to expose the abdominal aorta. A self-retaining retractor system (Omni-Tract Surgical, Minnesota, U.S.A.) was used routinely in both groups of patients. The surgical repair was performed using an inlay graft technique. All operations were performed by either of two consultant vascular surgeons.

Operative details including total operative time, aortic cross-clamp time and the amount of blood lost and transfused were recorded. All patients were transferred from the operating room to intensive care unit for the immediate postoperative period and later transferred to the vascular surgical ward when appropriate. All adverse clinical events were recorded.

**Blood sampling**

Venous blood samples were taken via the central venous catheter at pre-induction (PI), just before aortic cross-clamp time and the amount of blood lost and transfused were recorded. All patients were transferred from the operating room to intensive care unit for the immediate postoperative period and later transferred to the vascular surgical ward when appropriate. All adverse clinical events were recorded.

Eur J Vasc Endovasc Surg Vol 21, April 2001
count, liver and renal functions, and arterial blood gases. As patients were prescribed different concentrations of oxygen, the partial pressure of arterial oxygen (PaO₂) to concentration of inspired oxygen (FiO₂) was calculated. All assays were performed by investigators who were blinded to the randomisation.

**Neutrophil elastase/α₁-anti-trypsin (NE/AAT) complex assay**

Plasma concentrations of neutrophil elastase/α₁-anti-trypsin (NE/AAT) complex were measured using a Sandwich ELISA. A microtitre plate (Maxisorb, GIBCO BRL, Life Technologies, Paisley, U.K.) coated with anti-human neutrophil elastase IgG (The Binding Site, Birmingham, U.K.) was used. Diluted plasma test samples (1:100) and standards were assayed in duplicates and read at 450 nm on a ThermoMax kinetic reader (Molecular Devices, CA, U.S.A.). The sensitivity of the assay was 5 ng/ml and the intra and inter-assay coefficients of variation were 4.6% and 7.2%, respectively.

**APACHE II, SIR and MOD scores**

The APACHE II, systemic inflammatory response (SIR) and multiple organ dysfunction (MOD) scores were calculated daily after surgery.²²,²³

**Statistical analysis**

Statistical analysis was performed using the SPSS v8.0 (SPSS Inc., U.S.A.) statistical package. The data were expressed as median (interquartile range) and analysed using Kruskal–Wallis analysis of variance or Wilcoxon signed rank test as appropriate. For correlation, Spearman’s rank correlation coefficient (rₛ) was used. Significance was taken at the 5% level.

**Results**

Twenty patients were recruited and randomised into the TP (n = 10) and the EP (n = 10) groups. No significant difference was observed in the age, sex distribution, aneurysm size, ASA class, duration of surgery, aortic cross-clamp time, the amount of blood lost or transfused or the intraoperative intravenous fluids infused (Table 1). The preoperative haematological and biochemical parameters were similar in both groups (Table 2). In the TP group one patient died at day 2 postoperatively due to myocardial infarction. Another patient developed an ischaemic cerebrovascular accident at day 3 which significantly delayed discharge from the hospital. One patient developed chest infection confirmed on sputum culture and two other patients developed paralytic ileus which delayed enteral feeding. In the EP group one patient developed diarrhoea at day 2 with no other clinical signs of ischaemic colitis and settled spontaneously. Another patient developed a urinary tract infection requiring antibiotic treatment.

**Organ functions**

In the TP group the plasma concentrations of NE/AAT complex increased significantly after aortic cross-clamp release (631(498–881) ng/ml), at 6 h (799(455–921) ng/ml) and 12 h (397(364–936) ng/ml) compared to the PI level (219(150–378) ng/ml) (p<0.05, Wilcoxon signed rank test) (Fig. 1). There was a non-significant rise in the EP group at the same time points. The rise in the TP group of patients was significantly higher when compared to the EP group at 6 h (799(455–921) ng/ml vs 307(171–395) ng/ml, p<0.005) and at 12 h (397(364–936) ng/ml vs 319(134–352) ng/ml, p<0.05). The neutrophil counts were elevated in both groups reaching a maximum at D2, but there was no significant difference observed between the groups.
Table 1. Demographic and operative details (median, i.q.r.) (Mann–Whitney U test).

