Impact of adhesions in colorectal surgery

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Abstract

The extent of the problem of adhesions is considerable and poses a significant burden on healthcare systems, the workload of surgeons and the lives of patients. This paper reviews the work undertaken and the associated evidence for the impact of adhesions. It considers the various options and strategies to reduce adhesions alongside the fundamental necessity for good surgical technique.

Keywords Adhesions, surgery, risk, complications

Introduction

There is a wealth of literature on adhesions and their impact in abdominal surgery. It can be difficult to appreciate the scope of the problem and realize optimal prevention and treatment strategies. This review discusses the important concepts within this topic. We have restricted our discussion to acquired postoperative adhesions.

Adhesions are defined as abnormal attachments that form between tissues and organs. They result from a dysequilibrium between coagulation and fibrinolysis in the abdominal cavity in favour of the former. The net result is that of decreased fibrin degradation. Fibrin is deposited on the damaged peritoneal surface, be it the visceral or parietal peritoneum [1]. Adhesions can occur as a result of primary infective or malignant intra-abdominal disease processes or from the trauma of surgery. While adhesions commence formation in the perioperative period it is crucial to realize that their development occurs in the early postoperative period – in the first 3–5 days after peritoneal trauma has taken place [2]. Not all patients that develop postoperative adhesions will experience problems though any patient with adhesions facing further abdominal surgery will be at risk of complications [3–6]. Those patients who do develop complications may present with chronic abdominal and pelvic pain, small bowel obstruction and in women, infertility. Adhesion-related complications impact greatly on health economic models and cause considerable frustrations when encountered surgically, so much so that they can result in considerable perioperative and postoperative morbidity [3–6].

All age groups are affected and all will have a lifelong risk of developing complications – including small bowel obstruction. Small bowel obstruction (SBO) is the most serious adhesion-related complication with a 10% risk of mortality [7] if not diagnosed and treated immediately. While the risk of SBO is the highest after colorectal surgery, it is also a significant problem following gynaecological surgery, particularly total abdominal hysterectomy, the consequences of which will have to be dealt with by colorectal surgeons [8].

Although adhesions are now the most frequent complication of abdominopelvic surgery, it is not possible to identify which particular adhesions will cause complications. Duron et al. examined risk factors that led to recurrence of small bowel obstruction after surgical treatment in 286 patients [9]. They demonstrated by a Cox regression model that age under 40 years, prior adhesions and postoperative complications were independent risk factors in their aetiology. While recognizing adhesion-related small bowel obstruction can be a matter of clinical experience, radiological adjuncts are useful [10]. Although plain radiographs may provide a clue by showing obstructed loops of small bowel, contrast studies are increasingly being employed to confirm a clinical suspicion. However it is imperative in the emergency setting that radiological tests do not compromise regular clinical evaluation and timely operative intervention. Most adhesion-related small bowel obstruction can be satisfactorily managed conservatively but outcomes following medical management have been shown to be
worse if the adhesions resulted from previous appendectomy, tubal or ovarian surgery [11].

Triggers that induce adhesions are well established; they include intra-abdominal infection, irritation, surgical manipulation or destruction of tissues and disease processes. An interesting debate is whether the peritoneum should be approximated in routine abdominal closure. There is sufficient evidence to suggest that the peritoneum is regenerated when denuded; therefore it would seem logical not to close it. Furthermore closure of the peritoneum may itself induce adhesions to form as foreign materials are used to approximate tissues. It has been shown that not closing the peritoneum is safer [12].

