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TOPIC HIGHLIGHT

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Peritoneal adhesions after laparoscopic gastrointestinal surgery

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Abstract

Although laparoscopy has the potential to reduce peritoneal trauma and post-operative peritoneal adhesion formation, only one randomized controlled trial and a few comparative retrospective clinical studies have addressed this issue. Laparoscopy reduces de novo adhesion formation but has no efficacy in reducing adhesion reformation after adhesiolysis. Moreover, several studies have suggested that the reduction of de novo post-operative adhesions does not seem to have a significant clinical impact. Experimental data in animal models have suggested that CO_2 pneumoperitoneum can cause acute peritoneal inflammation during laparoscopy depending on the insufflation pressure and the surgery duration. Broad peritoneal cavity protection by the insufflation of a low-temperature humidified gas mixture of CO_2, N_2O and O_2 seems to represent the best approach for reducing peritoneal inflammation due to pneumoperitoneum. However, these experimental data have not had a significant impact on the modification of laparoscopic instrumentation. In contrast, surgeons should train themselves to perform laparoscopy quickly, and they should complete their learning curves before testing chemical anti-adhesive agents and anti-adhesion barriers. Chemical anti-adhesive agents have the potential to exert broad peritoneal cavity protection against adhesion formation, but when these agents are used alone, the concentrations needed to prevent adhesions are too high and could cause major post-operative side effects. Anti-adhesion barriers have been used mainly in open surgery, but some clinical data from laparoscopic surgeries are already available. Sprays, gels, and fluid barriers are easier to apply in laparoscopic surgery than solid barriers. Results have been encouraging with solid barriers, spray barriers, and gel barriers, but they have been ambiguous with fluid barriers. Moreover, when barriers have been used alone, the maximum protection against adhesion formation has been no greater than 60%. A recent small, randomized clinical trial suggested that the combination of broad peritoneal cavity protection with local application of a barrier could be almost 100% effective in preventing post-operative adhesion formation. Future studies should confirm the efficacy of this global strategy in preventing adhesion formation after laparoscopy by focusing on clinical end points, such as reduced incidences of bowel obstruction and abdominal pain and increased fertility.

Key words: Peritoneal adhesions; Laparoscopy; Abdomen; Gastrointestinal surgery; Inflammation; Learning curve; Anti-adhesion; Animal models; Clinical studies; Laparoscopic resection of gastrointestinal

Core tip: Laparoscopy reduces de novo adhesion formation but does not reduce adhesion reformation. Adhesion reduction does not necessarily impact clinical outcomes. CO_2 pneumoperitoneum causes peritoneal inflammation depending on the insufflation pressure and surgery duration. Broad peritoneal cavity protec-

tion by insufflating a low-temperature, humidified gas mixture of CO_2, N_2O, and O_2 seems to represent the best approach for reducing peritoneal inflammation due to CO_2 pneumoperitoneum. A global strategy to prevent adhesion formation following laparoscopy should combine broad peritoneal cavity protection with the local application of a barrier.

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INTRODUCTION

Peritoneal adhesion formation is the most prevalent complication of abdominal and pelvic surgery[1-4]. Peritoneal adhesions can cause small-bowel obstruction, infertility, chronic abdominal pain, and increases in surgical time and in the risk of bowel perforation during preoperative surgery[1-4]. Peritoneal adhesions are among the leading causes of abdominal reoperations up to 10 years following abdominal or pelvic surgery[1,2,4]. Despite the high healthcare costs associated with peritoneal adhesions and the medico-legal consequences of bowel damage due to adhesions complicating preoperative surgery[5,6], the clinical and social problem of adhesions remains underestimated among patients and surgeons[7,8]. In addition, informed consent before surgery is very often inadequate regarding the risk of post-operative adhesion formation[7,8].

The majority of papers dealing with the healthcare and patient burdens of complications related to peritoneal adhesions have focused on the consequences of laparotomy[1-4,9]. However, since the early 1990s[10-13] laparoscopy has offered increasing advantages compared to open surgery for a number of pelvic[12-14], abdominal[10,11,15,16], and cancer procedures[17-19]. The present review was aimed at retrieving all of the data available from the experimental and clinical surgical literature to clarify whether the progressive shift from open to laparoscopic access for many abdominal and pelvic surgical procedures has already had or, in the near future, could have the major impact of reducing post-operative peritoneal adhesion formation.

