

ORIGINAL ARTICLE

Cross-linked sodium hyaluronate, an anti-adhesion barrier gel in gynaecological endoscopic surgeryLISELOTTE METTLER^{1,2}, WAEL SAMMUR², THORALF SCHOLLMMEYER¹,
IBRAHIM ALKATOUT¹¹Department of Obstetrics & Gynecology, University Hospitals Schleswig-Holstein, Campus Kiel, Germany, and²German Medical Center, Dubai Healthcare City, United Arab Emirates**Abstract**

Objectives: In the context of common adhesion prevention in laparotomic, laparoscopic and hysteroscopic surgery this article details the effects of a cross-linked sodium hyaluronate anti-adhesion barrier gel. The observed adhesion score is expressed in the following three measurements: Severity, extent and incidents of adhesions. **Material and methods:** From a total of 85 patients treated by laparoscopy and hysteroscopy, a second look endoscopic procedure could be performed in 35 cases. **Results:** Our preliminary, short evaluation of 35 patients submitted to a second look laparoscopy or hysteroscopy revealed the beneficial effect of the applied HYAcorp endo gel, showing only a minimal amount of adhesions at the second look observation. **Conclusion:** Cross-linked sodium hyaluronate is highly effective in the prevention of adhesions at laparoscopic and hysteroscopic surgery.

Key words: Adhesion prevention, cross-linked sodium hyaluronate, laparoscopy**Introduction***General introduction*

In a selective pubmed/medline search using “adhesions”, “laparoscopy” and “prevention of adhesions” as key words for all known adhesion prevention techniques, barriers appeared to be the most effective method. In the forefront, however, stand the meticulous surgical technique and the aim to traumatize as little as necessary. Any peritoneal damage leads to an acute inflammatory response and to fibrous adhesions (Figures 1 and 2) which may provoke bowel obstruction, chronic pelvic pain, dyspareunia, infertility and a higher complication rate for subsequent surgeries (1–8). In laparoscopy and hysteroscopy the use of heated and moist gas definitely causes fewer adhesions. A continuous suction and irrigation at endoscopic procedures is also advisable.

The first generation of barriers consisted of meshes, such as Interceed (Johnson & Johnson

Patient Care, Inc., New Brunswick, NJ, USA). Later viscous solutions, such as Intergel (Lifecore Biomedical Inc., Chaska, MN, USA) and Tissucol (Baxter Healthcare Corp., Deerfield, IL, USA) were propagated. In recent years sprayable liquids, such as polyethylene glycols = PEGs (SprayShield, Covidien, Mansfield, MN, USA, and CoSeal, Baxter Healthcare) which polymerize to hydrogels with addition of colorants and without colour, revealed 65 – 70 % reduced adhesion formation compared to the use of saline solution and Ringer’s lactate. The extent of adhesions, the severity and the tenacity were evaluated.

Hydroflotation with several liters of icodextrin solutions (4 %) for rinsing and instillation at the end of surgery resulted in a significant adhesion reduction at the surgical site. HYAcorp endo gel is a hyaluronate-based product which has recently gained attention. It is the aim of the present paper to evaluate the site-specific barrier HYAcorp endo gel (BioScience GmbH, Ransbach-Baumbach, Germany).



Figure 1. Schematic presentation of genital adhesiolysis via laparoscopy.

Pathogenesis of adhesion formation

Many processes occur in response to adhesion stimulation. Peritoneal mesothelial damage leads to an acute inflammatory response promoting the growth of fibrous adhesions.

The fibrinous exudate leads to the formation of fibrin by activation of the coagulation cascade which transforms prothrombin into thrombin [Factor IIa]. Thrombin then triggers the conversion of fibrinogen into monomers of fibrin which polymerize and are deposited on the wound surface. Polymorphonuclear macrophages and mesothelial cells, which are present in the fibrinous exudate, migrate, proliferate and

differentiate. They release a variety of substances, such as plasminogen system components, arachidonic acid metabolites, cytokines and growth factors.

Although fibrinous exudates and fibrin deposition are a part of normal tissue repair, their complete resolution is required for normal healing. A balance between fibrin deposition and degradation is essential for deciding whether there will be normal peritoneal healing or adhesion formation. Upon full fibrin degradation there will be normal peritoneal healing. If fibrin is not completely degraded, fibroblasts and capillary ingrowths will occur. Vascular endothelial growth factor (VEGF) has also been implicated in having a role in adhesion formation. Cytokines are produced by fibroblasts and macrophages, which are present within the fibrin meshwork, and cause increased collagen synthesis (3).

