International Journal of Surgery (2008) 6, 253–260

INTERNATIONAL JOURNAL OF SURGERY

www.theijs.com

REVIEW

Peritoneal adhesions: Facing the enemy

Emre Ergul*, Birol Korukluoglu

Ankara Ataturk Teaching and Research Hospital, Bilkent, 06800 Ankara, Turkey

Available online 3 June 2007

KEYWORDS
Post-surgical intraperitoneal adhesions

Abstract *Background:* Postsurgical adhesions severely affect the quality of life of millions of people worldwide. Numerous attempts have been made to prevent or reduce the incidence of peritoneal adhesions, but with limited success.
Data sources: An extensive Medline search, textbooks, scientific reports and scientific journals are the data sources. We also reviewed reference lists in all articles retrieved in the search as well as those of major texts regarding postsurgical intraperitoneal adhesion formation.
Conclusions: A multifactorial approach including minimizing tissue injury, prophylactic antibiotic usage to reduce infectious morbidity, and biochemical agents with or without biomechanical barriers will reduce the amount and severity of adhesions. However, further research is needed to establish the safety, effectiveness and also the cost/benefit ratio of these substances in human subjects.

Introduction

Abdominal surgery can cause adhesions between tissues and organs. Approximately 93% of the patients who had undergone one or more previous surgeries had intra-abdominal adhesions.[1] Postsurgical adhesions are a consequence of injured tissue surfaces (following incision, cauterization, suturing or other means of trauma) fusing together to form scar tissue. Recently it was found[2] that all patients who had undergone at least one prior abdominal surgery developed between one to more than ten adhesions. Postsurgical adhesions severely affect the quality of life of millions of people worldwide, causing small-bowel obstruction,[1] difficult reoperative surgery,[3] chronic abdominal and pelvic pain,[4] and female infertility.[5]

Reoperating through a previous wound can be extremely difficult, risky, and potentially dangerous. Also, adhesiolysis extends operating time, anesthesia, and recovery time and causes additional risks to the patient such as blood loss, visceral damage including injury to the bladder, enterocutaneous fistulas, and resection of damaged bowel.[6]

Numerous attempts have been made to prevent or reduce the incidence of peritoneal adhesions, but with limited success.[7]

History

Intra-abdominal adhesions were described at postmortem examination of a patient with peritoneal tuberculosis[8] in 1836. Some studies suggested in 1849 that coagulated lymph

* Corresponding author. Tel.: +90 312 2912525; fax: +90 312 2123414.
E-mail address: dreergul@gmail.com (E. Ergul).

1743-9191/$ - see front matter © 2007 Surgical Associates Ltd. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijsu.2007.05.010

turns into fibrinous adhesions.[9] In 1872, Bryant described a fatal small bowel obstruction due to intra-abdominal adhesions after an ovarian cyst excision.[10] Gibson suggested, in a thousand patients between 1888 and 1898, that intraperitoneal adhesions cause 18 (6%) of the acute intestinal obstructions.[11] Vick suggested, in a retrospective study of 6982 patients admitted to 21 hospitals in Britain during the period 1925–1930, that strangulated hernias accounted for half of the total cases, while malignant disease was responsible for 13% and adhesions accounted for a mere 7%.[12]

Incidence

In 1930, only 7 (3%) of the acute intestinal obstructions were caused by adhesions,[12] but a study during 1942–1945 of 1252 patients with intestinal obstruction suggested that 31% of the acute intestinal obstructions were caused by adhesions. Between 1985–1986, McEntee et al. suggested that in 236 patients with intestinal obstruction, 32% of the acute intestinal obstructions were caused by adhesions.[13] Cox et al. suggested that postoperative adhesions accounted for 64–79% of admissions with small bowel obstruction.[14] Adhesions are the most common cause of large and small intestinal obstructions in the Western world and account for approximately one third to one half of all intestinal and 60–70% of the small-bowel obstructions.[15]

Congenital or inflammatory adhesions rarely give rise to intestinal obstructions, except for malformation.[16] However, between 49 and 74% of the small bowel obstructions are caused by post surgical adhesions.[4,17,18] Small bowel obstructions from adhesions are responsible for a large proportion of general surgical admissions and unavoidable operations in current surgical practice. Approximately 1% of all surgical admissions and 3% of lsaparotomies are the result of intestinal obstruction due to adhesions.[1] In pediatric patients bowel obstruction from adhesions is most prevalent; 8% of neonates undergoing abdominal surgery require a future laparotomy for this complication.[19]

Structure and function of the peritoneum

The peritoneal cavity encompasses the potential space defined by the mesothelial serous membrane and extends superiorly from the diaphragm to the pelvis in its most caudad extent.[20] Anteriorly the peritoneal cavity reflects onto the posterior aspect of the anterior abdominal musculature. Posteriorly the peritoneal lining lies superficial to the retroperitoneal viscera, including the aorta, vena cava, ureters, and kidneys. The anterior and posterior peritoneal layers are described collectively as the parietal peritoneum. The visceral peritoneum represents the mesothelial lining cells that are reflected onto the surface of the viscera, including the stomach, small bowel, spleen, liver, gallbladder, ovaries, uterus, and portions of the bladder, colon, and pancreas. The peritoneum covering the intestine is the serosa of the bowel. The peritoneum also lines the lesser sac, which communicates with the remainder of the peritoneal cavity via the epiploic foramen (foramen of Winslow). In women the peritoneal lining is reflected onto the fallopian tubes, which communicate through the open fimbriated ends with the uterus and vagina.[20]

The total area of the peritoneum is approximately 1.8 m^2. It is formed by a single layer of mesothelial cells with an underlying supporting layer of highly vascularized loose connective tissue.[20] Mesothelial cells are organized into two discrete populations: cuboidal cells and flattened cells. Gaps (stomata) between neighboring cells of the peritoneal mesothelium are found only among cuboidal cells. Peritonitis increases the width of these stomata. Beneath the mesothelial cells is a basement membrane of loose collagen fibers, which offers little resistance to diffusion of molecules smaller than 30 kDa. The basement membrane overlies a complex connective tissue layer that includes collagen and other connective tissue proteins, elastic fibers, fibroblasts, adipose cells, endothelial cells, mast cells, eosinophils, macrophages, and lymphocytes.[20]

