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Abdominal Adhesions: From Formation to Prevention - Part Two

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Abstract

The majority of patients with adhesions may remain asymptomatic for many years, if not for lifetime. Adhesions may cause mechanical intestinal obstruction: they are responsible of the majority of small bowel occlusions. Adhesions can also cause chronic abdominal pain, irregular bowel movements, dyspepsia, dyspareunia and infertility. Surgery is mandatory in case of acute intestinal obstruction, while an elective laparoscopic or laparotomic adhesiolysis in case of chronic pain or severe adhesion related disorder should be accurately weighed. Nowadays the main target should be prevention of adhesion. While it is essential a good surgical technique, several adhesion reducing products have been tested: systemic or local drugs, crystalloids or colloids, liquids agents, gels or films that can reduce contact between peritoneal surfaces. In view of pathophysiology of adhesion development process, molecular therapies are also available. To date, however, the ideal barrier has not been invented yet and the use of any products on the market is still not a substitute for a good surgical technique.

Symptoms

The majority of patients with adhesions may remain asymptomatic for many years, if not for lifetime. Congenital or post-inflammatory adhesions tend to remain asymptomatic longer than post-surgical ones. It should be noted that there is not a direct correlation between the extent of adhesions and their clinical manifestation: a single adhesion in a "dangerous" area can result in intestinal occlusion by itself, while a patient with an abdomen diffusely affected by adhesions may remain asymptomatic throughout his life. Adhesions may cause an acute intestinal obstruction acting as a fixity element that leads to bowel loop traction, twist or angle; they can also produce an obstacle to normal intestinal peristalsis, completely incorporating visceral portions up to compromise bowel loop vitality. Adhesions are obviously responsible of internal hernias formation with the consequent risk of occlusion. The clinic is the typical mechanical ileus related to the obstruction site. In contrast, chronically, adhesions lead to vague abdominal pain, especially pelvic pain, dyspareunia and infertility. The symptoms also include bloating, irregular bowel movements and dyspepsia (1-6). Adhesions were thought to be a cause of chronic pelvic pain in 13-40% of patients (5-7). Adhesions alter bowel loops and abdominal organs motility, causing distension of organs serosa, stretch of viscera wall, spasm of the smooth muscles, traction of ligaments and bowel mesentery leading to visceral pain. Sulaiman has analyzed the adhesions structure of patients undergoing laparotomy for chronic pelvic pain, demonstrating the presence of sensory nerve fibers (3, 4). Chronic abdominal pain impairs significantly the quality of life of patients and cause up to 30-50% of the exploratory laparoscopy and 5% of hysteroscopy (8). However, a randomized-controlled study conducted among patients affected by chronic pelvic pain related to adhesions treated with laparotomy and adhesiolysis compared to a conservatively treated group showed postoperatively no difference in the level of pain at 9 and 12 months (9). Similar results are reported in the study of Swank (10) which assessed pain and quality of life at one year. These data are supported by a recent Cochrane review because there is a percentage of adhesions recurrence even after minimally invasive surgery (11). It has been reported the reduction of pain at 12 months in patients undergoing only exploratory laparoscopy without adhesiolysis: maybe the pneumoperitoneum and an increased intra-

abdominal pressure release less tenacious adhesions reducing abdominal pain. It should also be considered the effect on the psychogenic component of pain: once patients are reassured about other diseases absence, their perception of pain improves. The diagnosis of adhesions is almost always intra-operative. Medical history and symptoms can give only a probability diagnosis; though with high-resolution ultrasound and functional magnetic resonance it is possible locate adhesive bands (12, 13). It has also been proposed a novel technique called Periumbelical Ultrasound Guided Saline Injection (PUGSI) to increase sensitivity of preoperative diagnostic ultrasound: ten ml of sterile saline are injected intraperitoneally under ultrasound guidance and saline dispersion is evaluated; this is obviously influenced by the presence of adhesions (14).