In this paper we only evaluate laparoscopic and hysteroscopic surgical procedures.

Laparoscopy and hysteroscopy and adhesion formation

In laparoscopy, trauma to the peritoneum is minimized relative to open surgery. Less haemorrhage results from laparoscopy and the fact that pneumoperitoneum is established may separate healing surfaces and reduce adhesion formation. However, some studies suggest that the pneumoperitoneum used in laparoscopy has some effect on adhesion formation. Elevated intra-abdominal pressure may result in local hypoxia and may lead to adhesion formation (9). Most studies indicate that adhesion formation is less after laparoscopy compared to laparotomy (10).

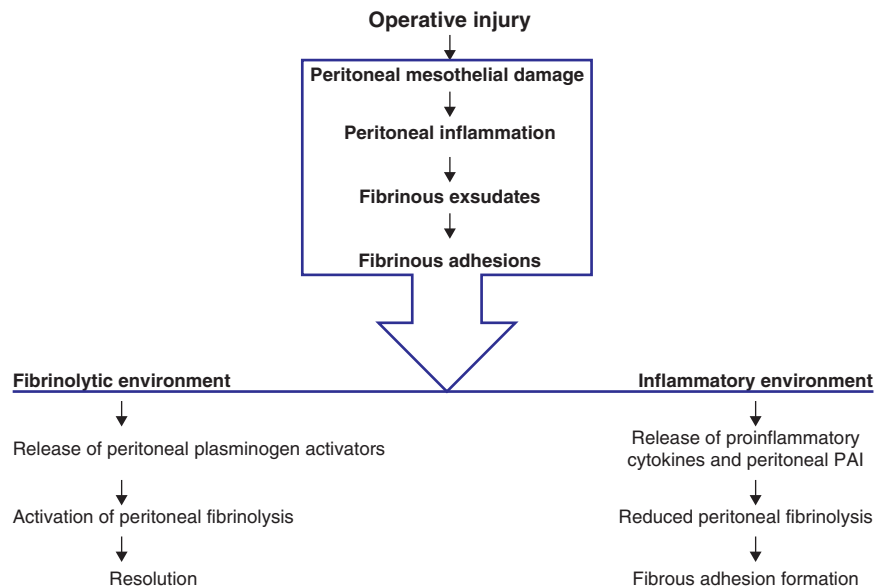


Figure 2. Consequences of operative surgery.

After intrauterine cavity surgery with polypectomy, myoma enucleation, septum resection or adhesiolysis the endometrial lining often produces adhesions due to the same mechanism as described for laparoscopy.

Adhesion-reducing agents

Most widely used are topical agents and barriers. Other categories, such as nonsteroidal anti-inflammatory drugs (NSAIDS) and others, are not discussed here.

Topical agents. Topical agents are divided into *liquids* and *gels*. Liquids are instilled into the abdominal cavity at the end of the surgery. They separate the bowels which float freely in the liquid, based on the principle of hydroflotation. Hereby, between 500 ml and three litres of fluid are instilled into the cavity; however, no significant evidence exists to support their use as the absorption rate of the peritoneum ensures that the fluid is absorbed into the vascular system within 24–48 hours. Hyperosmolar solutions such as peritoneal dialysis solution, may be reabsorbed more slowly and have been shown to be effective in rats (11) Intergel[®] (Lifecore Biomedical Inc.), a solution containing hyaluronic acid, has undergone clinical trials in laparoscopy and laparotomy and has revealed fewer adhesions. Adept[®], a 4% icodextrin solution of Baxter Healthcare Corp. (Deerfield, IL, USA), seems promising (12) and the results of the Gynaecological ENdoscopic EVALuation of Adept (GENEVA) study confirm a specific effect (13). The GENEVA study confirmed the safety of Adept[®] in laparoscopic surgery; however, the proportion of patients with *de novo* adhesion formation was surprisingly high. No significant difference was found in the reduction of *de novo* adhesion incidence between Adept[®] and lactated Ringer's solution with exception of the posterior uterine site. A site-specific barrier agent might best be combined with Adept[®] for a wider spectrum of anti-adhesion formation.

Barriers. The basic principle of these agents is that there should be separation of the operative surfaces with a mechanical barrier. There are certain properties that the agents should display to serve as barriers, e.g. the material should be easily degraded without a fibrous reaction. A series of experiments have demonstrated that adhesion formation does not progress after a mesothelial cell layer covers a foreign mesh at approximately one week (14).

