Royal College of Obstetricians & Gynaecologists

The Use of Adhesion Prevention Agents in Obstetrics and Gynaecology

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1. Introduction

Adhesions are fibrinous bands between and within organs that develop after aberrant healing; they are formed commonly after surgery and/or infection as a consequence of inflammation.

The clinical burden on the NHS of adhesions can be estimated from data extrapolated from the Surgical and Clinical Adhesions Research (SCAR) Study.[1] Following open gynaecological surgery, 2931 (34.5%) women had a total of 5433 readmissions over 10 years with 245 (4.5%) admitted for adhesion related disease. It is estimated that the direct cost of readmissions related to adhesions in the first year after lower abdominal surgery is £24.2 million, which increases to £95.2 million 10 years after the initial surgery.[2]

Surgical techniques such as laparoscopic surgery and microsurgery reduce the risk of adhesion formation, but do not eliminate it entirely. Once adhesions are surgically removed, they often reform. Various agents are available to reduce these consequences of surgery. Few prospective studies have assessed the direct clinical consequences of adhesions (subfertility, pain, intestinal obstruction, or complications during future surgical procedures) and the majority of studies have used the secondary outcome of the adhesion score at Second Look Laparoscopy (SLL). Reviewed intervention studies that are not specifically referenced in this article are all referenced in two Cochrane reviews of adhesion prevention agents in pelvic surgery.[3,4] Unless stated, all meta–analyses derive from these reviews.

This document aims to aid clinicians and policy makers on the use of effective adhesion prevention agents.

2. Evidence for the use of anti–adhesive agents in gynaecology

2.1 Pharmacological agents

Several pharmacological agents have been advocated to promote full healing over adhesion formation. The use of steroids although once widespread in fertility conserving pelvic surgery, is not supported by published evidence. Five randomised controlled trials (RCTs) investigated the effectiveness of steroids following open pelvic surgery. Meta–analysis failed to demonstrate a reduction in adhesion formation or improvement in pregnancy rate.[3] Furthermore, the use of steroids may impair the healing process and suppress the hypothalamic pituitary axis.

Antihistamines, heparin and nonsteroidal anti–inflammatory agents have not been found to be effective in adhesion prevention.[3]

2.2 Barrier agents (liquids/gels/solids)

Barrier agents work on the principle of separating; opposing injured peritoneal surfaces during the healing phase in order to reduce adhesion formation.

2.2.1 Hydro floatation agents

The use of several liquid agents including crystalloids, Icodextrin (Adept, R Baxter) and hyperosmotic solutions have been investigated.

A meta–analysis of 350 studies, although limited by their use of retrospective data and statistical heterogeneity, failed to reveal a reduction in postoperative adhesion formation with the use of crystalloids.[5] This is not surprising as 1000 ml of crystalloid is completely absorbed from the peritoneal cavity within 24 hours.

Dextran is a polysaccharide (Hyskon Pharmacia, Uppsala, Sweden) which facilitates transudation of fluids into the peritoneal cavity. Four RCTs compared the effect of Dextran to crystalloid in adhesion

prevention following pelvic surgery. Meta–analysis revealed no difference in the mean adhesion score or pregnancy rate with the use of Dextran at SLL. This is not surprising as the large transudate is likely to be completely absorbed before full healing has occurred. Reported side effects include anaphylaxis, pleural effusion, and peritonitis.[3]

Icodextrin, such as Adept® (Baxter, Thetford, Norfolk) is a high molecular weight iso–osmolar, alpha–1, 4–glucose polymer that is slowly absorbed from peritoneal cavity. Studies have revealed conflicting results. diZerega[6] found no significant benefit in an initial small study whereas Brown et al.[7] in a multicentre RCT revealed a beneficial effect with the use of Icodextrin when compared with Ringer Lactate solution. The use of Icodextrin was associated with significant reduction in de novo adhesions (53% vs 43%, $p < 0.05$) and adhesion sites (mean SD 2.6 [3.7] vs 2.0 [3.2], $p < 0.05$).

In a double blind RCT Trew et al.[8] compared the effectivenees of Icodextrin (Adept) and Ringer lactate as an adhesion prevention agent following laparoscopic gynaecological surgery. The use of Icodextrin (Adept) was not associated with a reduction in the incidence of de novo adhesion formation (mean 2.58, SD 2.11 for icodextrin and mean 2.58, SD 2.38 for Ringer respectively).[8] All three studies used different outcomes relating to adhesions at SLL and it has proved impossible to perform a meaningful meta–analysis.