PATHOGENESIS OF ADHESION FORMATION

Peritoneal adhesion formation is the consequence of abnormal repair of the peritoneum following different peritoneal injuries[20,21]. Surgical trauma, endometriosis, peritoneal infections, and peritoneal inflammation can cause peritoneal mesothelial defects and/or increased vessel permeability, which in turn produces inflammatory exudate[20,21]. Inflammatory exudate results in the presence of a fibrin mass in the peritoneal cavity[20,21]. The fibrin mass is entirely removed from the peritoneal cavity when peritoneal fibrinolytic activity is normal, and complete mesothelial regeneration occurs within 8 d[20,21].

The main cause of incomplete removal of the fibrin mass from the peritoneal cavity is the suppression of peritoneal fibrinolytic activity due to ischemia or the inflammation-induced over-expression of plasminogen activator inhibitors 1 and 2[20,21]. When fibrin persists in the peritoneal cavity, fibroblasts proliferate into fibrin bands, and these fibrin bands organize into adhesions (pathological bonds) between organ surfaces[20,21]. Therefore, many adverse factors can cause peritoneal adhesions, and many preventive factors have been proposed (Table 1).

Table 1 Adverse factors causing peritoneal adhesions and proposed preventive factors

Adverse factors	Proposed preventive factors
Surgical trauma	Minimal incisions (laparoscopy)
Infections	Minimal infection risk
Mesothelial defects	Minimal tissue handling (good surgery)
Increased vessel permeability	Corticosteroids and antihistamines
Inflammatory exudate	Corticosteroids and NSAIDs
Blood	Achieve hemostasis (good surgery)
Fibrin mass/fibrin bands	Fibrinolytic agents
Ischemia	Maintenance of vascularity (good surgery)
Thermal injury	Avoidance of thermal injury (good surgery)
Foreign bodies (starch powder)	Good surgery/laparoscopy (starch-free gloves)
Desiccation	Moistening of tissues (irrigation/humidified pneumoperitoneum)
Inflammation	Corticosteroids and NSAIDs/"peritoneum-friendly" pneumoperitoneum
Over-expression of PAI-1 and PAI-2	Reduction of inflammation/"peritoneum-friendly" pneumoperitoneum
Suppression of fibrinolytic activity	Fibrinolytic agents/"peritoneum-friendly" pneumoperitoneum
High-pressure CO_2 pneumoperitoneum	Reduction of pneumoperitoneum pressure
Long-duration CO_2 pneumoperitoneum	Rapid surgery
High intra-peritoneal temperature	Cooling of the peritoneal cavity
100% CO_2 pneumoperitoneum	Lower CO_2 concentration (gas mixture)

NSAID: Non-steroidal anti-inflammatory drug; PAI: Plasminogen activator inhibitor.

ATRAUMATIC SURGICAL TECHNIQUE FOR PREVENTING PERITONEAL ADHESIONS

Although intraperitoneal adhesions can be due to several injuries, such as cancer, peritoneal infections, or endometriosis, the trauma associated with surgery is the leading cause of peritoneal adhesion formation[20,21]. The formation of post-operative adhesions depends primarily on impaired fibrinolysis and inadequate blood supply[3,9,20-22]. The operative factors that potentiate intraperitoneal post-operative adhesion formation after open surgery include ischemia, thermal injury, infections, residual blood clots left in the peritoneal cavity at the end of surgery, residual macroscopic or microscopic foreign bodies in the peritoneal cavity and overly vigorous manipulation of structures distal to the operative sites[3,9,20-22].

To prevent post-operative adhesion formation after standard open surgery, in 1980, Gomel[23] described an open microsurgery technique for reconstructive tubal surgery. To reduce the operative factors that could potentiate peritoneal post-operative adhesion formation after standard open surgery, the key points of microsurgery include minimizing tissue handling and being gentle when handling tissue, minimizing foreign bodies and using very small sutures, avoiding the use of dry sponges and moistening tissues with constant irrigation, and achieving hemostasis while maintaining vascularity[23]. Since 1980, any surgical procedure that conforms to microsurgery principles has been considered a "good" atraumatic surgery that is able to reduce peritoneal trauma and post-operative peritoneal adhesion formation[24]. However, randomized clinical trials have not been performed in humans to compare adhesion formation after standard open surgery with adhesion formation after microsurgery[24].