At present, the following barriers are available: Hyaluronic acid, chitosin, carboxymethylcellulose, oxidised regenerated cellulose and expanded polytetrafluoroethylene. The adverse effects of peritonitis and abscesses have hindered the use of hyaluronic

acid (15). Chitosan has an antimicrobial action to bacteria, fungi, viruses and because of its haemostatic nature has been successfully used in the dressing of wounds.

Interceed[®] (Johnson & Johnson Patient Care Inc.) an oxidised regenerated cellulose, was one of the first barrier agents to be tested. It is a mesh-like barrier which is placed between the traumatized surfaces. It has been used in patients undergoing both laparoscopy and laparotomy for the treatment of conditions such as fibroids, endometriosis and ovarian masses. Larsson concluded that Interceed[®] was safe and effective in controlled human trials; however, it could not eliminate adhesions in all patients and the presence of blood in the matrix of the material negated any benefit (16). There is also a technical difficulty in introducing the material laparoscopically. However, level 1 evidence revealed a reduction of postoperative adhesions.

Seprafilm[®] (Genzyme Corp., Cambridge, MN, USA), a hyaluronic acid and carboxymethylcellulose modified to produce a clear film, is another anti-adhesion barrier. Level 1 evidence showed that Seprafilm[®] was safe and effective in reducing postoperative adhesions but its use was limited due to the difficulty to apply it laparoscopically.

Level 1 evidence also revealed that the barrier Goretex[®] (W.L. Gore & Associates, Flagstaff, AZ, USA), a polytetrafluoroethylene, reduced the severity of adhesions; however, its usefulness is limited by the need for suturing and later removal. There is also a potential risk of infection and difficulty in applying it laparoscopically.

SprayGel[®] (Covidien, formerly Confluent Surgical Inc., Mansfield, MN, USA), a polyethylene glycol, is another absorbable barrier. The synthetic gel adhesive barrier is easily applicable after both laparoscopic and open surgery (17,18). The barrier is formulated to adhere for five to seven days, after which it hydrolyses to water-soluble compounds. Today, Covidien markets a further development of this product under the name of SprayShield[®] with level 1 evidence.

CoSeal[®] is a commercially available barrier from Baxter Healthcare Corp. that has prevented adhesions in 60% of cases in a randomized trial (19).

Material and methods

HYAcorp endo gel is a bio-absorbable sterile, transparent, high viscous gel obtained by condensation of hyaluronic acid, one of the main components of human connective tissue and of epithelial and mesothelial tissues, and it perfectly adheres to the tissue surface and to the abdominal wall creating an anti adhesion barrier.

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Table I. Adhesion prophylaxis in 85 gynaecological endoscopic cases (2011 – 2012).

Laparoscopies	<i>n</i>
Myoma enucleations	24
Endometriomas	16
Ovarian cysts	20
Hysterectomies (TLH)	15
Total	75
Hysteroscopies	<i>n</i>
Septum resections	5
Myoma enucleations	5
Total	10

It is an absorbable, anti-adhesion barrier gel that helps to reduce the post-surgical adhesion formation in patients undergoing laparoscopic pelvic and hysteroscopic gynaecological surgery.

The gel is available in 10 mm syringes and is applied by a special cannular applicator by simple pressure on the syringe in 1 – 2 mm thick layers of gel. The operative site should be dry. Irrigation and aspiration has to be performed previously. After covering the surgical site it is not advised to apply any additional gel. The gel stays effective as a barrier for five to seven days and is then excreted through the kidneys.

Patients

In 75 laparoscopic surgical procedures and in ten hysteroscopic procedures 10 – 30 ml of the gel was applied in each case (Table I). After the primary surgery all sites were without adhesions at the end of the intervention.

Results

It appears to be the 20 mg of Na hyaluronate in the cross-linked gel that makes the essential difference to other “hyaluronate” products. The parameters to be checked in each batch are Na hyaluronidate, sodium chloride and water for injection. The specifications of the product are detailed in Table II.

Of the 85 patients who had received an anti-adhesive treatment with HYAcorp endo gel after

Table II. Qualitative and quantitative composition of HYAcorp endo gel.