2.2.2 Gels including hyaluronic acid derivatives

Hyaluronic acid is a linear polysaccharide with disaccharide units composed of sodium D–glucuronate and N–acetyl–D–glucosamine. It is absorbed from the peritoneal cavity within 7 days. Several derivatives of hyaluronic acid, are or have been, commercially available. They produce a gel based barrier. Ferric hyaluronate gel was withdrawn from the market in 2003.

Meta–analysis of four RCTs (one study investigated laparoscopic myomectomy, and the rest investigated laparotomy for benign gynaecological conditions) demonstrated a significant reduction in the proportion of adhesions (OR 0.31, 95% CI 0.19, 0.51) with the use of hyaluronic acid derivatives (Intergel: 0.5% ferric hyaluronate gel, Hyalobarrier Gel: auto cross–linked hyaluronic acid gel and Sepracoat: dilute hyaluronic acid solution) when compared to placebo or no treatment.[3] Furthermore, a recent meta–analysis of 5 RCTs demonstrated a significant reduction in intrauterine adhesions after hysteroscopic surgery (OR 0.41, 95% CI 0.22, 0.77) and intraperitoneal adhesions after laparoscopic surgery (OR 0.248, 95% CI 0.09, 0.63) with the use of auto cross–linked hyaluronan gel (ACP gel, Hyalobarrier Gel, Baxter,Italy).[9] Pellicano et al.[10] demonstrated a significant improvement in pregnancy rate (number of women, % of women pregnant: 14/18 [77.8%] vs 7/18 [38.8%]), 12 months after a laparoscopic myomectomy with the use of auto cross–linked hyaluronan gel (Hyalobarrier Gel, Anika Therapeutics Inc).

Seprafilm® (Genzyme Corporation, Cambridge, USA) is composed of chemically derived sodium hyaluronate and carboxymethylcellulose. It is absorbed from the peritoneal cavity within 7 days. In a meta–analysis of 6 RCTs, Kumar et al.[11] reported a significant reduction in the incidence (OR 0.15, 95% CI 0.05, 0.43, $p < 0.001$), extent (WMD –25.9%, 95% CI –40.56, –11.26, $p < 0.001$) and severity of peritoneal adhesions in nongynaecological abdominal surgery with the use of hyaluronic acid and carboxy–methyl membrane. However, a comparable reduction in the incidence of intestinal obstruction necessitating surgery was not found.

Polyethylene Glycol (PEG) based liquid precursors (SprayGel™, Confluent Surgical, Waltham, MA) when sprayed onto target tissue reacts and forms a gel barrier within seconds of its application. It is absorbed from the peritoneal cavity within 30 days. In a meta–analysis of three RCTs (n = 113), Ten Broek et al.[13] demonstrated a reduction in the incidence of adhesion formation (OR 0.27, 95% CI 0.11, 0.67) with the use of PEG in fertility conserving gynaecological surgery.[3,12,13]

2.2.3 Solid barrier anti–adhesive agents

Gynecare Interceed® (Ethicon Inc, Somerville, NJ), an oxidised regenerated cellulose, is a synthetic barrier which forms a gelatinous protective coat over the raw surfaces. Meticulous haemostasis and application of this membrane is essential as layering or contact with adjacent organs and blood can

increase adhesion formation. In a meta–analysis of 12 RCTs at SLL, the use of Interceed was associated with a reduced incidence of adhesions when compared with no treatment for both de novo adhesions (OR 0.30, 95% CI 0.12, 0.79), and reformation of adhesions (OR 0.19, 95% CI 0.09, 0.42) in the laparoscopy group.[4] There was also a reduction in the incidence of reformation of adhesions following adhesiolysis and ovarian surgery in the laparotomy subgroup (OR 0.39, 95% CI 0.28, 0.55). However the included studies were small. A lower initial score when measuring de novo adhesions introduces a bias, with reduced chance of demonstrating efficacy.[4]

Gore–Tex® surgical inert membrane (W. L. Gore & Associates, Arizona, USA), is an unabsorbable adhesion prevention agent, which requires suturing and a second surgical procedure for removal. It has no effect on coagulation. There is limited evidence of its effectiveness as an anti–adhesive agent. Two studies revealed contradictory results when Intercede was compared to Gore–Tex for adhesion prevention. Hanny et al.[4] demonstrated effectiveness in preventing reformation of adhesions following the application of Gore–Tex (OR 0.16, 95% CI 0.03, 0.80), however the incidence of adhesions in the Intercede group was substantially higher than reported in studies comparing Gynecare Intercede® with placebo. Furthermore, the need for suturing and later removal makes Gore–Tex an unlikely choice.