LAPAROSCOPY AS A THEORETICALLY ATRAUMATIC SURGICAL TECHNIQUE

Theoretically, laparoscopy has the potential to be a "good surgery" for reducing peritoneal trauma and post-operative peritoneal adhesion formation[25]. In fact, laparoscopic access to the peritoneal cavity allows the surgeon to perform only minimal incisions of the parietal peritoneum, to minimize tissue handling and to handle tissues gently with atraumatic instruments, to minimize the risk that foreign bodies might be introduced into and left in the peritoneal cavity, and to avoid the use of dry sponges. However, other key points of microsurgery depend on the surgeon's attitude and/or the surgical procedure to be performed through laparoscopy.

Constant irrigation to moisten tissues, accuracy of hemostasis, the suturing technique, and attention to vascularity mainly depend on the surgeon's attitude. Surgeons very often underestimate the clinical problems of adhesions and their complications and only surgeons with the proper perception and knowledge of the problem of adhesions are likely to undertake adhesion prevention during surgery[7,8].

Bleeding during surgery and residual blood left in the peritoneal cavity at the end of surgery depend on the surgical procedure to be performed through the laparoscopic access more than on the access itself. Some procedures, such as myomectomy, liver resection, or rectal resection, are often complicated by excessive bleeding although laparoscopic procedures have been reported to decrease the need for blood transfusions compared to open surgery[13,15,26,27].

PERITONEAL POST-OPERATIVE ADHESION FORMATION AFTER LAPAROSCOPY OR OPEN SURGERY IN ANIMAL MODELS

Very few comparative experimental studies are available, and the data have been equivocal, likely because of the different animal models and experimental settings. In 1994, Marana *et al*[28] were unable to identify significant differences in post-operative adhesion formation in female rabbits undergoing conservative ovarian surgery *via* laparoscopy or laparotomy.

In 1998, Chen *et al*[29] reported fewer post-operative adhesions in female pigs after pelvic and paraaortic lymphadenectomy performed *via* transperitoneal laparoscopy than after the same procedure performed *via* transperitoneal laparotomy. Krähenbühl *et al*[30] evaluated post-operative adhesion formation after laparoscopic or open fundoplication in male Sprague-Dawley rats and reported a reduction in the number and severity of adhesions with laparoscopy. Schippers *et al*[31] compared post-operative adhesion formation after cecal resection and deserosation of the abdominal wall *via* laparoscopy or laparotomy in dogs and found a significant reduction in adhesions to the abdominal incision but no reduction in adhesions at the site of cecal resection following laparoscopy. In 2009, Dubcenco *et al*[32] reported a significant decrease in adhesion formation in female pigs undergoing liver biopsy *via* laparoscopy compared to laparotomy. In 2013, Shimomura *et al*[33] observed a decrease in post-operative adhesion scores associated with the preservation of peritoneal fibrinolysis in male rats undergoing cecal cauterization *via* laparoscopy with CO_2 pneumoperitoneum at 5 mmHg compared to rats undergoing the same procedure through open surgery.

A possible interpretation of the above equivocal results could come from the observations made by Jacobi *et al*[34] in 2001 and by Arung *et al*[35] in 2012. The first authors reported a significant decrease in adhesion formation in rats with peritoneal infections undergoing resection of the cecum *via* laparoscopy with helium pneumoperitoneum compared to rats with peritoneal infections undergoing the same procedure through open surgery or laparoscopy with CO_2 pneumoperitoneum[34]. Arung *et al*[35] reported a decrease in adhesion formation in male rats undergoing peritoneal injury *via* laparoscopy with air pneumoperitoneum compared to rats undergoing peritoneal injury through open surgery or laparoscopy with CO_2 pneumoperitoneum. Thus, depending on the insufflation pressure, pneumoperitoneum with CO_2 seems to induce peritoneal inflammation and ischemia of the intra-peritoneal viscera[33-35]. In fact, high intra-peritoneal CO_2 pressure decreased the fibrinolytic activity of peritoneal tissue in mice[36]. Severe alterations in the circulation of the intra-peritoneal viscera with resulting tissue ischemia have been observed in dogs during 14 mmHg pneumoperitoneum for 60 min using either CO_2 or helium[37]. An experimental study in pigs demonstrated that the effects of intra-peritoneal pressure on the blood circulation of the intra-peritoneal viscera were independent on the gas (air or CO_2) when the intra-peritoneal pressure was greater than 12 mmHg[38].