Peritoneal fluid is secreted by the peritoneal serosa and has the properties of lymph. Diaphragmatic lymphatic channels provide a means for the entry of peritoneal fluid (and any bacteria and proinflammatory mediators) through the thoracic duct into the venous circulation. Inspiration decreases intrathoracic pressure relative to intra-abdominal pressure, creating a pressure gradient favoring fluid movement out of the abdomen.[20]

Under normal circumstances the peritoneal cavity is largely a potential space, as only a thin film of fluid separates the parietal and visceral layers. This fluid layer serves as a lubricant, allowing the abdominal viscera to slide freely within the peritoneal cavity. The capacity of this space is illustrated during peritoneal dialysis, as 2–3 L of fluid are instilled into the peritoneal cavity without any patient discomfort.[20]

Any inflammatory event in the peritoneal cavity results in local peritoneal irritation with loss of regional mesothelial cells. The defect in the mesothelial lining is repaired by ''metastasis'' of nearby mesothelial lining cells. Peritoneal defects heal everywhere simultaneously. A large peritoneal defect heals in the same amount of time as a small defect, usually 3–5 days. This process is rapid and usually reconstitutes the peritoneal continuity without adhesion formation. The origin of the migrating mesothelial cells remains obscure; they may arise from submesothelial stem cells.[20]

Peritoneal healing and adhesion formation

A peritoneal injury invokes an inflammatory response from the serosal surface with the concurrent loss of the mesothelium.[21] Increased permeability of the blood vessels in the traumatized tissues due to the release of PGE_2 and histamine produces an outpouring of serosanguineous exudates rich in inflammatory cells. This exudate coagulates within a period as short as 3 h. Normally, the majority of fibrinous attachments so formed are lysed within a few days of development.[22] If they persist for 3 days or longer, fibroblastic proliferation may occur within them, causing adhesion formation.

Following surgery, the macrophages increase in number and change function. These postsurgical macrophages are entirely different from the resident macrophages and secrete variable substances, including cyclooxygenase and lipoxygenase metabolites, plasminogen activator, plasminogen activator inhibitor (PAI), collagenase, elastase,

interleukins (IL) 1 and 6, tumor necrosis factor (TNF), leukotriene B_4, prostaglandin E_2 etc.[23–25] Postsurgical intraperitoneal macrophages recruit new mesothelial cells onto the surface of the injury. These mesothelial cells later and in response to cytokines and other macrophage-secreted mediators form small islands which proliferate into sheets of mesothelial remesothelialization.[17]

The organization of the fibrin gel matrix is of major importance in adhesion formation. This matrix forms in several steps: from fibrinogen to fibrin monomer, then to soluble fibrin polymer, and finally, by rinsing tissues with irrigating solutions (during surgery), becomes insoluble fibrin polymer. This last product interacts with proteins, including fibronectin, to form the fibrin gel matrix. This matrix includes leukocytes, erythrocytes, platelets, endothelium, epithelium, mast cells, and cellular and surgical debris. Two damaged peritoneal surfaces coming into apposition while covered with fibrin gel matrix may form an adhesion, not only at the time of surgical injury, but also during the next 3–5 days.[26,27] Saed and Diamond suggested that the adhesion fibroblasts develop a specific phenotype which in part is characterized by the over-expression of alpha smooth muscle cell actin.[28] The over-expression of alpha smooth muscle cell actin in adhesion fibroblasts indicates a possible response to peritoneal injury.

Among the earliest factors identified as inducing peritoneal adhesion formation was ischemia.[29] Recent investigators have found that the production of ischemic tissue is the most reliable means of inducing adhesion formation for the evaluation of prophylactic modalities. Induction of ischemia by coagulation, ligation, or devascularization as with a free peritoneal graft has all been associated with the induction of peritoneal adhesions. More recent data from a number of investigators[22,30–34] have established that the peritoneum which has been made ischemic loses its spontaneous ability to lyse fibrin. This loss of ability may take as long as 24 h to occur maximally. Moreover, ischemic tissue also inhibits fibrinolysis by adjacent normal tissue.[22]

Weapons of a surgeon to prevent peritoneal adhesions

Surgical technique

Grafting or suturing peritoneal defects increases ischemia, devascularization, and necrosis, predisposing the site to decreased fibrinolytic activity and increased adhesion formation.[35] Ryan et al. also reported that normal saline, Ringer's solution, and Medium 199 were equally ineffective in reducing adhesion formation when fresh blood was dripped intraperitoneally immediately after a wetting procedure.[36] Thus, it appears that simply keeping the serosa moist does not prevent a significant impairment of fibrinolytic function. Polubinska et al.[37] reported that exposure of the peritoneal mesothelial cells to 0.9% NaCl, Hanks', Earle's salts solution, or peritoneal dialysis fluid with high concentration of glucose degradation products results either in reduction of their viability or in loss of their fibrinolytic activity. They also suggested that peritoneal dialysis fluid with low content of glucose degradation products appears to be the optimal solution causing the least damage to mesothelial cells and therefore may be the ideal solution for rinsing the abdominal cavity with low risk of inducing deterioration of the mesothelial cells' fibrinolytic activity and formation of adhesions.[37] They postulated that the hypertonic dialysis fluids may be used for rinsing the abdominal cavity.