3. Evidence for the use of anti–adhesive agents in obstetrics

In the UK, caesarean section rates have increased from 12% in 1990 to 25% in 2012. Any intervention that reduces the incidence of lower segment caesarean section (LSCS) or prevents adhesion formation at LSCS would reduce the maternal morbidity associated with repeat LSCS. To date there are no RCTs examining the use of adhesion prevention agents after caesarean section although one retrospective study (n = 45) and two prospective studies (n = 28, 52) demonstrated a reduction in the incidence of adhesions after the use of solid barriers (oxidised regenerated cellulose: Interceed; and sodium hyaluronate and carboxymethylcellulose: Seprafilm respectively).[14–16] A reduction in the incidence and severity of adhesions in women undergoing repeat LSCS was associated with a significant reduction in operative time (38.7 minutes vs 45.3 minutes, $p < 0.01$) but not time to delivery (5.7 minutes vs 7.5 minutes, $p = 0.14$).[15,16]

3.1 Cost effectiveness

Although the development of postoperative adhesions is common, there is general reluctance among the clinicians to use anti–adhesive agents. It is clear from the evidence that many of the studies evaluating the cost effectiveness of anti–adhesive agents are underpowered and their methodologies would be deemed suboptimal by current standards. This potentially leads to bias and over estimates of intervention effects. Cost effectiveness models might also be unreliable. Many studies were performed more than 10 years ago, and the more recent studies performed were based on a different healthcare tariff system.[2,17,18] In a study to evaluate cost effectiveness, it was suggested that the use of an anti–adhesive agent costing up to €130 and with 25% efficacy could save €40 million over a 10 year period.[19] In a recent study, and based on the financial model of the payment by results system adopted in England, the use of an effective anti–adhesion agent costing around £110 per unit, and leading to a 25% reduction in adhesion prevalence could have saved the NHS around £700 000 during the studied period of 2004–2008.[18] This business model would be expected to differ across different parts of UK, such as in Scotland where a different financial system exists, but the potential advantage of adhesion prevention agents in lessening the economic burden on any health service remains. Nevertheless, a general conclusion can be drawn in that cost effectiveness can be achieved if the agents are used at the lowest cost possible (around £110 per usage), assuming 25% reduction in adhesions. However, not many products on the market with data showing clinical efficacy fall into this price target and ideally need to be evaluated in contemporary gold standard studies.

Although with limited evidence of efficacy in obstetrics, barrier anti–adhesive agents are being marketed in United States. In the only cost effectiveness analysis of adhesion barriers to date, it was not possible to demonstrate cost effectiveness of the use of synthetic adhesion barriers. It was noted that the use of these agents could only be justified if the rate of postoperative small bowel obstruction was 2.4%, a rate

much higher than noted routinely.[20] Although intra–abdominal adhesions from prior caesarean delivery may influence the operating time, however they rarely cause maternal harm and have not been demonstrated to affect perinatal outcome.

4. Opinion

Any surgery in the abdomen can lead to adhesion formation and potential morbidity. There is evidence to support the use of hyaluronic acid derivatives, PEG based derivatives and solid barrier agents derived from oxidized regenerated cellulose, namely Interceed, during laparoscopy or laparotomy in benign gynaecological surgery to reduce the incidence, severity and proportion of adhesion formation. There is also evidence to support the use of hyaluronic acid derivatives during hysteroscopic surgery to reduce the incidence of intra–uterine adhesion formation. However, there is little evidence to support the use of pharmacological and hydrofloatation agents including Icodextrin in gynaecological surgery. There is no apparent benefit of using adhesion prevention agents at caesarean section. As most of the economic modelling is not based in contemporary health economies, further evidence is required before recommending anti–adhesion agents in current gynaecological practice. Further studies should also use clinical outcomes such as further surgery for adhesion related complications rather than the formation of adhesions per se, which may not have clinical impact.