PERITONEAL POST-OPERATIVE ADHESION FORMATION AFTER LAPAROSCOPIC OR OPEN SURGERY IN CLINICAL TRIALS

A few comparative clinical studies have addressed this issue, but they have all agreed in suggesting that laparoscopic surgery results in a decrease in post-operative peritoneal adhesion formation. In 2000, Audebert and Gomel[39] showed that women undergoing laparotomy *via* a midline incision had a 50% incidence of umbilical adhesions, whereas women undergoing laparoscopy had only a 1.6% incidence of umbilical adhesions.

Polymeneas *et al*[40] retrospectively compared post-operative peritoneal adhesion formation following laparoscopic or laparotomic cholecystectomy and showed that patients treated *via* laparoscopy had significantly fewer adhesions than patients treated *via* laparotomy. Dowson *et al*[41] performed an observational study to compare adhesion formation after laparoscopic colectomy with that after open colectomy and reported that laparoscopic colectomy resulted in a lower incidence of post-operative peritoneal adhesions compared to open colectomy.

CLINICAL IMPACT OF LAPAROSCOPY ON READMISSION RATES FOR SMALL-BOWEL OBSTRUCTION

A recent meta-analysis of randomized clinical trials compared laparoscopic versus open resection for rectal cancer and showed that laparoscopic rectal resection resulted in a lower rate of readmissions for adhesion-related bowel obstruction[26]. In contrast, several previous studies have suggested that the reduction in peritoneal post-operative adhesions in patients undergoing laparoscopy was not associated with a significant clinical impact[42-44].

Lower *et al*[42] performed a very large epidemiological study that demonstrated similar adhesion-related readmission rates following gynecological laparoscopy or laparotomy. Taylor *et al*[43] reported similar readmission rates for adhesion-related small-bowel obstruction in patients who previously underwent laparoscopically assisted or open surgical procedures for colorectal cancer. Schölin *et al*[44], in a randomized trial comparing laparoscopic versus open resection for colon cancer, reported that the incidence of bowel obstruction episodes in patients treated *via* laparoscopy did not differ from the incidence in patients treated *via* laparotomy.

GAS INSUFFLATION CHARACTERISTICS DURING PNEUMOPERITONEUM

The above contradictory data obtained in clinical studies can be explained by observations made in animal models. Experimental data have suggested that CO_2 pneumoperitoneum can cause peritoneal inflammation during laparoscopy depending on the insufflation pressure and the duration of surgery[33-36].

Over the last ten years, using a laparoscopic mouse model, Koninckx and coworkers have obtained an enormous amount of information aimed at understanding the process by which CO_2 pneumoperitoneum enhances adhesion formation. In 2004, Binda *et al*[45] demonstrated that reductions in body and intra-peritoneal temperatures, the addition of 3% of O_2 to CO_2, and peritoneum humidification were all factors that were able to reduce adhesion formation caused by CO_2 pneumoperitoneum. In the same year, Elkelani *et al*[46] reported that the ideal concentration of O_2 to be added to CO_2 was 3% because higher O_2 concentrations added to CO_2 were unable to reduce adhesion formation caused by pneumoperitoneum. In 2006, Binda *et al*[47] confirmed that intra-peritoneal cooling and the prevention of desiccation were important, mutually dependent factors for preventing adhesions during CO_2 pneumoperitoneum.

In 2011, Corona *et al*[48] demonstrated that inflammation of the peritoneal cavity not only resulted in adhesions of the entire cavity but also enhanced adhesion formation at specific intra-peritoneal sites. The same authors also reported that desiccation depended on CO_2 flow rates and intra-peritoneal relative humidity, whereas intra-peritoneal temperature depended on desiccation[49]. Therefore, with a specific CO_2 humidifier, desiccation could be prevented while maintaining a low intra-peritoneal temperature[49].