1 ml of HYAcorp endo gel contains:	
Na-hyaluronate, cross-linked hylan gel	20 mg
Na-hyaluronate	10 mg
Sodium chloride	6.9 mg
Water for injection add	1 ml

laparoscopic or hysteroscopic surgery, 35 underwent a second look laparoscopy ($n = 25$) or hysteroscopy ($n = 10$) within two to three months after the initial procedure. Adhesion scores (0 – 3) expressed in severity, extent and incidence of adhesions were evaluated in the 35 patients at a second look laparoscopy (Table III). Compared to normal adhesion formation reported in the literature the obtained results clearly speak for the adhesion prevention capacity of HYAcorp endo gel.

Discussion and conclusions

In our preliminary, short time evaluation of 35 cases treated with HYAcorp endo gel in a second look laparoscopy we consider the gel to be highly effective in the prevention of adhesions at laparoscopic and hysteroscopic surgery. Although this is no more than an observation, we conclude that the cross-linked hyaluronate of Bio Science may be a helpful tool to prevent adhesions in gynaecological laparoscopic (20–23) and hysteroscopic (24–26) surgery. Correlation to similar results in the literature is given (27).

Hyaluronic acid is a natural complex sugar found throughout all living organisms that retain water and add volume to the tissue. In addition, hyaluronic acid binds with collagen and elastin and transports essential nutrients to these fibres.

In its natural form, unbound hyaluronic acid forms a liquid, made of highly hydrated individual polymers that are metabolized in the body in just 12 hours. Cross-linking of hyaluronic acid refers to a process in which the individual chains of hyaluronic acid are chemically bound (or “cross-linked”) together, transforming the liquid hyaluronic acid into a soft solid, or gel. The firmness of the gel depends on the degree of cross-linking of the individual hyaluronic acid chains. The body metabolizes cross-linked hyaluronic acid more slowly, resulting in a longer duration of the effect when hyaluronic acid is used therapeutically.

Postsurgical adhesions develop following abdominal, gynaecological and vaginal surgery as a consequence of abnormal wound healing. Major complications that arise from postoperative adhesions include intestinal obstruction, infertility, chronic pain and loss of bone structure. A wide variety of barrier substances has been tested to prevent adhesions after surgery.

Barrier materials are interposed between adjacent surfaces to avoid direct contact; however, unsatisfactory results have often been reported. To obtain low tissue reaction and, consequently, better clinical results, biodegradable barriers are desirable.

One particularly promising biopolymer that effectively acts as a barrier is hyaluronic acid (HA). HA has

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Table III. Adhesion scores expressed in severity – extent and incidence (0–3) after endoscopic surgery in a second look endoscopic evaluation.

Laparoscopies	n	Severity of adhesions			Extent of adhesions			Incidence of adhesions		
		0–1	2	3	0–1	2	3	0–1	2	3
Myomectomies	7	6	1	./.	6	./.	./.	7	./.	./.
Endometriomas	5	3	2	./.	5	./.	./.	3	2	./.
Ovarian cysts	7	6	1	./.	7	./.	./.	7	./.	./.
Hysterectomies (TLH)	6	6	./.	./.	7	./.	./.	6	./.	./.
Total	25	21	4		25			23	2	
Hysteroscopies	n									
Septum resections	7	7	./.	./.	7	./.	./.	7	./.	./.
Myoma enucleations	3	3	./.	./.	3	./.	./.	3	./.	./.
Total	10	10			10			10		

been experimentally shown to reduce postoperative adhesion formation after abdomino-pelvic and orthopaedic surgery. The anti-adhesive effects depend on the molecular weight as well as on the concentration of the preparation. However, the results are variable because unmodified HA is subject to rapid degradation and is cleared from the site of administration within hours.

HA modified (cross-linked) with foreign molecules in the form of a resorbable gel has been reported to significantly reduce the incidence and severity of adhesions. In gynaecologic surgery no negative effects are reported.

In 2002 and 2003 Beck et al. and Acunzo et al. carried out studies on the prevention of adhesions (25,28). Di Zerega et al. emphasize this prevention in every publication (3).

Swank et al. (29) could not find a difference in pain score and life quality after laparoscopic adhesiolysis compared to purely diagnostic laparoscopy but the amount of postsurgical rehospitalisation after laparotomy (30) and laparoscopy is evident (31). Therefore, any product without side effects which diminishes postsurgical adhesions is welcome. Hyalobarrier and definitely HYAcorp endo gel are reasonably priced and effective substances which can be easily applied during endoscopic surgery.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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