Foreign bodies have been found in a large percentage of examined postoperative adhesions.[38] Most frequently found are: surface powders from surgical gloves; lint from packs, drapes, or gowns; wood fibers from disposable paper items; and suture materials are also common contaminants. However, recent data suggest that in the absence of an additional peritoneal injury foreign bodies are an infrequent cause of adhesion induction.[39–42]

Minimizing the production of ischemic tissue remains a crucial concept. If necessary, reperitonealization should be performed with a minimal number of sutures which do not produce significant tension along the suture line. The use of microsutures may be beneficial, because their low tensile strength limits the potential for developing ischemia.[41] The application of free peritoneal or omental grafts is also contraindicated. Precise hemostasis is necessary to limit the amount of tissue rendered ischemic by crushing, ligation, or cautery. The employment of topical hemostatic agents has not been found to increase the incidence of postoperative adhesion formation and may on occasion be advantageous when obtaining hemostasis in areas of generalized oozing.[43] Several studies have found that the use of oxidized cellulose (surgicel) actually decreased subsequent adhesion formation.[44,45] Tingstedt et al. suggested that intra-abdominal administration of different charged polypeptides significantly decreased postoperative bleeding and postoperative adhesions in mice.[46] These polypeptides consisted of a combination of positively charged poly-L-lysine and negatively charged poly-L-glutamate.

Minimal atraumatic handling of tissues is essential for reducing serosal abrasion and is also recognized to reduce fibrinolytic activity. Manipulation of tissues with gloved fingers has been implied by some microsurgeons to be less traumatic than contact with surgical instruments. However, electron-microscopic studies indicate that both produce substantial serosal injury.[47]

In animal models large clots produced adhesion, but small clots did not in the absence of the peritoneal injury.[48] Hemostasis is essential, and blood should be aspirated in irrigation solution. If pinpoint electrocautery cannot provide adequate hemostasis, then the smallest gauged synthetic suture should be used, with special consideration to avoid tissue strangulation.[49]

The use of the CO_2 laser in gynecologic microsurgery has also been implied to be beneficial.[50,51] Sutton and MacDonald have been reported that laser laparoscopic adhesiolysis is safe, effective and relatively easy.[52]

Further studies suggested that compresses, which were moistened with hot saline (over 45 °C), significantly increased intraperitoneal adesions.[53] Also, Smith has found saline warmed to 37 °C to be more effective than room-temperature saline or Hanks' solution.[54]

The majority of studies indicate that laparoscopy may reduce postoperative adhesion formation relative to laparotomy.[55–57] Brokelman et al. found in a randomized trial that there were no differences in tPA antigen, tPA-activity,

uPA antigen, or PAI-1 antigen concentrations in biopsies taken at the beginning compared to samples taken at the end of the operation. Different intra-abdominal pressures, light intensities and the choice dissection device did not affect any of the measured parameters. They suggested that short-term laparoscopy does not affect the peritoneal fibrinolytic activity. Intra-abdominal pressure, light intensity and choice of dissection device do not affect peritoneal activity during short-term laparoscopy.[57]

Prophylactic pharmacological modalities

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit prostaglandin and thromboxane synthesis by changing cyclooxygenase activities. By this inhibition NSAIDs decrease vascular permeability, plasmin inhibitor, platelet aggregation, and coagulation and also enhance macrophage function. NSAIDs modulate a number of aspects of inflammation and have reduced peritoneal adhesion formation in some animal models.[58–60] However, NSAIDS impair wound healing and increase the risk of bleeding.[4,61]

Glucocorticoids

Corticosteroid therapy attenuates the inflammatory response by reducing vascular permeability and liberation of cytokines and chemotactic factors. They are administered intravenously, enterically or intraperitoneally. This therapy has had mixed results.[59] Corticosteroids were studied alone or with antihistamines.[61] Antihistamines inhibit fibroblast proliferation and are usually used with corticosteroids. However, corticosteroids have side effects, such as immunosuppression and delayed wound healing.[24,59,61]

Progesterone/estrogen

Progesterone prevents adhesion formation in animal models but human studies either failed to confirm this finding or an increase in adhesion formation was noted when medroxyprogesterone acetate was used intramuscularly or intraperitoneally.[61] Neither estrogen nor gonadotropin-releasing hormone prevented adhesion formation but fewer adhesions formed than untreated animals.[62] It remains unknown whether a hypoestrogenic state leads to less postsurgical adhesions in humans.[63]

Anticoagulants

In animal models, low molecular weight heparin (LMWH) reduces peritoneal adhesion by increasing the fibrinolysis due to serine esterase activity.[64] Many authors suggested that LMWH, at standard treatment doses, prevents postsurgical intraperitoneal adhesions when administered intraoperatively either subcutaneously or intraperitoneally.[65,66]

Fibrinolytics

Fibrinolytic agents caused hemorrhagic complications, although recombinant tPA, when applied locally, reduced adhesions in animal models without increasing complication rates.[24,48,60] A promising approach in postsurgical adhesion prophylaxis was described with the use of tPA. The administration of recombinant tPA succeeded in reducing adhesion formation when studied in the rabbit model. The evidence of further studies suggests that all these approaches have had only limited success, impeded lack of safety, efficacy, and many adverse effects without eliminating the problem of postoperative adhesion formation.[17,67–70]

Antibiotics

Broad-spectrum antibiotics are commonly used for prophylaxis against postoperative infections and adhesion formation. Less intraperitoneal infection means less intraperitoneal adhesion formation. However, intra-abdominal application causes adhesion formation.[60]

Vitamin E

Vitamin E theoretically has interesting biological properties and action for the prevention of peritoneal adhesions. In vitro studies have shown that vitamin E has antioxidant, anti-inflammatory, anticoagulant, and antifibroblastic effects, and decreases collagen production. It has been successfully used, administered by the oral route, intramuscularly and especially intraperitoneally, diluted in olive oil, in animal models. Vitamin E was found effective for reducing adhesion formation by some authors.[71–73]

Methylene blue

Methylene blue is known to inhibit the generation of oxygen radicals such as superoxide by competing with oxygen for the transfer of electrons from flavor-enzymes, primarily xanthine oxidase.[74–76] This low molecular weight, partially liposoluble, vital dye, is also a known inhibitor of guanylate cyclase. It organizes the smooth muscle relaxation effects of nitric oxide, blocking its activation by blocking NO binding sites of guanylate cyclase.[77,78] In recent studies, it has been suggested that intraperitoneal application of methylene blue can be used as an effective agent in the prevention of postoperative adhesions.[79–81] Dinc et al. suggested that methylene blue prevents peritoneal adhesions but causes a significant impairment of anastomotic bursting pressure during the early phase of the wound healing process by its transient inhibitory effect on the nitric oxide pathway.[82]

