Evidence-based prevention of post-operative adhesions

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Despite decades of research, numerous new product ideas and ‘carefully considered opinions’ of recognized experts, very few products for the prevention of post-operative adhesions have met the requirements for Level 1 evidence of safety and efficacy. Those that have are useable only at laparotomy. Several new liquid products intended for use at laparoscopy are in various stages of development and clinical investigation. Hopefully, some will prove to be both simple to use and efficacious. Even if this occurs, it must be remembered that a reduction in post-operative adhesions does not necessarily produce a better clinical outcome. Our common sense suggests that fewer adhesions logically result in less pain, more pregnancies, fewer bowel obstructions and less long-term morbidity. We believe that ‘fewer adhesions’ is a good thing, but we have no controlled human trials to prove this. How much of a reduction in post-operative adhesions is necessary before it is clinically relevant? A single adhesion in the wrong anatomic location may be catastrophic. How do we measure this? Until these and other questions have been answered (if ever), we have nothing more than educated guesses that all these efforts are warranted.

Key words: adhesion barriers/anti-adhesion liquids/evidence-based prevention/post-operative adhesions/surgical technique

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Introduction

Adhesions resulting from gynaecological surgery may well be the most significant iatrogenic factor contributing to infertility, pelvic pain or both. Operative site adhesions and de-novo adhesions (those developing at sites where no surgical procedure was performed) may create more problems than the original pathology leading to surgery. Understanding the pathogenesis of adhesion formation and development of methods to prevent these adhesions has consumed an enormous amount of time, effort and money from scientists, gynaecologists and industry. Are these efforts warranted? Do these adhesions really matter? A recent article reviewing the extent of the clinical problems resulting from adhesions may have answered this question (Ellis et al., 1999). Does anything really influence the development of these adhesions for better or worse? What does ‘evidence-based medicine’ say about these questions?

Several different approaches have been taken to minimize or prevent the formation/reformation of adhesions following surgery. These include minimizing tissue injury, removing the fibrin deposits in injured areas, physically separating injured surfaces, and inhibiting the proliferation of fibroblasts in injured areas. In the operating room, this translates into ‘good’ surgical technique, ‘barriers’ (absorbable and non-absorbable, solid and liquid), and fibrinolytic products.

Surgical Technique

One of the earliest descriptions of ‘microsurgical technique’ appeared in Victor Gomel’s textbook in 1983 (Gomel, 1983). He described what are now standard microsurgical methods that have been applied in other gynaecologic reconstructive procedures, particularly in infertile patients.

The principles of microsurgery are well known: gentle tissue handling, precise haemostasis, constant irrigation, small and non-reactive sutures, minimal use of electrosurgery, etc. It is assumed that strict adherence to these principles increases the chances of success (tubal patency) in tubal reanastamosis and decreases the likelihood of adhesions following other gynaecologic surgery. It seems logical and reasonable—good surgical technique produces superior results.

No one would suggest that we revert to ‘bad’ surgical techniques that must have been common practice before microsurgery became popular. However, there have been no randomized, blinded clinical trials comparing microsurgery (good) and macrosurgery (bad) with respect to any definable outcome. Obviously, such a study will never be done. No one would agree to be in the ‘bad’ arm of the study. Likewise, no
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reasonable, competent gynaecologist would perform surgery using ‘bad’ techniques.

Although the use of ‘good’ technique and microsurgical principles has been widely taught and practised since the 1980s, scientific evidence supporting such a practice is not based on randomized clinical trials in humans. It is solidly based on animal studies and the carefully considered opinions of recognized authorities in our profession.

Does the method of access matter? Several studies have addressed this question. It has been shown that the incidence of adhesion reformation after gynaecologic surgery is between 55–100% (Diamond et al., 1991), whether the procedure is done by laparotomy or laparoscopy. The incidence of de-novo adhesions however is much lower if the procedure is done by laparoscopy as compared with laparotomy (Diamond et al., 1987). In addition, Lundorff published a prospective randomized trial comparing the incidence of post-operative adhesions following the treatment of ectopic pregnancy by either microsurgical techniques at laparotomy or traditional laparoscopic surgery. Second-look laparoscopy revealed adhesions in >50% of patients treated at laparotomy versus 15% in the laparoscopic group (Lundorff et al., 1991).