References

1. Lower AM, Hawthorn RJ, Ellis H, O'Brien F, Buchan S, Crowe AM. The impact of adhesions on hospital readmissions over ten years after 8849 open gynaecological operations: an assessment from the Surgical and Clinical Adhesions Research Study. *BJOG* 2000;107:855–62.
2. Wilson MS, Menzies D, Knight AD, Crowe AM. Demonstrating the clinical and cost effectiveness of adhesion reduction strategies. *Colorectal Dis* 2002;4:355–60.
3. Metwally M, Watson A, Lilford R, Vandekerckhove P. Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2006;(2):CD001298.
4. Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, et al. Barrier agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2008;(2):CD000475.
5. Wiseman DM, Trout JR, Diamond MP. The rates of adhesion development and the effects of crystalloid solutions on adhesion development in pelvic surgery. *Fertil Steril* 1998;70:702–11.
6. diZerega GS, Verco SJS, Young P, Kettel M, Kobak W, Martin D, et al. A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. *Human Reprod* 2002;17:1031–8.
7. Brown CB, Luciano AA, Martin D, Peers E, Scrimgeour A, di Zerega GS. Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double–blind, randomized, controlled study. *Fertil Steril* 2007;88:1413–26.
8. Trew G, Pistofidis G, Pados G, Lower A, Mettle L, Wallwiener D, et al. Gynaecological endoscopy evaluation of 4% icodextrin solution: a European, multicentre, double–blind, randomized study of the efficacy and safety in the reduction of de novo adhesions after laparoscopic gynaecological surgery. *Hum Reprod* 2011;26:2015–27.
9. Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Efficacy of auto–crosslinked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy: a systematic review and meta–analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol* 2012;160:1–5.
10. Pellicano M, Guida M, Bramante S, Acunzo G, Di Spiezio Sardo A, Tommaselli GA, et al. Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy. *Fertil Steril* 2005;83:498–500.

11. Kumar S, Wong PF, Leaper DJ. Intra–peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non–gynaecological abdominal surgery. *Cochrane Database Syst Rev* 2009;(1):CD005080.
12. Mettler L, Hucke J, Bojahr B, Tinneberg HR, Leyland N, Avelar R. A safety and efficacy study of a resorbable hydrogel for reduction of post–operative adhesions following myomectomy. *Hum Reprod* 2008;23:1093–100.
13. Ten Broek RP, Kok–Krant N, Verhoeve HR, van Goor H, Bakkum EA. Efficacy of polyethylene glycol adhesion barrier after gynecological laparoscopic surgery: Results of a randomized controlled pilot study. *Gynecol Surg* 2012;9:29–35.
14. Kim TH, Kim JS, Lee HH, Nam KH, Lee KH, Lee JJ. *Prevention of vesicouterine adhesion after cesarean with Interceed*. Korean Society of Fetal Medicine, 10th Annual Congress of Perinatal Society of Australia & New Zealand; 3–6 April 2006; Perth, Australia.
15. Fushiki H, Yuki H, Nakajima A. Usefulness of Seprafim during a caesarean section. *Ob Gyn Surgery* 2002;99–105.
16. Fushiki H, Ikoma T, Kobayashi H, Yoshimoto H. Efficiency of Seprafilm as adhesion prevention barrier in cesarean sections *Obstet Gynecol Treat* 2005;91:557–61.
17. Menzies D, Parker M, Hoare R, Knight A. Small bowel obstruction due to postoperative adhesions: treatment patterns and associated costs in 110 hospital admissions. *Ann R Coll Surg Engl* 2001;83:40–6.
18. Cheong Y, Sadek K, Watson A, Metwally M, Li TC. Adhesion reduction agents in gynaecological procedures: can NHS afford it? An economic cost efficiency analysis. *J Obstet Gynaecol* 2011;31:631–5.
19. Wilson MS. Practicalities and costs of adhesions. *Colorectal Dis* 2007;9(Suppl 2):60–5.
20. Allbright CM, Rouse DJ. Adhesion barriers at cesarean delivery: advertising compared with the evidence. *Obstet Gynecol* 2011;118:157-60.

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