Pentoxifylline

Pentoxifylline, a methyl xanthine derivate, enhances plasma fibrinolytic activity, reduces plasma fibrinogen levels, inhibits platelet aggregation and increases erythrocyte and leukocyte flexibility.[83–85] Tarhan et al. suggested that pentoxifylline prevents postoperative intraabdominal adhesions either by intraperitoneal or intravenous administration.[86]

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA-I)

Either Lovastatin or Atorvastatin increases tPA and decreases PAI-1 in human mesothelial cell incubation.[87] Aarons et al. suggested that Lovastatin and Atorvastatin reduced adhesion formation by 26% and 58%, respectively, without affecting anastomotic burst pressure, intraperitoneal administration in rats.[87]

Adjuvant barrier therapy

The ideal barrier, besides being safe and effective, should be non-inflammatory, non-immunogenic, persist during the

critical remesothelialization phase, stay in place without sutures or staples, remain active in the presence of blood and be completely biodegradable. Also, it should not interfere with healing, promote infection, or cause adhesions.[27]

Barrier solutions

Adept (Shire GmbH and Co. KG) is a 4% icodextrin solution (α-1,4-linked dextrin polymer of glucose) and reduces the extent and severity of adhesion formation in animal models.[88–93] It has also been used widely as a peritoneal dialysis solution for several years. Adept is a non-viscous adhesion barrier applied intra-abdominally after surgery. The presence of the polymer creates a constant fluid layer between peritoneal surfaces and acts to reduce adhesion formation by inducing hydroflotation throughout the abdominal cavity for several days. It is reabsorbed gradually through the lymphatic system.[94]

Hyalobarrier (Baxter GmbH) is a tissue precoating solution and forms a selective barrier made of purified autocrosslinked hyaluronan with increased density, viscosity, and adhesive properties. It remains intra-abdominally for 3–7 days.[95,96] It provides lubrication and gliding effects. After surgical trauma, the peritoneal area affected (approximately 25 $\times$ 15 mm) was covered to a depth of 3 mm by expelling successive trails of the gel out of the syringe across the surface.[97] Martin-Cartes et al. suggested that hyaluronidase gel was moderately superior to obtain reduction of consistency of the adhesion with fibrin glue.[98] Hyaluronidase gel also has the advantage of being inexpensive.

Phospholipids in the form of phosphoric acid diesters were defined as a surfactant-like substance in effluent peritoneal dialysis fluid, and possess good release and lubricating properties.[99] Experimental results in rat studies with peritoneal instillation of phosphatidylcholine upon abdominal closure seemed to reduce adhesion formation.[100–103] It may reduce the risk of adhesion development by diminishing fibrin formation between peritoneal surfaces and defects.[59]

Solid barriers

Experimental studies have demonstrated that covering lesions of the parietal peritoneum with microsurgically applied autologous peritoneal transplants can completely prevent severe adhesion formation.[27] The advantage of a synthetic barrier is that the material does not need to be obtained surgically and can be cut to size outside of the abdomen and then applied without sutures.[104]

Carboxymethylcellulose is a derivative of cellulose. Carboxymethylation of the glucosidic hydroxyl groups makes the polymer hydrophilic. It is negatively charged at physiological pH and freely soluble. It is spontaneously broken down.[63,105] It has heavy molecular weight and slow peritoneal absorption.[65] Nevertheless, it cannot completely eliminate postoperative adhesions in all cases.[106,107] Mediana et al. suggested that while carboxymethylcellulose film has been shown to decrease adhesions in other models, healing of a rabbit colonic anastomosis even in the presence of an anastomotic defect takes place, further suggesting that the stimulus for adhesion formation can overcome the antiadhesion properties of carboxymethylcellulose.[108]

Interceed TC7® is made of oxidized regenerated cellulose. It is already in routine clinical use as a ''first generation'' adhesion barrier.[89,109–112] As a mesh like product, it rapidly forms a soft gelatinous mass that provides a protective coating around healing tissue during the first 7–10 days after application.[113–115] It is absorbed in the abdominal cavity within 2 weeks.[93]

Polytetrafluoroethylene (PTFE) is a non-reactive, antithrombogenic, non-toxic synthetic fabric with small pores that inhibit cellular transmigration and tissue adherence. A PTFE barrier prevents adhesion formation and reformation regardless of the type of tissue injury or whether hemostasis is achieved.[27] It was found that expanded PTFE was associated with fewer postsurgical adhesions to the sidewall than oxidized regenerated cellulose.[116]

TachoComb H® is a tissue glue-coated collagen sponge. A statistically significant reduction in all adhesion score criteria was found by Schneider et al. in an animal model.[117]

Poly-DL-lactide (PDLA) is an absorbable copolymer system which has not been formally investigated as a barrier agent for peritoneal adhesions. Wallwiener et al. suggested that PDLA was significantly more effective in preventing adhesions than Ringer's lactate sollution.[93]

Gene therapy

Hepatocyte growth factor (HGF), also known as scatter factor, exerts multiple effects on a variety of cells, including mesothelial cells. It can stimulate the proliferation and migration of mesothelial cells, inhibit collagen deposition and has a fibrinolytic capacity.[118–120] Liu et al. demonstrated that local application of recombinant adenovirus carrying the HGF gene reduces adhesion formation in rat model.[121]

Conclusion

Strategies to reduce adhesion formation include improving surgical techniques, optimizing laparoscopy conditions, using pharmacologic interventions targeted at the inflammatory response and/or fibrin deposition, and using agents that provide a physical barrier to adhesion formation. While these strategies have provided some success, none have yet proved totally successful in abolishing adhesions. Further research to ensure that adhesion prevention is optimal is therefore essential.