Treatment

Surgical management of post-operative adhesions must be accurately weighted, since a new operation is a stimulus to more adhesions development anyway. Regeneration or "de novo" formation of adhesions after laparoscopic or laparotomic adhesiolysis has been observed up in 85% of cases (15). Accordingly patients with intestinal obstruction related to adhesions treated surgically compared to those treated conservatively have similar hospital re-admission rates (32% vs 34%), though those treated conservatively tend to develop a new bowel occlusion earlier (16). There are no absolute criteria to define the duration of conservative therapy in case of intestinal obstruction; certainly the old Anglo-Saxon clinical pearl *“not letting the sun set on a case of small bowel obstruction”* should not be longer followed. Especially in more complex cases, with history of repeated laparotomies and multiple obstructions episodes, a conservative management is certainly safer than a surgical approach that would definitely carry higher risks for the patient (16). A different issue is constituted by cases of early postoperative occlusion (in the first postoperative days) due to adhesions: in these cases a spontaneous resolution is frequent and a conservative approach has to be preferred (17). It must be also emphasized that the ideal timing for adhesiolysis would be at least 3 months after the onset of adhesions, when they begin to be less vascular, less dense and better defined, allowing a simpler dissection and minimizing complications related to such surgery (18). Adhesiolysis can be carried out both by a laparotomic and laparoscopic approach, considering the tendency towards adhesions recurrence in any case. In case of laparoscopic adhesiolysis, it should be preferred an open access to gain pneumoperitoneum, rather than the Verres needle. If possible, the abdominal incision, in case of suspicion of adhesions, would be performed on an area of “virgin” abdomen; if this is not possible, the old incision should be extended in a "healthy" area, for example a median sovra-pubic incision can be extended slightly upward facilitating access to the abdominal cavity. Facing important adhesions, it would be preferred an access to the abdominal cavity with "cold" knife rather than electrocoagulation. Adhesiolysis can be done with electrocoagulation, if distance from the bowel wall is sufficient, otherwise it is preferable a cold dissection with scalpel or scissors, to minimize bowel injury risk. CO2 laser can also be used. Dissection is made easier by proper traction of adhesion itself. Bokey and Kockeriling (19, 20) described hydrodissection to facilitate adhesiolysis, by making a small incision in the tissue to be dissected and injecting inside hot sterile saline to unglue surgical plans.

Surgical Prophylaxis

Prevention of adhesions can be divided into a series of technical measures that operators can and must put in place to try to minimize the mesothelial damage and possibly drug therapies that can be used (table 1). It is crucial to emphasize that the use of these measures, still subject of ongoing studies, do not obviously exclude a good surgical technique that represents the fundamental substrate for prevention.

STRATEGIES FOR "GOOD SURGICAL PRACTICE"	
1	Prefer microinvasive surgical techniques and small incisions
2	Minimize: a. operating time b. abdominal cavity exposure to heat sources c. dehydration of peritoneal surface during intervention
3	Minimize contact with serous surfaces
4	Ensure accurate hemostasis, without excess determining necrotic tissue
5	Avoid the use of intra-abdominal foreign materials (meshes, patches, non-absorbable suture materials) and prefer as much as possible resorbable materials (e.g. sutures)
6	Prefer the use of latex and powder free gloves and surgical drapes "without fibers"
7	Diffuse irrigation of abdominal cavity with saline or Ringer lactate after surgery to remove blood depots
8	Reduce the risk of infection by ensuring sterile procedures and using prophylactic antibiotic therapy when required
9	During laparoscopy use the lowest insufflation pressure possible with the addition of humidification
10	Use appropriate agent or barrier to reduce adhesion formation in high risk patients

Table 1 "Good surgical practice for prevention of peritoneal post-operative adhesions".

Patients, who have undergone abdominal surgery, especially with a laparotomic access, have to be considered at risk. The risk of adhesions significantly increases after 3 or more operations. Beck has shown that adhesions are present in 83% of patients who had undergone to more than one operation, compared with 7% of those with history of a single intervention. In addition it has been demonstrated that patients who had undergone to several interventions tend to have more tenacious adhesions than those induced in "virgin" abdomen (21). Furthermore it should be noted the increased risk related to the type of surgery: colon-rectal surgery, particularly if conducted with open technique, is associated with higher risk, as well as open gynaecological surgery on ovaries or hysterectomy. All patients undergoing laparoscopic or laparotomic adhesiolysis are to be considered at risk of adhesion recurrence also. It is still matter of debate the need of suturing the peritoneum at the end of intervention (22-25). The current trend is to not suturing, thus reducing adhesions development following mesothelium proliferation in "leopard spots". In fact, adhesions have been described in 22% of cases following surgery with peritoneum suture compared 16% of those without peritoneum closure (24, 25). After gynaecological oncology surgery, peritoneum closure seems to be associated with an increased risk of adhesions (22), as well as after the first caesarean section (26, 27). Although it is common ground that a good surgical practice is fundamental to prevent adhesions, it is impossible to create a randomized clinical trial in vivo to confirm this theory, since it would not be ethical to assign a patient to the "less good" surgery arm.