Virtually every gynaecologist performing reproductive pelvic surgery by laparoscopic techniques believes that this results in fewer post-operative adhesions than similar procedures performed at laparotomy. Some animal data and far fewer human studies seem to confirm this belief (at least with respect to de-novo adhesions). Unfortunately, we have no randomized, controlled clinical trials addressing this issue. Therefore the concepts of ‘microsurgical techniques’ and ‘minimal access’ surgery are beneficial in theory only.

Barriers

The original ‘barriers’ consisted of peritoneal and omental grafts placed over traumatized surfaces and sewn in place. This practice places a layer of dead necrotic tissue on top of traumatized peritoneal surfaces, providing an abundant supply of substrate for adhesion formation. Subsequent animal studies have shown that placing devascularized tissue over damaged peritoneal surfaces increases (rather than decreases) adhesion formation. Although no human randomized trials dealing with gynaecological surgery have been performed, the animal data is convincing enough that this practice has been abandoned.

Similarly, reperitonealization of surgically produced peritoneal defects in the pelvis has not proven to be of any benefit in animal trials. The combination of suture material (required for closure) and interruption of peritoneal blood supply by stretching of the tissue seems to be more adhesiogenic than no treatment at all.

In the industrial arena, this concept of ‘barriers’ placed between traumatized surfaces to prevent adhesions has continued to be a favourite scenario. Both absorbable and non-absorbable barriers have been conceived, designed and tested. Before any of these products can be marketed and sold in the USA, controlled clinical trials must be performed and evaluated by the Food and Drug Administration (FDA). This significantly improves our ability to objectively evaluate these products.

One of the first barriers to be evaluated was Interceed® (oxidized regenerated cellulose), a mesh-like product designed to be placed over or between injured surfaces. It is also one of the most critically and extensively evaluated of the barriers. It has been studied in patients undergoing laparotomy and laparoscopy for treatment of myoma, endometriosis, benign ovarian masses and adhesions (Nordic Adhesion Prevention Study Group, 1995).

A review of 13 clinical trials published by Larsson in 1996 concluded that Interceed® is ‘safe and effective in all controlled human clinical trials’. Unfortunately it did not eliminate adhesions in all patients and all clinical situations. Some of the reviewed studies showed no benefit. Larsson concluded that this product is efficacious in very limited situations, specifically those where injured areas or structures can be completely covered with the material (Larsson, 1996). In addition, this is true only when the entire area is completely haemostatic. The presence of blood in the matrix of the material completely negates any benefit. Technical difficulties in the application of this product during laparoscopic procedures further limit its usefulness. Nevertheless, controlled trials have produced Level 1 evidence (well designed, randomized controlled trials) of the safety and efficacy of Interceed® in reducing the incidence of post-operative adhesions.

Seprafilm® (hyaluronic acid and carboxymethylcellulose modified to produce a clear film) has also undergone extensive clinical evaluation to assess its ability to reduce post-operative adhesions in patients undergoing conservative gynaecologic surgical procedures by laparotomy (Diamond, 1996). It has also been evaluated in a population of general surgery patients undergoing a variety of bowel procedures (Beck, 1997). In both cases, Seprafilm® has been shown to be safe and efficacious in reducing the incidence, extent and severity of post-operative adhesions (Level 1 evidence). Its handling characteristics make it difficult to apply, limiting its usefulness. It cannot be used at laparoscopy.

Gore-Tex Surgical Membrane®, a non-absorbable barrier (expanded polytetrafluoroethylene), has also undergone evaluation in a randomized multicentre controlled trial (Haney et al., 1995). This product must be sewn in place and is usually removed during a second surgical procedure. In patients undergoing gynaecological surgery by laparotomy for adhesions or myoma, Gore-Tex Surgical Membrane® was shown to decrease the severity, extent and incidence of adhesions in the treated areas (Level 1 evidence). Its usefulness is limited by the nature of the product: it must be sutured in place and, in most cases, should be removed at a subsequent surgery. It is very difficult to apply at laparoscopy.