References

1. Menzies D, Ellis H. Intestinal obstruction from adhesion: how big is the problem? *Ann R Coll Surg Engl* 1990;**72**:60–3.
2. Luijendijk RW, de Lange DC, Wauters CC, Hop WC, Duron JJ, Pailler JL, et al. Foreign material in postoperative adhesions. *Ann Surg* 1996;**223**:242–8.
3. Suslavich FJ, Turner NA, King PS, Brown HK. Intra-abdominal adhesions: intraoperative US. *Radiology* 1989;**172**:387–9.
4. Monk BJ, Berman ML, Montz FJ. Adhesions after extensive gynecologic surgery: clinical significance, etiology and prevention. *Am J Obstet Gynecol* 1994;**170**:1396–403.
5. Luciano AA. Prevention of postoperative adhesions. In: Nezhat CR, Berger GS, Nezhat FR, et al., editors. *Endometriosis:*

advanced management and surgical techniques. New York: Springer; 1995. p. 193—9.
6. Scovill W. Small bowel obstruction. In: Cameron JL, editor. *Current therapy in surgery*. St.Louis: Mosby; 1995. p. 100—4.
7. Ellis H. The causes and prevention of intestinal adhesions. *Br J Surg* 1982;**69**(5):241—3.
8. Hodgkin T. *Lectures on the morbid anatomy of the serous and mucous membranes*, Vol 1. London: Simpkin Marshall and Co; 1836.
9. Rokitansky C. *A Manual of pathological anatomy*, Vol 2. London: Sydenham Society; 1849.
10. Bryant T. Clinical Lectures on intestinal obstructions. *Medical Times Gazette* 1872;**1**:363.
11. Gibson CL. A study of 1000 operations for acute intestinal obstruction. *Ann Surg* 1900;**32**:486.
12. Vick RM. Statistics of acute intestinal obstruction. *BMJ* 1932; **2**:546.
13. McEntee G, Pender D, Mulvin D, McCullough M, Naeeder S, Farah S, et al. Current spectrum of intestinal obstruction. *Br J Surg* 1987;**74**:976—80.
14. Cox MR, Gunn IF, Eastman MC, Hunt RF, Heinz AW. The operative aetiology and types of adhesions causing small bowel obstruction. *Aust N Z J Surg* 1993;**63**:848—52.
15. Soybel DI. Ileus and bowel obstruction. In: Greenfield LJ, editor. *Surgery: scientific principles and practice*. Philadelphia: Lippincott-Raven; 1997. p. 817—31.
16. Ellis H. The clinical significance of adhesions: focus on intestinal obstruction. *Eur J Surg Suppl* 1997;**557**:5—9.
17. Menzies D. Peritoneal adhesions: incidence, cause, and prevention. *Surg Annu Surg* 1992;**24**:27—45.
18. Stricker B, Blanco J, Fox HE. The gynecologic contribution to intestinal obstruction in females. *J Am Coll Surg* 1994;**178**: 617—20.
19. Wilkins BM, Spitz L. Incidence of postoperative adhesion obstruction following neonatal laparotomy. *Br J Surg* 1986;**73**: 762—4.
20. Solomkin JS, Wittmann DW, West MA, Barie PF. Intra-abdominal infection. In: Schwartz SL, Shires GT, Spencer FC, Daly JM, Ficher JE, Galloway AC, editors. *Principles of surgery*. 7th ed, Vol 2. New York: McGraw-Hill; 1999. p. 1515—34.
21. Trompke R, Siegner R. Ein Beitrag zu den Verhütungsmabnahmen postoperativer interabdomineller Verwachsungen. *Arch Klin Chir* 1956;**281**:323.
22. Buckman Jr RF, Buckman PD, Hufnagel HV, Gervin AS. A physiologic basis for the adhesion-free healing of deperitonealized surfaces. *J Surg Res* 1976;**21**:67.
23. Drolette CM, Badawy SZA. Pathophysiology of pelvic adhesions: modern trends in preventing infertility. *J Reprod Med* 1992;**37**:107—22.
24. Di Zerega GS. The peritoneum: postsurgical repair and adhesion formation. In: Rock JA, Murphy AA, Jones HW, editors. *Female reproductive surgery*. Baltimore: Williams & Wilkins; 1992. p. 2—18.
25. Rodgers KE, di Zegera GS. Functions of peritoneal exudate cells after abdominal surgery. *J Invest Surg* 1993;**6**:9—23.
26. Di Zerega GS. Biochemical events in peritoneal tissue repair. *Eur J Surg Suppl* 1997;**577**:10—6.
27. Liakakos T, Thomakos N, Fine PM, Dervenis C, Young RL. Peritoneal adhesions: etiology, pathophysiology, and clinical significance. *Dig Surg* 2001;**18**:260—73.