**The Surgical and Clinical Adhesions Research studies**

Appreciation of the magnitude of the problem of adhesions is complicated by the marked heterogeneity between studied populations and failure to adhere to rigorous follow up of patients. This is compounded by populations that move from one health region to another, introducing significant bias and making the study of such patients difficult. Taking small bowel obstruction from adhesions as an example, Zbar et al. showed that this occurred following a simple procedure such as appendicectomy in 11% of patients over a 64 month period [13]. Andersson et al. similarly demonstrated that the incidence of small bowel obstruction after appendicectomy at 1 year was 0.63% rising to 1.3% of cases at 30 years [14]. Clearly the impact of adhesions is significant. The Surgical and Clinical Adhesions Research (SCAR) Study Group was formed to analyse the magnitude of adhesions as a problem objectively. Its aim was to eliminate the issue of confounding bias and it focused on a relatively stable population elicited from validated data sets from the Scottish National Health Service medical record linkage database [15,16]. The objective of the first SCAR study was to assess the frequency of complications from adhesions in the general population. The group analysed hospital re-admissions in patients undergoing initial abdominal and pelvic surgery in 1986. Patients were followed for 10 years for re-admissions for defined outcomes. These outcomes were classified as being directly related to adhesions (e.g. medical or surgical treatment for adhesion-related small bowel obstruction or other adhesiolysis procedures), possibly related to adhesions (e.g. treatment for SBO but without specific coding of adhesiolysis), and open or laparoscopic re-operations that while unrelated to adhesions would be potentially complicated by pre-existing adhesions. Specific coding tools (OPCS-3, OPCS-4, ICD-9) assisted in classifying the diagnosis and nature of procedures and ensured that each hospital re-admission would be listed in only one classification. Internal audit by the SCAR steering group ensured the validity of the collected data. Of 54 380 patients initially identified, 41 841 were selected as the incident population. Of these 29 790 had open surgery. Of this population 12 584, 8717 and 8489 had midgut or hindgut surgery, foregut or other abdominal surgery, or surgery on the female reproductive tract respectively. From each group the number of patients that had one or greater than one adhesion-related re-admission during the 10 year follow-up period was 4101 (32.6%), 3294 (37.8%) and 2931 (34.5%) respectively. The mean number of patient re-admissions ranged from 1.9 to 2.2. Analysing the outcome measures of those re-admissions directly related to adhesions \((n = 1209)\), the majority (768 patients) underwent adhesiolysis procedures with or without small bowel obstruction, while 401 patients had these events treated non-operatively. The remaining 40 patients had gynaecological adhesions treated operatively. The re-admissions possibly related to adhesions numbered 8240 and repeated surgery complicated by adhesions numbered 11 898. Although the data analysis was robust, the SCAR study group interpreted the results for directly related re-admissions cautiously. Consequently despite estimates that 5.7% of hospital outcome re-admission over the 10-year period were directly attributable to adhesions, with 3.8% managed operatively, these relatively high values were deemed to be conservative. Further analysis of the data showed that the highest rate of re-admissions directly related to adhesions was from surgery to the mid and hindgut. Parker et al.’s analysis concentrated on those who had lower gastrointestinal surgery within the group reported by the SCAR study [16]. In this analysis up to 32.6% of patients were re-admitted for an adhesion related problem a mean of 2.2 times over the next 10 years. It was shown that surgery on the rectum was associated with the highest risk of re-admissions. In summary it was concluded from these publications that up to one in three patients were re-admitted at least twice over the 10-year period and at least one in 14 outcome re-admissions were directly related to adhesions [15,16]. This translates into a significant utilization of healthcare time and expenditure, which is often disregarded – let alone any impact on the lives of patients.

While it was clear by this stage that adhesions posed a significant clinical problem, the true impact of colorectal surgery on adhesion-related complications was still not clear. The SCAR-2 study focused on colorectal surgery and examined the real-time burden of adhesion-related complications [17]. This study identified three cohorts of patients during the financial years 1996–1997,
Reducing adhesions – operative strategies

Meticulous surgical technique is essential in reducing postoperative adhesion formation. The surgeon should take particular care to reduce unnecessary handling of tissues, minimize blood loss, avoid contamination with foreign bodies, such as suture remnants and starch from gloves and avoid tissue exposure to a dry environment. Other forms of damage, such as thermal injury from coagulating devices should be born in mind and judicious use practised. In some instances where dense adhesions between loops of bowel and/or the peritoneum occur, a blade is often the ideal instrument. In laparoscopic surgery, reduction of pressure and duration of pneumoperitoneum is important. It is always important to focus on planned surgery and if any secondary pathology is identified to question the risk benefit of surgical treatment before proceeding given that many of the traumas that cause adhesions are a routine part of surgery.