<table>
<thead>
<tr>
<th></th>
<th>Transperitoneal group (n=10)</th>
<th>Extraperitoneal group (n=10)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>77.5 (67.5–79.5)</td>
<td>67 (61.5–79)</td>
<td>ns</td>
</tr>
<tr>
<td>AAA size (mm)</td>
<td>6.6 (5.7–7.7)</td>
<td>6.9 (6.4–7.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (M, F)</td>
<td>9M, 1F</td>
<td>10M</td>
<td>ns</td>
</tr>
<tr>
<td>ASA class</td>
<td>2 (2–3)</td>
<td>2 (2–3)</td>
<td>ns</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>130 (120–140)</td>
<td>152 (129–168)</td>
<td>ns</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>62 (50–69)</td>
<td>55 (48–68)</td>
<td>ns</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>2208 (1021–2342)</td>
<td>1425 (1071–2321)</td>
<td>ns</td>
</tr>
<tr>
<td>Blood transfused (units)</td>
<td>2 (0–4)</td>
<td>2 (0–3.3)</td>
<td>ns</td>
</tr>
<tr>
<td>IV fluids infused (ml)</td>
<td>3800 (3250–4600)</td>
<td>3500 (3000–4488)</td>
<td>ns</td>
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Table 2. Preoperative haematological and biochemical parameters (median, i.q.r.) (Mann–Whitney U test).

<table>
<thead>
<tr>
<th></th>
<th>Transperitoneal group (n=10)</th>
<th>Extraperitoneal group (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>14 (12.1–15.7)</td>
<td>13.7 (12.6–14.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Platelet count (× 10^9/l)</td>
<td>190 (143–217)</td>
<td>202 (179–239)</td>
<td>ns</td>
</tr>
<tr>
<td>White cell count (× 10^9/l)</td>
<td>8 (5–9.7)</td>
<td>8.5 (7.8–9.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>6.4 (4.9–8.4)</td>
<td>7 (5.9–8.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (umol/l)</td>
<td>103 (89–125)</td>
<td>94 (86–98)</td>
<td>ns</td>
</tr>
<tr>
<td>Bilirubin (umol/l)</td>
<td>11 (7.8–16)</td>
<td>11.5 (8–12)</td>
<td>ns</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>22 (20–23.3)</td>
<td>25 (20.5–27.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>39 (37–43)</td>
<td>40 (38–42)</td>
<td>ns</td>
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</table>

Fig. 2. Partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratios (median, i.q.r.) from pre-op (PO) to day 5 (D5). (∗) p<0.05, Kruskal–Wallis test. (■) TP group; (Φ) EP group.

the EP group but there was a significant increase in serum creatinine concentrations in the TP group at D1 and a significant difference between the two groups was found at D1 and D2 (Fig. 3). No correlation was observed between the amount of intraoperative intravenous fluids infused and the postoperative serum urea and creatinine concentrations.

A significant elevation in serum bilirubin and aspartate transaminase (AST) concentrations was found preoperatively in the TP group but not in the EP group. The increase in serum concentrations in the TP group was significant when compared to the EP group (Fig. 4). There was no significant difference observed between the two groups in the serum alanine transaminase or alkaline phosphatase concentrations.
APACHE II, SIR, MOD scores

The APACHE II scores increased significantly in both groups during the postoperative days but there was no significant difference between the two groups. A significant increase in SIR and MOD scores was found in the TP group ($p<0.05$) but not in the EP group and this increase was highly significant ($p<0.005$) when the two groups were compared (Fig. 5).

No correlation was observed between the increased concentrations of NE/AAT complex and the operating time, aortic cross-clamp time, amount of blood lost and transfused. There was also no correlation between the postoperative serum bilirubin concentrations and the amount of blood lost and transfused in the TP group.

Discussion

Multiple organ dysfunction syndrome has been suggested to be the leading cause of death after elective infrarenal aortic reconstruction.\textsuperscript{3,24} Although the primary pathology causing MODS may vary, it is found to be the “final common pathway” leading to the demise of these patients in up to 50% of cases. Visceral organ dysfunction has been demonstrated to be the most common aetiological factor in the development of MODS.\textsuperscript{3,24,25} Transient organ dysfunction affecting the heart, lung, gut or kidney, due possibly to an increase in microvascular permeability, may affect the majority of patients undergoing aortic reconstruction.\textsuperscript{26}

The pathophysiology of the perioperative inflammatory reaction and organ dysfunction following open repair of AAA is complex. Experimental and clinical evidence supports the development of a systemic inflammatory response and neutrophil activation as important factors which may be triggered by surgical trauma and ischaemia-reperfusion injury to the intestine and lower limbs.\textsuperscript{11,27–30} Reperfusion of the gut and lower limbs after aortic cross-clamp release produces oxygen-derived free radicals which may damage tissues by direct toxicity or indirectly via the activation of eicosanoids, cytokine and complement cascades. Some of the by-products of these latter cascades are potent chemoactivators that are capable of initiating neutrophil activation and chemotaxis.\textsuperscript{12} Neutrophils can cause endothelial injury through elastase, lysosomal enzyme and superoxide radical production, resulting in organ damage.\textsuperscript{31,32}
This study demonstrates significant increases in neutrophil activation, systemic inflammatory response and organ dysfunction in transperitoneal AAA repair compared to the extraperitoneal approach. As the amount of blood lost, aortic cross-clamp time and duration of surgery were similar in the two groups of patients, the differences observed in the host response and organ impairment may be explained by the technical differences in the two approaches. This supports the findings by others who argued that the extraperitoneal route in aortic exposure offers some protection from organ dysfunction. Nevelsteen et al. and O’Sullivan et al. have reported in separate prospective studies that pulmonary function and perioperative oxygenation were significantly better in the extraperitoneal approach in comparison to the transperitoneal approach. The finding of significantly higher PaO$_2$/FiO$_2$ ratios in the extraperitoneal group during the postoperative period in the current study concurs with their observations. Neutrophil activation and release of cytokines have been shown to be associated with transient pulmonary dysfunction following elective aortic reconstruction. However, no correlation was found between the increased NE/AAT complex concentrations and the reduction in the PaO$_2$/FiO$_2$ ratios in this cohort of patients. This may suggest that factors other than neutrophil activation are involved in the postoperative pulmonary dysfunction following AAA surgery.