Very recently, using a laparoscopic mouse model, Corona *et al*[50] investigated the effects of adding different concentrations of nitrous oxide (N_2O) to CO_2 pneumoperitoneum on peritoneal adhesion formation and the effects of adding different amounts of whole blood, plasma, or red blood cells to the peritoneum. N_2O at a 10% concentration was the most effective in preventing adhesion formation, while the presence of plasma in the peritoneum increased adhesion formation in an amount-dependent manner[50]. N_2O at a 10% concentration was able to reduce plasma-induced adhesions[50].

From all of the above data, we can conclude that the combination of hemostasis accuracy and surgery with broad peritoneal cavity protection, obtained by insufflating a low-temperature, humidified gas mixture of CO_2, N_2O, and O_2 should represent the best approach for the prevention of peritoneal adhesion formation during laparoscopic surgery.

MULTI-PORT *VS* SINGLE-PORT LAPAROSCOPY

The extension of the midline incision has been suggested to be the key factor in inducing peritoneal adhesion formation in open surgery[51]. Therefore, single-port laparoscopy should have the potential to further reduce peritoneal trauma compared to multi-port laparoscopy. Unfortunately, no studies have investigated the differences between multi-port and single-port laparoscopy with regard to post-operative peritoneal adhesion formation. Thus far, studies evaluating differences between single-port and multi-port laparoscopic procedures have compared operative outcomes, short-term post-operative parameters, complications, and cosmetic results without addressing the issue of post-operative adhesion formation[52].

GENETICS AND SURGEONS' LEARNING CURVES FOR ADHESION PREVENTION

Technical factors play key roles in adhesion prevention during laparoscopic surgery, but one should always bear in mind that surgeons operate on living human beings, and individuals can have different genetic constitutions. In fact, Molinas *et al*[53] demonstrated that the extent of adhesion formation in mice after laparoscopic surgery depended on the different animal strains. These data strongly suggest that genetics are a cofactor in peritoneal adhesion formation.

In contrast, surgeons perform surgery and surgeons are also human beings. Everyone knows that every surgical procedure must be learned well before the best possible results can be achieved. Therefore, the concept of the learning curve should also be applied to "the good surgery" aimed at preventing peritoneal adhesion formation. The impact of the learning curve on peritoneal adhesion formation has already been demonstrated in a laparoscopic mouse model[54]. In this model, peritoneal adhesion formation decreased with the decreasing duration of surgery[54]. Training allowed both senior surgeons and junior surgeons to decrease the duration of laparoscopy and, consequently, adhesion formation, although the senior surgeons had shorter surgery durations compared to the junior surgeons when starting training[54].

The concept that the effects of a laparoscopic learning curve also have an impact in clinical settings can be inferred from the results of previous randomized, controlled clinical trials performed to test the efficacy of different anti-adhesion barriers in the prevention of peritoneal adhesion formation after laparoscopic myomectomy[55,56]. In 1995, women included in a control group undergoing only "good surgery" had an 88% incidence of adhesions, whereas in 2006, the control group undergoing only "good surgery" had a 62% incidence of adhesions, a decrease of 26%[55,56].

The clinical importance of this observation is obvious. The impact of the surgeon's learning curve in reducing adhesion formation in different laparoscopic clinical settings should be always considered when planning future studies to test new anti-adhesion products.

CHEMICAL ANTI-ADHESIVE AGENTS

Theoretically, fibrinolytic agents, anticoagulants, and anti-inflammatory agents (corticosteroids and non-steroidal anti-inflammatory drugs) have the potential to be efficacious in reducing peritoneal adhesion formation[20,25]. However, systemic administration of fibrinolytic agents is not safe because the concentration needed to prevent adhesions is too high and can cause post-operative hemorrhage and delayed healing[20,25]. In contrast, intra-peritoneal administration of fibrinolytic agents results in absorption that is too rapid to be effective[20,25]. Similarly, intra-peritoneal administration of heparin at low doses is ineffective in reducing peritoneal adhesion formation whereas high doses are effective in reducing adhesions, but they can induce post-operative hemorrhage and delayed healing[20,25].