Material Prophylaxis

Prevention should also be done with products whose characteristics are listed in table 2:

Ensure adequate tissue separation during wound healing
Completely cover the damaged peritoneum
Biocompatible material with a minimal inflammatory reaction and minimal foreign body reaction
Manageable, especially in laparoscopic surgery
Easily degraded and reabsorbed avoiding a second operation to remove it
Have non-toxic degradation products
Ease wound healing process

Table 2 "Characteristics of the ideal barrier", modified from Brochhausen (70)

Prevention of adhesion formation by using *ad hoc* products can be classified in:

1. Use of local or systemic drugs
2. Use of crystalloid and colloid solutions and fluid separators
3. Use of "mechanical separators" of peritoneal surfaces (gel or film)
4. New molecular therapies

1. Among the drugs available, steroids (28, 29) and nonsteroidal anti-inflammatory drugs (NSAIDs) have been extensively tested (30-34); this because of mechanism of adhesion formation previously discussed. The balance between systemic side effects and local adhesions reduction is difficult, especially considering the bleeding risk associated with NSAIDs (including bleeding at the surgical site, with possible increase of adhesions secondary to intraperitoneal blood deposits) or the delayed wound healing determined by steroids. The positive effect of steroids was also seen in patients with ulcerative colitis undergoing bowel resection: there was a reduced rate of adhesions in those previously treated with steroids. Free radical scavengers (35, 36) including methylene blue (37), vitamin E (38), inhibitors of proinflammatory cytokines (39), antihistamines (40-42) have been tested in animal trials, but none of these has obtained consensus to clinical use. Heparins, fibrinolytic drugs and solutions of antibiotics were also tested either alone or in association with crystalloids or colloids or other separators. However, none of these agents have shown a clear benefit in reducing adhesion formation (42). Despite low molecular weight heparins are commonly used for deep venous thrombosis prophylaxis, they do not reduce significantly fibrin deposits within peritoneum and have not any clinical benefit (43-47). It has been also proposed the use of mitomycin C as inhibitor of fibroblast proliferation, but its application was severely limited by side effects of the drug itself (48, 49). An interesting animal study has shown a reduction of adhesion formation with intraperitoneal application of simvastatin with increased levels of t-PA (50). While, on the other hand, the addition of atorvastatin in treatment with Seprafilm, a film based on hyaluronic acid, does not lead to any benefit (51). Reduction of adhesion formation was achieved with postoperative gastrointestinal stimulation using prokinetic agent (Cisapride) in animal model; accordingly intestinal motility inhibition with anticholinergic drugs has resulted in increase and greater extension of adhesions (52). Camptothechin, cytotoxic quinoline alkaloid, has also been taken into account, using film coated by this drug which has strong antiproliferative, antiangiogenic, anti-inflammatory action reducing postoperative adhesions in animal model. The fibrinolytic balance can also be influenced by administration of GnRH analogs (53, 54) that act increasing the ratio tPA/PAI and thus resulting in a decreased adhesion formation in animal models; while in women GnRH-A induce reduction of TIMP levels. The exact mechanism

by which GnRH analogs act on the fibrinolytic system, however, still remains unknown.

2. The first solutions tested have been crystalloid like saline, Ringer lactate or Hartmann's solution (55). The abdominal cavity was filled at the end of intervention with 500 ml up to 3 liters of saline solution to determine hydroflotation of bowel loops: the aim was to avoid contact between mesothelial surfaces, to reduce adhesion formation. The underlying principle could be valid, but the majority of crystalloid will be reabsorbed within 24-48 hours (average of 30-50 ml/h) while adhesion formation requires more time. No randomized clinical trial has shown that hydroflotation prevents post-operative adhesions formation (5). Colloid solutions have been tested, similar to those used for intraperitoneal dialysis, with a greater osmolarity, to try to keep them longer in the abdominal cavity, demonstrating some degree of adhesion reducing action (56, 57). The 4% glucose polymer icodextrin (Adept ®, Shire Pharmaceuticals Group, UK) has an oncotic pressure that keep fluid in the abdominal cavity up to 3-4 days after surgery. Randomized, multicenter, double-blind studies, especially in gynecology (56, 58), but also in general surgery after Hartmann procedure (59), showed the properties of icodextrin as adhesion reducing agent. Icodextrin compared with Ringer solution reduces the incidence (32% vs. 52%), extension (47% vs. 52%) and severity (37% vs. 65%) of adhesions. A clinical improvement was registered in 49% of patients treated with icodextrin vs. 38% of patients treated with Ringer lactate (56-59). The POPA study (Prevention of Postoperative Abdominal Adhesions) from an Italian group in 2011 has demonstrated how instillation of icodextrin 4% reduced to 2.19% (2/91) adhesion reformation in patients undergoing surgery for intestinal occlusion related to adhesion compared to 11.11% (10/90) of the control group with an average follow-up of 41.4 months ($p < 0.05$) (60). Adept® effectiveness is not affected by the presence of abdominal drainage: it has been seen that the amount of icodextrin lost through drainage is moderate (around one third of instilled volume) and this loss usually takes place within the first postoperative hour. This, however, do not reduce the efficacy of the product for postoperative adhesions prevention (60). Icodextrin is easy to use and safe for patients, since it has been widely used in peritoneal dialysis for several years with a concentration of 7.5% (56, 58, 60-62). It is not associated with anastomotic dehiscence or impaired wound healing (57). Adept® has been approved by the FDA for use in laparoscopy and is contraindicated in patients with ongoing infection, allergic to cornstarch or in case of bowel resection or appendectomy (57.58). The Hyskon® is also an example of a solution containing Dextran 70 with a concentration of 32%. It has both hydroflotation effect and “siliconization” effect (preventing the damaged surfaces from facing each other by covering the intraperitoneal surfaces). No significant effects of postoperative adhesion reduction were reported while it determines an overload of fluids with ascites, vulvar and lower limbs edema and pleural effusion. Furthermore cases of coagulopathy, disseminated intravascular coagulation (DIC), anaphylactic shock, and hypotension have been reported and therefore its use was abandoned (63). More recently it has been proposed a solution based on hyaluronic acid combined with iron ions (0.5%) (Intergel® Johnson & Johnson) to increase viscosity and permanence inside abdominal cavity. Intergel was able to reduce the number, severity and extent of postoperative adhesion in a multicenter, randomized prospective study. It was, however, found an increased risk of anastomotic and wound dehiscence within a clinical picture defined as "possible Intergel Reaction Syndrome" (pIRS) which also includes a prolonged postoperative ileus; hence this product was withdrawn from the market (64, 65). The Tisseel VH®