Importantly, while surgical adhesiolysis is the current method of managing adhesions, regardless of the method of adhesiolysis or the type of adhesion, it results in further traumatic disruption and a high rate of adhesion re-formation (mean 85%) as well as the development of de novo adhesions [19]. Studies indicate that, compared with unaffected peritoneal tissue, adhesive tissue contains higher levels of growth factors, suggesting a greater propensity for adhesion re-formation. These factors (fibroblast growth factor) depress fibrinolytic activity and induce tissue fibrosis, and thus re-formed adhesions tend to be more dense and severe than de novo adhesions [20,21].

Reducing adhesions – adhesion-reduction adjuvants

The anti-adhesion agents that are available can be classified broadly into pharmacological agents, physical barriers including solid mechanical barriers and bioabsorbable films or gels, or broad-coverage fluid agents to keep tissue surfaces physically separated during the healing process.

Most of the work on these agents has been in gynaecological surgery, in part because gynaecologists have generally been concerned about adhesions for longer than colorectal surgeons. Good outcomes from fertility surgery can be so adversely affected by adhesion formation and furthermore it had been easier to undertake studies because a second laparoscopy used to be common to check on outcomes of initial surgery. Also this allows lysis of adhesions to improve fertility outcomes.

The general quality of research on many adhesion-reduction agents is variable. Studies required for regulatory approvals of adhesion-reduction agents have focused on adhesion reduction [22]. In the majority of cases, the studies have compared the use of an agent with no treatment, sometimes in the same patient. Few studies have been blinded, with most evaluations of adhesion-reduction made by the operating surgeon. The variation in adhesion classifications, mode of application of agents,
Impact of adhesions

R. Bhardwaj & M. C. Parker

lack of uniformity in surgical approaches and variations in interpretation of results, all make assessment of the efficacy of the many agents difficult and almost impossible to compare. There are very few studies that have looked at the impact of an agent on clinical outcomes, such as reduction in SBO, pregnancy or ease of reoperative surgery. This is largely because of the complexity of undertaking clinical outcome studies. The number of patients needed to power a study to show a reduction in SBO is considerable [23]. Looking at pregnancy as an outcome in women with infertility, which is multifactorial, is problematic. Likewise requiring many centres or a lengthy period to undertake work can lead to bias with inter-centre and inter-surgeon variables and changes in surgical practice [24].

While the processes of adhesion formation present various theoretical opportunities for pharmacological intervention and a number of agents have been investigated, to date, no clinical studies have shown adhesion-reduction benefits using pharmacological regimens [25] and there have been significant safety concerns with some agents [26,27].

However, various physical barriers have been approved as anti-adhesion agents and used with varying degrees of success in colorectal surgery. Of the solid mechanical barriers available Preclude® (Gore-tex – expanded polytetrafluoroethylene – PTFE, WL Gore & Associates, Inc., Flagstaff, AR, USA) was approved and available in Europe but must be sutured in place and subsequently removed. It has not been used much in colorectal surgery and has largely been superseded by bioabsorbable barriers.

Bioabsorbable films include Interceed® (Johnson & Johnson Medical Inc., New Brunswick, NJ, USA), Seprafilm® (Genzyme Corporation, Cambridge, MA, USA) and Surgiwrap® (Mast Biosurgery, San Diego, CA, USA). A meta-analysis of Interceed (oxidized, regenerated cellulose adhesion barrier) by Wiseman et al. extracted data from seven suitable studies and showed a 24% reduction in the incidence of adhesions between barrier treated and untreated sites [28]. They also showed that the extent of adhesion formation was reduced. Recent work with Interceed, albeit in a limited number of patients has indicated that its effect on reducing adhesions results in improved pregnancy outcomes in infertile women [29]. Use of Interceed resulted in a significant increase in the pregnancy rate compared with surgical controls. Meticulous haemostasis is important as the incidence of adhesions results in improved pregnancy outcomes in infertile women [29]. Use of Interceed as an anti-adhesive agent has largely been superseded by bioabsorbable barriers.