In summary, Level 1 evidence supports the efficacy of three barrier methods for prevention of post-operative adhesions. All three products are currently available. Unfortunately, two of these cannot be easily applied at laparoscopy, and none has been FDA-approved for use at laparoscopy.

Liquids

Liquid substances used for the prevention of post-operative adhesions fall into three categories. The first, such as large volume isotonic solutions (normal saline, Ringer’s lactate, etc.), are intended to produce a ‘hydro flotation’ effect. From 500 ml to 3 l of fluid is instilled into the peritoneal cavity at the end of the laparoscopic procedure (depending on the operator). Regardless of volume, the absorption rate of the peritoneum ensures that this fluid is absorbed into the vascular system within 24–48 h, far too short a time to influence adhesion formation. No randomized
controlled clinical trial has demonstrated ‘hydro flotation’ to have any effect on post-operative adhesion formation (Duffy and diZerega, 1996).

The second category of ‘liquids’ consists of combinations of heparin, antihistamines, steroids, promethazine and isotonic saline or crystalloids. Various combinations of these substances are left in varying amounts in the peritoneal cavity at the conclusion of surgery. In theory, any or all of these adjuvants could reduce adhesions by a variety of pharmacological means. All were based on sound science and some animal studies. Although cited by ‘authorities’ as being their personal ‘preferences’, none of the pharmacological or liquid agents or combinations thereof, have been shown to improve pregnancy rates or decrease post-operative adhesion formation in randomized controlled human trials (Watson et al., 2000).

Thirty-two percent Dextran 70 (Hyskon®) has been used intra peritoneally for the purpose of reduction of post-operative adhesions. It has not been approved by the FDA for this purpose. By producing a ‘siliconizing’ effect, hydro flotation, and directly affecting the clotting cascade, it should decrease the formation of adhesions. Four human randomized clinical trials have been conducted. The combined outcomes of these trials (two showed efficacy, two did not) suggest that the product does not produce noticeable reductions in post-operative adhesions. Allergic reactions to this product have also been reported. The combination of these factors has virtually eliminated its use in gynaecological reconstructive surgery.

More recently, several liquid agents have been produced in an attempt to combine hydro flotation, barrier and pharmacological effects in a single product. Two have completed clinical trials. HAL-C® (a liquid form of carboxymethylcellulose and hyaluronic acid) was studied after completion of the clinical trial on Seprafilm®. Unfortunately, the results did not lead to continued development and promotion of the product.

Another solution containing hyaluronic acid has been developed and has completed clinical trials. Intergel® (0.5% ferric hyaluronate gel) has undergone randomized, placebo-controlled clinical trials in patients undergoing both laparotomy and laparoscopy (Thornton et al., 1998). Second look laparoscopy was used to evaluate (and treat) adhesions resulting from the first procedure. Statistical analysis of both groups indicated that the treated patients had significantly fewer adhesions than the control group. If adhesions formed, they tended to be less extensive and less severe (vascular and cohesive) in the treated group. The FDA is currently evaluating this data.

Several other ‘barrier’ liquids are currently in clinical trials. In the United States at the time of this publication, there are no liquid products available and approved for use at laparoscopy for the prevention of post-operative adhesions.

Others

Hellebrekers et al. recently published an extensive review of fibrinolytic agents in the prevention of post-operative adhesions (Hellebrekers et al., 2000). Streptokinase, first evaluated in 1950, was later studied in 1981–1990 in three human trials (Sievers and Eckert, 1981; Meier et al., 1985; Tuchmann et al., 1990). Only one of these had a control arm and all were very small studies from which no definitive evidence-based conclusions can be made.

Prevention of post-operative adhesions

More recently, recombinant human tissue plasminogen activator has been evaluated for its effectiveness in the prevention of post-operative adhesions. Numerous animal studies have demonstrated a significant decrease in the occurrence of post-operative adhesions (both reformed and de-novo adhesions). One human pilot study published in 1994 demonstrated safety in a group of 15 patients, but no further work has followed (Dunn and Mohler, 1994).

Based on years of animal studies, this group of agents holds significant promise. Unfortunately, we are years away from clinical relevance.

References


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