28. Saed GM, Diamond MP. Differential expression of alpha smooth muscle cell actin in human fibroblasts isolated from intraperitoneal adhesions and normal peritoneal tissues. *Fertil Steril* 2004;**82**(3):1188—92.
29. Ellis H. The aetiology of post-operative abdominal adhesions: an experimental study. *Br J Surg* 1962;**50**:10.
30. Buckman Jr RF, Buckman PD, Hufnagel HV, Gervin AS. A unifying pathogenetic mechanism in the etiology of intraperitoneal adhesions. *J Surg Res* 1976;**20**:1.
31. Myhre-Jensen O, Larsen SB, Astrup T. Fibrinolytic activity in serosal and synovial membranes. *Arch Pathol* 1969; **20**:80.
32. Porter JM, McGregor Jr FH, Mullen DC, Silver D. Fibrinolytic activity of mesothelial surfaces. *Surg Forum* 1969;**88**:623.
33. Raftery AT. Regeneration of peritoneum: a fibrinolytic study. *J Anat* 1979;**129**:659.
34. Raftery AT. Effect of peritoneal trauma on peritoneal fibrinolytic activity and intraperitoneal adhesion formation. *Eur Surg Res* 1981;**13**:397.
35. Gomel V, Urman B, Gurgan T. Pathophysiology of adhesion formation and strategies for prevention. *J Reprod Med* 1996;**41**: 35—41.
36. Ryan GB, Grobety J, Majno G. Postoperative peritoneal adhesions. *Am J Pathol* 1971;**65**:117.
37. Polubinska A, Winckiewicz M, Staniszewski R, Breborowicz A, Oreopoulos DG. Time to reconsider saline as the ideal rinsing solution during abdominal surgery. *Am J Surg* 2006; **192**:281—5.
38. Weibel MA, Majno G. Peritoneal adhesions and their relation to abdominal surgery. *Am J Surg* 1973;**126**:345.
39. Ellis H, Harrison W, Hugh TB. The healing of the peritoneum under normal and pathological conditions. *Br J Surg* 1965; **52**:471.
40. Down RHL, Whitehead R, Watts JMcK. Do surgical packs cause peritoneal adhesions? *Aust NZ J Surg* 1979;**49**:379.
41. Holtz G. Adhesion induction by suture of varying tissue reactivity and caliber. *Int J Fertil* 1982;**27**:134.
42. Holtz G. Prevention and management of peritoneal adhesions. *Fertil Steril* 1984;**41**(4):497—507.
43. Sanfilippo JS, Barrows GH, Yussman MA. Comparison of Avitene, topical thrombin, and Gelfoam as sole haemostatic agents in tuboplasties. *Fertil Steril* 1980;**33**:660.
44. Larsson B, Nisell H, Grandberg I. Surgicel-an absorbable haemostatic material in prevention of peritoneal adhesions in rats. *Acta Chir Scand* 1978;**133**:375.
45. Raftery A. Absorbable haemostatic materials and intraperitoneal adhesion formation. *Br J Surg* 1980;**67**:57.
46. Tingstedt B, Nehez L, Lindman B, Andersson R. Efficacy of bioactive polypeptides on bleeding and intra-abdominal adhesions. *Eur Surg Res* 2007;**39**(1):35—40.
47. Goldberg EP, Sheets JW, Habal MB. Peritoneal adhesions: prevention with the use of hydrophilic polymer coatings. *Arch Surg* 1980;**115**:776.
48. Diamond MP, De Cherney AH. Pathogenesis of adhesion formation/reformation: application to reproductive pelvic surgery. *Microsurgery* 1987;**8**:103—7.
49. Frankfurter D, De Cherney AH. Pelvic adhesive disease. *Postgrade Obstet Gynecol* 1996;**16**:1—5.
50. Choe JK, Dawood MY, Andrews AH. Conventional versus laser reanastomosis of rabbit ligated uterine horn. *Obstet Gynecol* 1983;**61**:689.
51. Pittaway DE, Maxson WS, Daniell JF. A comparison of the CO_2 laser and electrocautery on postoperative intraperitoneal adhesion formation in rabbits. *Fertil Steril* 1983;**40**: 366.
52. Sutton C, MacDonald R. Laser laparoscopic adhesiolysis. *J Gynecol Surg* 1990;**6**(3):155—9.
53. Erdogan G., Prevention of postoperative intraperitoneal adhesions by Methylene blue, carboxymethyl cellulose with sodium hyaluronic acid [unpublished observation].
54. Phillips JM. Gynecologic microsurgery, a déjà vu of laparoscopy. *J Reprod Med* 1979;**22**:135.
55. Kothari SN, Fundell LJ, Lambert PJ, Mathiason MA. Use of transabdominal ultrasound to identify intraabdominal