Seprafilm is a sodium hyaluronate and carboxymethylcellulose bioabsorbable membrane. Alongside the main pivotal studies [32,33], there is mounting literature on its use and it is the only agent to have been investigated for reduction of SBO [34]. Fazio et al. conducted a prospective, randomized, multicentre, multinational, single-blind controlled study to examine the effect of Seprafilm in reducing adhesions in patients undergoing intestinal re-sections [34]. Patients were randomized to receive either Seprafilm or no Seprafilm. The results showed that while there was no difference between the incidence of adhesive small-bowel obstruction in either group, the incidence of those patients with adhesive small-bowel obstruction requiring re-operation was lower in those in whom Seprafilm was used. Interestingly the investigators also showed that in both groups half of first adhesive small-bowel obstruction episodes occurred within 6 months after the initial surgery. Seprafilm in addition to reducing adhesions in other reports also appears not to cause any oncological detriment in those receiving adjuvant chemotherapy [35]. Therefore Seprafilm was deemed suitable in colorectal cancer surgery. Seprafilm was re-formulated after it first became available to make it easier to handle and more malleable allowing better conformation to shape around organs. While work on its use laparoscopically has been undertaken [36] it is generally difficult to handle and its use in laparoscopic surgery is not realistic. Is Seprafilm a safe agent to use? This was examined as part of the SBO study [34,37] involving 1791 patients and it was noted that while the incidence of abscesses or pulmonary emboli were not different, fistulae and peritonitis occurred more frequently in those in whom Seprafilm was used [37]. Foreign body reaction was not observed in either group. In addition where Seprafilm was wrapped around a fresh bowel anastomosis, leak-related events, which included anastomatic leak, fistulae, peritonitis, abscesses and sepsis occurred more frequently. The study highlighted that use of Seprafilm at the site of an anastomosis is to be avoided due to increased anastomotic leaks and this is now an explicit warning. While there are sporadic case reports in the literature highlighting various foreign body reactions or aseptic peritonitis [38–40], Seprafilm use has generally been without problems.

Surgiwrap (polylactide: copolymer of 70:30 Poly [l-lactide-co-d, l-lactide]) is a biodegradable polymer film, which has recently been introduced in Europe. The supplying company claims that the product has improved handling over alternative film products and a long resorption period of up to 6 months, after which it is subsequently metabolized to lactic acid, CO2 and water. The polymer film needs to be sutured in place to prevent it from moving during this period. With the exception of one preclinical study in 44 rats [41], published data are lacking on which to assess the product’s safety or its
efficacy in reducing peritoneal adhesions. In light of failures of other agents due to long-term safety concerns and in the absence of evidence of clinical efficacy, it is questionable whether SurgiWrap should be considered for use as an adhesion-reduction agent at this time.

The Bioabsorbable gels available include Spraygel® (Confluent Surgical, Waltham, MA, USA), Hyalobarrier® (Fidia Farmaceutici SpA, Abano Terme, PD, Italy) and Oxiplex®/AP (FzioMed Inc., San Luis Obispo, CA, USA). Spraygel [synthetic polyethylene glycol (PEG) solutions] consists of two water-based PEG solutions, one clear and one coloured with methylene blue, to make it easy to see where it has been used. When sprayed together they form a hydrogel film that provides a physical barrier. While its effectiveness has been evaluated in early preliminary clinical studies [42,43] a larger scale pivotal study, which commenced in the USA was then stopped due to lack of efficacy in the treatment compared with the control arm and has not, to date, been resumed. Its use can be quite cumbersome needing a complex set-up of the equipment and the skill and time required to spray and coat tissues evenly, and it is expensive.

Hyalobarrier (Hyaluronic acid cross-linked to Hyaluronic acid) is a viscous gel, available in Europe as an adhesion-reduction barrier for use after abdominopelvic surgery. It is similar in mode of action to local site-specific film barriers as it stays at the site to which it is applied, dissolving some days later. There are few published clinical data using gynaecological study models. These include a small uncontrolled study in open myomectomy [44] and two randomized controlled studies in patients undergoing laparoscopic myomectomy [45,46]. Although the studies used only limited numbers of patients, they showed a reduction in adhesions and a significant improvement in clinical outcomes, as measured by pregnancy rate, was seen compared with surgical treatment control [47]. Hyalobarrier is not widely available nor has it been readily adopted for clinical use, mainly because it is very sticky and has a tendency to float away from sites when irrigated. These mucoadhesive properties are essential for its efficacy and irrigation is not recommended.