Many studies have focused on aortic cross-clamping and unclamping as sources of cardiovascular stress during aortic surgery, with very little attention focused on the earlier phases of the operation. Some workers have shown that the most pronounced haemodynamic change seems to occur after evisceration of the small intestine in preparation for aortic reconstruction, and not after clamping or unclamping of the aorta. This is further supported by the decrease in mean arterial blood pressure and systemic vascular resistance associated with an increase in the heart rate and cardiac output during exteriorisation of the small intestine when the mesentery is under traction. This haemodynamic response was found to be absent when an extraperitoneal approach was used. These physiological changes have been attributed to the generation of endogenous prostacyclin as pretreatment with ibuprofen attenuates their development. Nevertheless, these haemodynamic effects may lead to splanchnic hypoperfusion which is compounded by aortic cross-clamping, ligation of mesenteric vessels and hypotension due to hypovolaemia. The resultant ischaemia may lead to gut mucosal barrier dysfunction with endotoxaemia and bacterial translocation.

The greater increase in serum AST and bilirubin in the TP group may be explained by the greater degree of endotoxaemia demonstrated in patients undergoing transperitoneal AAA repair in comparison to the extraperitoneal approach. Endotoxaemia may be deleterious to hepatocytes. The high levels of tumour necrosis factor-α demonstrated in the portal circulation during transperitoneal aortic surgery even before aortic cross-clamping further supports the significant role of intestinal manipulation and mesenteric traction on gut mucosal barrier dysfunction.

Mesenteric traction may cause ischaemia-reperfusion injury to the intestine and the generation of oxygen-derived free radicals and other pro-inflammatory mediators. These deleterious products, although initially confined to the ischaemic region, when generated in large quantities will spill into the systemic circulation and consequently lead to remote organ injury. An increase in pulmonary permeability and hepatocellular injury have been observed when ischaemic intestine is revascularised. A fall in the concentrations of α-tocopherol, the major lipid phase anti-oxidant, has been found in patients undergoing aortic surgery, suggesting its consumption by free-radical induced lipid peroxidation.
greater pulmonary, hepatic and renal impairment in the TP group compared to the EP group may indicate remote organ injury secondary to a more severe reperfusion insult to the bowel.

There were two major postoperative complications (myocardial infarction and cerebrovascular accident) in the TP group of patients but none in the EP group. However, the number of patients in this study is inadequate for any useful clinical outcome analysis. Most of the organ dysfunction in this cohort of patients was detected only as biochemical changes without major clinical manifestation. The use of the SIR and MOD scores may give more accurate information about the pathophysiological state of the patients and allow better management of the patients. The significantly higher SIR and MOD scores in the TP group merely support the greater degree of host inflammatory response and organ impairment in these patients.

The results of this study demonstrate that the transperitoneal approach to the aorta is associated with a greater degree of systemic inflammatory response, neutrophil activation and postoperative organ dysfunction. This may be related to intestinal manipulation and mesenteric traction which are avoided in the extraperitoneal approach. These results support the concept that the gut plays a leading role in the aetiology of SIRS and MODS. This is supported by the more recent use of the endovascular technique which completely avoids laparotomy and intestinal manipulation. Workers have shown a reduction in bowel ischaemia, endotoxaemia and cytokine generation following endovascular repair of AAA compared to the open technique. Unfortunately, others have found contradictory results. Neutrophil activations have been demonstrated following endovascular surgery, suggested to be a result of radiological contrast used during the endovascular procedure which may have putative neutrophil activating effects. However, it is difficult to know if the reduction in inflammatory response in both the endovascular and extraperitoneal techniques is associated with improved clinical outcome. A study to determine this will require a larger patient population.

Acknowledgements

This study was supported by the Vascular Research Funds from the Vascular Surgery Unit of the Belfast City Hospital.

References


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Accepted 6 January 2001