adhesions prior to laparoscopy: a prospective blinded study. *Am J Surg* 2006;**192**:843–7.
56. Kavic SM, Kavic SM. Adhesions and adhesiolysis: the role of laparoscopy. *JSLS* 2002;**6**(2):99–109.
57. Brokelman WJ, Holmdahl L, Bergstrom M, Falk P, Klinkenbijl JH, Reijnen MM. Peritoneal fibrinolytic response to various aspects of laparoscopic surgery: a randomized trial. *J Surg Res* 2006;**136**(2):309–13.
58. Di Zerega GS. Contemporary adhesion prevention. *Fertil Steril* 1994;**61**:219–35.
59. Risberg BO. Adhesions: preventive strategies. *Eur J Surg Suppl* 1997;**577**:32–9.
60. Gutmann JN, Penzias AS, Diamond MP. Adhesions in reproductive surgery. In: Wallach EE, Zaccur HA, editors. *Reproductive medicine and surgery*. St. Louis: Mosby; 1995. p. 681–93.
61. Sarr MG, Tito WA. Intestinal obstruction. In: Zuidema GD, editor. *Shackelford's surgery of the alimentary tract*. 4th ed, Vol 5. Philadelphia: WB Saunders Company; 1996. p. 387–9.
62. Blauer KL, Collins RL. The effect of intraperitoneal progesterone on postoperative adhesion formation in rabbits. *Fertil Steril* 1988;**49**(1):144–9.
63. Tulandi T. Adhesion prevention in laparoscopic surgery. *Int J Fertil Menopausal Stud* 1996;**41**:452–7.
64. Turkcapar AG, Ozarslan C, Erdem E, Bumin C, Erverdi N, Kutlay J. The effectiveness of LMWH on adhesion formation in experimental rat model. *Int Surg* 1995;**80**(1):92–4.
65. Sahin Y, Saglam A. Synergistic effects of carboxymethylcellulose a low molecular weight heparin in reducing adhesion formation in the rat uterine horn model. *Acta Obstet Gynecol Scand* 1994;**73**:70–3.
66. Arikan S, Adas G, Barut G, Toklu AS, Kocakusak A, Uzun H, et al. An evaluation of low molecular weight heparin and hyperbaric oxygen treatment in the prevention of intraabdominal adhesions and wound healing. *Am J Surg* 2005; **189**:155–60.
67. Menzies D. Postoperative adhesions: their treatment and relevance in clinical practice. *Ann R Coll Surg Engl* 1993;**75**: 147–53.
68. Montz FJ, Fowler JM, Wolff AJ, Lacey SM, Mohler M. The ability of recombinant plasminogen activator to inhibit post-radical pelvic surgery adhesion in the dog model. *Am J Obstet Gynecol* 1991;**43**:141–5.
69. Thompson JN, Paterson-Brown S, Harbourne T, Whawell SA, Kalodiki E, Dudley HA. Reduced human peritoneal plasminogen activating activity: possible mechanism of adhesion formation. *Br J Surg* 1989;**76**:382–4.
70. Doody KJ, Dunn RC, Buttram Jr VC. Recombinant tissue plasminogen activator reduces adhesion formation in a rabbit uterine horn model. *Fertil Steril* 1989;**51**:509–12.
71. Sanfilippo JS, Booth RJ, Burns CD. Effect of vitamin E on adhesion formation. *J Repro Med* 1995;**40**(4):278–82.
72. de la Portilla F, Ynfante I, Bejarano D, Conde J, Fernandez A, Ortega JM, et al. Prevention of peritoneal adhesions by intraperitoneal administration of vitamin E: an experimental study. *Dis Colon Rectum* 2004;**47**(12):2157–61.
73. Tokmak H, Tibet HB, Balkanli M, Koksal O, Aydin R. Postoperatif yapisikliklarin onlenmesinde vitamin E'nin sinerjistik etkileri. *Turk J Surg* 1995;**11**(3):162–7.
74. Salaris SC, Babbs Cf, Voorhees III WD. Methylene blue as an inhibitor of superoxide generation by xanthine oxidase. A potential new drug for the attenuation of ischemia/reperfusion injury. *Biochem Pharmacol* 1991;**42**(3):499–506.
75. Kelner MJ, Bagnell R, Hale B, Alexander NM. Potential of methylene blue to block oxygen radical generation in reperfusion injury. *Basic Life Sci* 1988;**49**:895–8.
76. Kelner MJ, Bagnell R, Hale B, Alexander NM. Methylene blue competes with paraquat for reduction by flavo-enzymes resulting in decreased superoxide production in the presence of heme proteins. *Arch Biochem Biophys* 1988; **262**(2):422–6.
77. Ignarro LJ, Kadowitz PJ. The pharmacological and physiological role of cyclic GMP in vascular smooth muscle relaxation. *Annu Rev Pharmacol Toxicol* 1985;**25**:171–91.
78. Matsuoka I, Sakurai K, Ono T, Nakanishi H. Involvement of endogenous noradrenaline release in Methylene blue induced contraction of isolated rabbit aorta. *Jpn J Pharmacol* 1987; **44**(1):23–33.
79. Galili Y, Ben-Abraham R, Rabau M, Klausner J, Kluger Y. Reduction of surgery-induced adhesions by Methylene blue. *Am J Surg* 1998;**175**:30–2.
80. Kluger Y, Weinbroum A, Ben-Avraham R, Galili Y, Klausner J, Rabau M. Reduction in formation of peritoneal adhesions by methylene blue in rats: a dose response study. *Eur J Surg* 2000;**166**:568–71.
81. Cetin M, Ak D, Duran B, Cetin A, Guvenal T, Yanar O. Use of methylene blue and N, O-carboxymethylchitosan to prevent postoperative adhesions in rat uterine horn model. *Fertil Steril* 2003;**80**:698–701.
82. Dinc S, Ozaslan C, Kuru B, Karaca S, Ustun H, Alagol H, et al. Methylene blue prevents surgery-induced peritoneal adhesions but impairs the early phase of anastomotic wound healing. *Can J Surg* 2006;**49**(5):321–8.
83. Jarret PE, Moreland M, Browse NL. The effect of oxpentifylline (''Trental'') on fibrinolytic activity and plasma fibrinogen levels. *Curr Med Res Opin* 1977;**4**:492–5.
84. Schroer RH. Antithrombotic potential of pentoxifylline. A hemorheologically active drug. *Angiology* 1985;**36**: 387–98.
85. Alkharfy KM, Kellum JA, Matzke GR. Unintended immunomodulation: part II. Effects of pharmacological agents on cytokine activity. *Shock* 2000;**13**:346–60.
86. Tarhan OR, Barut I, Sutcu R, Akdeniz Y, Akturk O. Pentoxifylline, a methyl xanthine derivative, reduces peritoneal adhesions and increases peritoneal fibrinolysis in rats. *Tohoku J Exp Med* 2006;**209**:249–55.
87. Aarons CB, Cohen PA, Gower A, Reed KL, Leeman SE, Stucchi AF, et al. Statins (HMG-CoA Reductase inhibitors) decrease postoperative adhesions by increasing peritoneal fibrinolytic activity. *Ann Surg* 2007;**245**(2):176–84.
88. Holmdahl L. Making and covering of surgical footprints. *Lancet* 1999;**353**:1456–7.
89. Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM. Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% Icodextrin. *Drug Delivery* 2001;**8**:9–12.
90. Gilbert JA, Peers EM, Brown CB. Intraperitoneal fluid dynamics of 4% icodextrin in non-ESRD patients. *Perit Dial Int* 1999; **19**(1):S79.
91. diZerega GS, Verco SJ, Young P, Kettel M, Kobak W, Martin D, et al. A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynecological surgery. *Hum Reprod* 2002;**7**:1031–8.
92. van den Tol P, ten Raa S, van Grevenstein H, Marquet R, van Eijck C, Jeekel H. Icodextrin reduces postoperative adhesion formation in rats without affecting peritoneal metastasis. *Surgery* 2005;**137**:348–54.
93. Wallwiener M, Brucker S, Hierlemann H, Brochhausen C, Solomayer E, Wallwiener C. Innovative barriers for peritoneal adhesion prevention: liquid or solid? A rat uterine horn model. *Fertil Steril* 2006;**86**(3):1266–76.
94. Davies D. Kinetics of icodextrin. *Perit Dial Int* 1994;**14**(2): 45–50.
95. Belluco C, Meggiolaro F, Pressato D, Pavesio A, Bigon E, Dona M, et al. Prevention of postsurgical adhesions with an autocrosslinked hyaluronan derivate gel. *J Surg Res* 2001; **100**:217–21.