Oxiplex/AP [carboxymethylcellulose (CMC) and polyethylene oxide (PEO)] composite gel is a viscoelastic gel recently approved for use in Europe as an adhesion-reduction barrier for abdominal/pelvic surgery. It has been used in another formulation for a number of years for the reduction of adhesions in spinal surgery [48]. Two clinical pilot studies in laparoscopic gynaecological surgery comparing use of this gel with no treatment have recently been published [49,50]. They are primarily safety studies and are thus powered to assess safety and not efficacy of the agent. However, in both studies there was an improvement in adhesion scores compared with the no-treatment controls and the European pilot study demonstrated a significant reduction in adnexal adhesions [49]. However, the agent is not yet widely available.

Like the film barriers the available gel agents are site specific, requiring surgeons to predict sites at which adhesions may form and thus where the barrier needs to be applied. As the pathogenesis of adhesion formation reaches beyond the operative site of actual surgical trauma agents providing protection throughout the peritoneal cavity could be advantageous. Various broad-coverage agents have been developed, but most have been abandoned (Hyskon® [51]) or withdrawn due to safety issues (Intergel® [52]) or lack of efficacy (Hyskon® [53], Sepracote®).

While initial experience with Intergel (0.5% ferric hyaluronate gel) was favourable [54,55] and it was easier to use in both open surgery and laparoscopy, providing broader coverage than previous agents it was however, withdrawn from the market early in 2003 due to serious problems with late-onset postoperative pain, noninfectious foreign body reactions and tissue adherence [52], and a study in colorectal surgery, recently reported, was halted due to unacceptably high rates of postoperative complications [56].

Hydroflotation has long been suggested as a technique preventing apposition of damaged peritoneal surfaces both at the site of application and elsewhere in the abdominopelvic cavity. Crystalloid solutions such as saline, lactated Ringer’s solution (LRS) or Hartmann’s solution have all been widely used as postoperative instillates at the end of the procedure to provide a physical, fluid barrier. Though cheap and relatively easy to use, however, these crystalloids are rapidly absorbed and they do not reduce adhesions [57]. They are absorbed from the peritoneal cavity at the rate of 30–50 ml/h, so that by 24 h after surgery, little, if any, crystalloid solution is left in the pelvis [58–60].

Adept® (icodextrin 4% solution, Baxter Healthcare Corporation, Deerfield, IL, USA) is the only approved and available adhesion-reduction solution that has a sufficiently long intraperitoneal half-life [61] to provide coverage throughout the peritoneal cavity and persist through the critical period of adhesion formation. Adept has been approved in Europe since 2000 as an adhesion-reduction agent in open and laparoscopic gynaecological and general surgery. In the USA it was recently approved by the FDA as the first anti-adhesion agent for use as an irrigant and postoperative instillate in gynaecological laparoscopy with adhesiolyis.

An initial pilot study provided encouraging efficacy data [62] and further efficacy findings have now been statistically confirmed in a recently published, large RCT
undertaken in the USA for regulatory purposes [63]. This gynaecological second-look model was the largest and first double-blind study of an anti-adhesion agent and compared use of Adept to LRS both as an irrigant and postoperative instillate. Conventional adhesion studies have used surgery only as the comparator. Despite the use of LRS which appeared to have some benefit itself, the data demonstrated that Adept provides a significant reduction in adhesions throughout the peritoneal cavity compared with LRS. These benefits appeared to be enhanced in more clinically complex patients, including those with a higher adhesion burden or endometriosis.

The use and safety of Adept in routine open and laparoscopic gynaecological and general surgery in 4620 patients has been assessed through the ARIEL Registry (Adept Registry for Clinical Evaluation) [64,65]. This followed 2882 patients undergoing gynaecological surgery (813 laparotomy and 2069 laparoscopy,) and 1738 general surgery patients (1469 laparotomy and 269 laparoscopies). Cancer, pain and/or bowel obstruction were the most frequent presenting symptoms or conditions reported in the general surgery patients. Findings from both the general surgery and gynaecological registries showed that in routine use, Adept is easy to use, is well tolerated by patients and has a good safety profile. The Registry closely scrutinized all reported events and the reported types and frequencies of adverse events were similar to published literature reports of what would normally be expected following surgery without the use of an anti-adhesion agent.