Non-steroidal anti-inflammatory drugs have been used in experimental animal models, but no clinical trials have been published[20,25]. Corticosteroids are effective in the majority of animal models, but only limited clinical studies have reported contrasting results on adhesion scores and the occurrence of some adverse events, such as immunosuppression and delayed healing[20,25].

ANTI-ADHESION BARRIERS

A recent systematic review and meta-analysis of randomized, controlled trials evaluated the efficacy of and side effects experienced with the intra-peritoneal application of four anti-adhesion barriers (an oxidized regenerated cellulose absorbable barrier, a sodium hyaluronate/carboxymethylcellulose absorbable barrier, a polyethylene glycol sprayable barrier, and icodextrin 4% solution) after abdominal surgery[57]. None of the barriers showed serious side effects compared to controls[57]. Both the oxidized regenerated cellulose absorbable barrier and the sodium hyaluronate/carboxymethylcellulose absorbable barrier significantly reduced peritoneal adhesion formation[57]. The sodium hyaluronate/carboxymethylcellulose absorbable barrier reduced the incidence of small-bowel obstruction[57].

The sodium hyaluronate/carboxymethylcellulose film was not produced for laparoscopic application. In a recent experimental study in two animal models, its efficacy was compared with that of a sodium hyaluronate/carboxymethylcellulose powder having the same composition as the film but developed for laparoscopic application[58]. Both the film and the powder reduced adhesions to the same extent after local application to peritoneal defects, but only the powder was able to reduce adhesions after application at sites distant from the peritoneal defects[58].

New barrier gels have been produced in the last few years. Some of these gels have already been evaluated in clinical settings, such as an auto-cross-linked hyaluronan gel[56,59-61]. Other gels, such as an ultrapure alginate-based gel, have been efficacious in reducing peritoneal adhesion formation only in experimental animal models[62].

ANTI-ADHESION BARRIERS AND LAPAROSCOPIC SURGERY

Data obtained in a laparoscopic mouse model by Binda *et al*[62,63] demonstrated that further reductions in peritoneal adhesion formation could be achieved in the model by adding the intra-peritoneal use of anti-adhesion barriers to the broad protection of the peritoneal cavity (obtained by insufflating a low-temperature, humidified gas mixture). However, very few human clinical trials have evaluated the effects of the intra-peritoneal use of anti-adhesion barriers during laparoscopic surgery.

An oxidized regenerated cellulose absorbable barrier has been evaluated in four gynecological clinical trials dealing with laparoscopic surgery for myomectomy, severe pelvic endometriosis, or electrosurgical treatment for polycystic ovarian syndrome[55,64-66]. The barrier reduced peritoneal adhesion formation after laparoscopic myomectomy and laparoscopic surgery for severe pelvic endometriosis[55,64,66], but it was apparently unable to reduce ovarian adhesions after laparoscopic electrosurgical treatment for polycystic ovarian syndrome[65].

A modified hyaluronic acid/carboxymethylcellulose powder was recently evaluated in a multicenter, randomized, reviewer-blinded trial performed in women undergoing laparoscopic myomectomy[67]. The laparoscopic application of this sprayable adhesion barrier was associated with a reduction in post-operative peritoneal adhesion development[67].

Polyethylene glycol has been evaluated in three clinical trials investigating laparoscopic myomectomy[68-70]. This sprayable barrier seems to be efficacious in reducing de novo peritoneal adhesion development[68-70].

Auto-cross-linked hyaluronan gel has been evaluated in women undergoing laparoscopic myomectomy[56,59-61]. The barrier gel not only significantly reduces post-operative peritoneal adhesion development[56,59,61] but also increases the pregnancy rates of women undergoing laparoscopic myomectomy and gel application compared to women undergoing laparoscopic myomectomy alone[60].