(Baxter) is used as a hemostatic and agglutinative agent. It is a concentrate of protein, thrombin and inhibitors of fibrinolysis. Recently it has been assessed for adhesion prevention in animal model (66, 67). The results of human studies are limited and controversial (68, 69). In addition Tisseel® is a biological material derived from human blood and then presents potential problem of infections transmission.

3. The idea of using barriers to separate peritoneal surfaces is really dated. Initially in animal studies peritoneum or omentum patches have been placed above "damaged" surfaces and sutured in place. However, it has been showed that devascularized tissue placed on damaged tissue only leads to an increased incidence of adhesions, rather than reduce them. Experimental trials are looking for a perfect barrier, which can be used in all patients and adaptable to both open and laparoscopic surgery. The idea of using gel (Spraygel ®, Hyalobarrier ®, Oxiplex ®) is an attempt to overcome the quick reabsorption of solutions. The material used must stay in place for a sufficiently long period to allow restoration of surgical injury as well as it must be degraded in time to avoid any irritant action as foreign body (70). The gels are more readily usable in minimally invasive surgery compared to solids separators, being possible introduction into the abdominal cavity through the trocar, not requiring any suture to stay in place and not requiring full coverage of all damaged tissue. Numerous natural viscous polysaccharides have been tested such as cellulose, chitosan, dextran and hyaluronic acid or synthetic such as polylactic acid and polyethylene glycol (71). In case of non-absorbable material (e.g. polytetrafluoroethylene: Goretex ®) it must be taken into account the need of device surgical removal (though still matter of debate), the potential chronic infective power of the material, and the need of device fixing during its positioning to prevent intra-abdominal migration. However fixation with sutures requires additional foreign material, increasing the risk of adhesion formation; furthermore laparoscopic fixation is technically demanding. It is possible to avoid fixation using liquid substances that become gel only once introduced into the abdominal cavity. Multiple studies have demonstrated the adhesion reducing benefit of these substances, so they could be recommended in all patients without specific contraindications. However it must be stressed that all studies demonstrate reduction of incidence, extent and severity of adhesions but no one proves an effective reduction of the incidence of intestinal occlusions or the need of re-interventions which should be the desired aim of future studies (72). Barrier agents are listed in table 3.

Considering the molecular basis of pathophysiology of adhesion development process it is possible to postulate new preventive strategies enhancing the fibrinolytic system using recombinant tPA (73). The tPA can be given as a gel and be absorbed into the peritoneal cavity (74-76). Possible side effects of tPA include the risk of postoperative bleeding and delayed wound healing, nevertheless none study has demonstrated impaired wound healing, while only one reported bleeding complications (77). Falk studied the intraperitoneal injection of PAI-1 antibodies, blocking its activity and reducing adhesions incidence (78). New preventive approaches also include IL-10 administration which has been tested in rats or the administration of IL-1, IL-6 and TNF-α antibodies blocking profibrotic action. Alternatively it is possible to block the cellular interaction with ECM (extracellular matrix) acting on ICAM and VCAM.

Conclusion

There is no doubt that adhesions are directly connected to disorders; but their presence diagnosis can be done only operating. Every action useful to their prevention must be put in place. What is the required reduction of adhesion formation to have a significant clinical improvement is a question far from having an answer (71). To date, no a single

product on the market is a substitute for a good surgical technique.

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