The experience of use of Adept in routine surgery and from clinical trials is very encouraging. Further data are needed to evaluate its role in adhesion prevention in bowel surgery.

**Surgical technique and adhesions**

What can we infer from the effect of surgical technique on adhesion formation? Moreno et al. examined the influence of abdominal incision on the formation of postoperative peritoneal adhesions in a rat model [66]. Three groups of 10 rats underwent supraumbilical midline laparotomy, right subcostal laparotomy or infraumbilical transrectal laparotomy. After 30 days the animals were sacrificed. The investigators demonstrated that infraumbilical incisions away from the midline are more traumatic, damage more of the peritoneum, and are more likely to come into contact with the omentum, peritoneal fat, bowel loops and pelvic contents. Luijendijk et al. examined the effect of various surgical strategies and their consequences on subsequent adhesion formation [67]. More adhesions were noted in patients who had multiple previous laparotomies, and in patients who had developed surgical complications such as abscesses, haematomas and intestinal leaks. Where recent adhesions were noted suture granulomas were found in large numbers. The authors suggested that foreign material was important in adhesion formation and that unnecessary contamination of the abdominal cavity with foreign materials should be avoided.

**Laparoscopy and adhesions**

As disruption to the peritoneum is implicated in the development of adhesions it would seem feasible that laparoscopic procedures would result in fewer adhesions. Gutt et al. examined 15 studies from 1987 to 2001 and revealed that there were fewer adhesions with laparoscopic procedures than after open surgery [68] but further analysis of the data was difficult due to the heterogeneity of the studies. However there are further important inconsistencies when epidemiological data from the SCAR-2 study on adhesion-related outcomes are considered [69]. This showed that the burden of adhesion-related outcome readmissions following most gynaecological procedures undertaken laparoscopically were similar to those following comparative open procedures. It is no surprise that the most important predictor of future adhesions is a history of previous surgery. The potential advantages of a laparoscopic approach in encouraging adhesiolysis is the decreased incidence of wound infection, a reduction of postoperative pneumonia, earlier return of bowel function and shorter hospital stay.

There is rising concern that the CO₂ pneumoperitoneum may be an important adhesiogenic factor associated with laparoscopy. This may be due to the CO₂ inducing local changes such as intraperitoneal acidosis [70–72] or, in the absence of moistening, desiccation of the mesothelium [73]. The intraperitoneal pressure associated with prolonged pneumoperitoneum may also induce adverse effects on the microcirculation [74,75], possibly inducing hypoxaemia [76]. This hypoxia, together with other mesothelial insults, may stimulate expression of factors, such as vascular endothelial growth factor (VEGF), resulting in an increase in adhesion formation [76]. As a result of this animal work, active research for other potential adhesion-reduction strategies involving insufflators has begun [77,78].

**Conclusion**

There is no doubt that the development of anti-adhesion strategies has implications for health economists. The SCAR studies have alluded to the nature and volume of the problem. Ellis described the medicolegal consequences of adhesions and their associated contribution to morbidity with subsequent surgery [79,80]. The
Impact of adhesions

spectre of negligence has on occasions been associated with adhesions. The most common claims made include failure or delay of diagnosis, damage to bowel at laparotomy, pelvic pain, infertility and unnecessary usage of foreign materials at surgery. It is common practice for surgeons while consenting patients for laparotomy to omit to mention the effect of postoperative adhesions and there is little in the way of legal precedent so to do. In the light of the above data we should re-evaluate our practice and incorporate this in consent forms. Furthermore we as a colorectal and general surgical community have to anticipate future studies and take a direct responsibility to minimize adhesions in our patients. With ever increasing recognition of the clinical and health economic implications of adhesions it may be the time to conduct appropriate properly powered multicentre trials to try to find the ideal adhesion prevention agent.

References


Impact of adhesions