The use of icodextrin 4% solution following gastrointestinal surgery has been investigated in 269 laparoscopies performed for adhesiolysis, cholecystectomy, hernia repair, or bowel resection with anastomosis[71]. General surgeons from five European countries considered icodextrin 4% solution to be easy to use and acceptable in patients, demonstrating that this fluid barrier could be safely used in a broad range of gastrointestinal surgical procedures[71]. However, this study was only a safety study. The results of multicenter, randomized trials designed to assess the efficacy of icodextrin 4% solution have been ambiguous and are difficult to understand[72,73]. In 2007, Brown *et al*[72] reported a significant reduction in reformed adhesions after laparoscopic surgery for adhesiolysis using the solution, whereas in 2011, Trew *et al*[73] reported no evidence of a clinical effect of the solution in reducing de novo adhesion formation. Apparently, icodextrin 4% solution had the same efficacy as Ringer's solution in reducing de novo adhesions after laparoscopic surgery[73].

A GLOBAL STRATEGY FOR PREVENTING ADHESIONS IN LAPAROSCOPY

To translate the concept of broad peritoneal cavity protection by insufflating "peritoneum-friendly" pneumoperitoneum from animal models to humans, in December 2013, Koninckx *et al*[74] published the first randomized, controlled trial aimed at evaluating the anti-adhesive efficacy of insufflation of a low-temperature (31°C), humidified gas mixture of 86% CO_2, 10% N_2O and 4% O_2 at a pressure of 15 mmHg in a clinical setting (laparoscopic surgery for deep endometriosis).

To obtain the best protection of the entire peritoneal cavity, the gas mixture was humidified by sprinkling Ringer's solution with heparin 1000 IU/L, and the patients also received dexamethasone (5 mg) intramuscularly at the end of surgery[74].

Because site-specific, local treatment with barriers was previously demonstrated to be synergistic with broad peritoneal cavity protection in preventing adhesion formation in an animal model[63], auto-cross-linked hyaluronan gel was applied at the end of surgery in the same patients undergoing broad peritoneal cavity protection[74].

The combination of broad peritoneal cavity protection with local application of a gel barrier was highly effective in preventing post-operative adhesion formation compared to standard laparoscopic surgery with humidified CO_2 pneumoperitoneum. Adhesions were completely absent in 12 of 16 patients, and the other 4 patients who received broad peritoneal cavity protection and local gel barrier application had very low adhesion score[74].

The trial included only a small number of patients (16 treated and 11 controls), but the results were very promising because the patients underwent laparoscopic surgery for deep endometriosis, and endometriosis is one of the primary adverse factors causing peritoneal adhesion formation and reformation[20,25,64].

CONCLUSION

The state of the art regarding the prevention of peritoneal adhesions after laparoscopic gastrointestinal surgery is quite disappointing. Although laparoscopy has the potential to be "the good surgery" for reducing peritoneal trauma and post-operative peritoneal adhesion formation, only a few comparative clinical studies have addressed this issue. Moreover, several studies have suggested that the reduction of de novo post-operative adhesions obtainable by operating *via* laparoscopy has no clinical impact[42-44].

Experimental data in animal models have suggested that CO_2 pneumoperitoneum can cause peritoneal inflammation during laparoscopy depending on the insufflation pressure and duration of surgery[33-35]. Broad peritoneal cavity protection, obtained by insufflating a low-temperature, humidified gas mixture of CO_2, N_2O, and O_2, represents the best approach for reducing peritoneal inflammation due to CO_2 pneumoperitoneum[45-50]. However, as of December 2013, these experimental data have had no impact in modifying laparoscopic instrumentation[74].

Anti-adhesion barriers have been used in laparoscopy. Spray, gel, and fluid barriers are easier to apply in laparoscopic surgery than solid barriers. The results have been encouraging for solid, spray and gel barriers, but have been ambiguous for fluid barriers[55-57,59-61,67,68,71-73].

Future studies should evaluate the efficacy of a global strategy to prevent adhesion formation during laparoscopy in larger numbers of patients. This global strategy should combine broad peritoneal cavity protection, obtained by insufflating a low-temperature, humidified gas mixture of CO_2, N_2O and O_2, with low-dose intra-peritoneal heparin and low-dose intramuscular dexamethasone and local treatment with barriers of proven efficacy.

These future studies should focus on specific clinical end points, such as reduced instances of bowel obstruction and abdominal and pelvic pain and increased fertility, rather than simply investigating adhesion reduction.

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