96. Carta G, Cerrone L, Iovenitti P. Postoperative adhesion prevention in gynecologic surgery with hyaluronic acid. *Clin Exp Obstet Gynecol* 2004;**31**:39—41.
97. Burns JW, Skinner K, Colt J, Sheidlin A, Bronson R, Yaacobi Y, et al. Prevention of tissue injury and postoperative adhesion by precoating tissues with hyaluronic acid solution. *J Surg Res* 1995;**59**:644—52.
98. Martin-Cartes JA, Morales-Conde S, Suarez-Grau JM, Bustos-Jimenez M, Cadet-Dussort H, Socas-Macias M, et al. Prevention of peritoneal adhesions to intraperitoneal prostheses. An experimental study in pigs. *Cir Esp* 2006;**80**(4):214—9.
99. Hills BA. Role of surfactant in peritoneal dialysis. *Perit Dial Int* 2000;**20**:503—15.
100. Ar'Rajab A, Snoj M, Larsson K, Bengmark S. Exogenous phospholipid reduces postoperative peritoneal adhesions in rats. *Eur J Surg* 1995;**161**:341—4.
101. Snoj M, Ar'Rajab A, Ahren B, Bengmark S. Effect of phosphatidylcholine on postoperative adhesions after small bowel anastamosis in the rat. *Br J Surg* 1992;**79**:427—9.
102. Snoj M, Ar'Rajab A, Ahren B, Larsson K, Bengmark S. Phospholipase-resistant phosphatidylcholine reduces intra-abdominal adhesions induced by bacterial peritonitis. *Res Exp Med (Berl)* 1993;**193**:177—222.
103. Muller SA, Treutner KH, Anurov M, Titkova S, Oettinger AP, Schumpelick V. Experimental evaluation of phospholipids and icodextrin in re-formation of peritoneal adhesions. *Br J Surg* 2003;**90**:1604—7.
104. Wallwiener D, Meyer A, Bastert G. Adhesion formation of the parietal and visceral peritoneum: an explanation for the controversy on the use of autologous and alloplastic barriers? *Fertil Steril* 1998;**69**:132—7.
105. De Cherney AH, di Zerega GS. Clinical problem of intraperitoneal postsurgical adhesion formation following general surgery and the use of adhesion prevention barriers. *Surg Clin North Am* 1997;**77**:671—88.
106. Elkins TE, Bury RJ, Ritter JL, Ling FW, Ahokas RA, Homsey CA, et al. Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat. *Fertil Steril* 1984;**41**:926—8.
107. Fredericks CM, Kotry I, Holtz G, Askalani AH, Serour GI. Adhesion prevention in the rabbit with carboxymethylcellulose. *Am J Obstet Gynecol* 1986;**155**:667—70.
108. Mediana M, Paddock HN, Connelly RJ, Schwaitzberg SD. Novel antiadhesion barrier does not prevent anastomotic healing in a rabbit model. *J Invest Surg* 1995;**8**(3):179—86.
109. Li TC, Cooke ID. The value of an absorbable adhesion barrier, interceed, in the prevention of the adhesion reformation following microsurgical adhesiolysis. *Br J Obstet Gynaecol* 1994;**101**:335—9.
110. Qeralt CB, Laguens G, Lozano R, Morandeira JR. Prevention of peritonitis with oxidized regenerated celluloses. *Infect Surg* 1987;**12**:659—60.
111. Haney AF, Hesla J, Hurst BS, Kettel LM, Murphy AA, Rock JA, et al. Expanded polytetrafluoroethylene (Gore-Tex® surgical membrane) is superior to oxidized regenerated cellulose (Interceed TC7+) in preventing adhesions. *Fertil Steril* 1995; **64**:668.
112. Sawada T, Nishizawa H, Nishio E, Kadowaki M. Postoperative adhesion prevention with an oxidized regenerated cellulose adhesion barrier in infertile woman. *J Reprod Med* 2000;**45**:387—9.
113. Diamond MP, Linsky CB, Cunningham T, Constantine B, diZerega GS, DeCherney AH. A model for sidewall adhesion in the rabbit; reduction by an absorbable barrier. *Microsurgery* 1987;**8**:197.
114. Diamond MP. *Animal adhesion models: design, variables and relevance*. *Pelvic surgery*. Heidelberg, Germany: Springer Verlag; 1997. p. 65—70.
115. Franklin RROvarian study group. Reduction of ovarian adhesions by the use of Interceed. *Obstet Gynecol* 1995;**86**: 335—40.
116. Haney AF. Removal of surgical barriers of expanded polytetrafluoroethylene at second-look laparoscopy was not associated with adhesion formation. *Fertil Steril* 1997;**68**:721—3.
117. Schneider A, Bennek J, Olsen KO, Weiss J, Schmidt W, Rolle U. Experimental study evaluating the effect of a barrier method on postoperative intraabdominal adhesions. *Digest Disea Sci* 2006;**51**(3):566—70.
118. Warn R, Harvey P, Warn A, Foley-Comer A, Heldin P, Versnel M, et al. HGF/SF induces mesothelial cell migration and proliferation by autocrine and paracrine pathways. *Exp Cell Res* 2001;**267**:258—66.
119. Duan HF, Wu CT, Wu DL, Lu Y, Liu HJ, Ha XQ, et al. Treatment of myocardial ischemia with bone marrow derived mesenchymal stem cells overexpressing hepatocyte growth factor. *Mol Ther* 2003;**8**:467—74.
120. Yang J, Dai C, Liu Y. Systemic administration of naked plasmid encoding Hepatocyte growth factor ameliorates chronic renal fibrosis in mice. *Gene Ther* 2001;**8**:1470—9.
121. Liu HJ, Wu CT, Duan HF, Wu B, Lu ZZ, Wang L. Adenoviral-mediated gene expression of Hepatocyte growth factor prevents postoperative peritoneal adhesion in rat model. *Surgery* 2006;**140**(3):441—7.