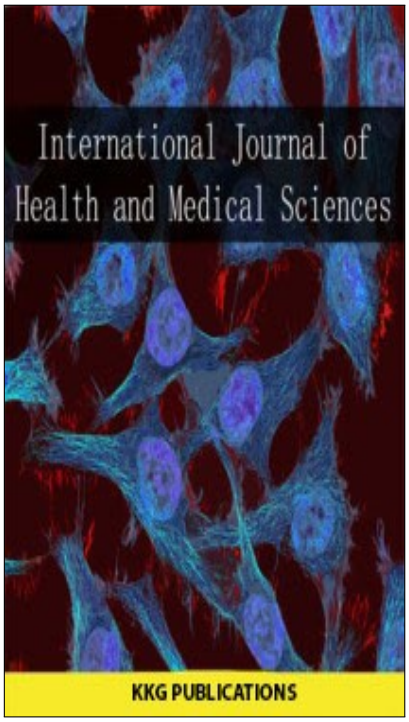

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Prophylaxis of Peritoneal Adhesions: Practical Issues to Consider When Using Antiadhesion Agents

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PROPHYLAXIS OF PERITONEAL ADHESIONS: PRACTICAL ISSUES TO CONSIDER WHEN USING ANTIADHESION AGENTS

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Abstract. As the most frequent complication of abdominal surgery, peritoneal adhesions produce significant morbidity and an increased risk of vascular, bowel, and organ injury in subsequent surgeries. Yet, antiadhesion agents are not routinely used in most abdominopelvic surgeries. We present a review on the safety, efficacy, and applicability of available antiadhesion agents to support the surgeons decision-making process and provide accurate counseling to patients regarding the type of agent to be used. Searches were conducted in MEDLINE, Pubmed, Wiley Online Library, Directory of Open Access Journals, and Orbis. Though singular agents have been subjected to randomized controlled trials, few head-to-head case-control studies comparing multiply available and in-research antiadhesion agents have been performed as of yet. Available agents are safe and effective in reducing the incidence of de novo adhesions after abdominopelvic surgery or adhesiolysis (up to 89%), but no single agent can fully prevent adhesion formation. The proposed "full conditioning" (86% CO_2+ 10% N_2O + 4% O_2 for the pneumoperitoneum, cooling of the peritoneal cavity, humidification, heparinized rinsing solution and 5 mg of dexamethasone, and hyaluronic acid), showed no adhesion formation (p = 0.0001) in 12/16 women with endometriosis. Surgeons should choose the antiadhesion agent most suitable to the underlying disease, type of surgery, and extent of surgical trauma, although no single available agent or surgical strategy can completely prevent adhesions. Guidelines on adhesion prophylaxis are needed. Future research should focus on comparison and combination of available agents.

INTRODUCTION

Adhesions are recognized to be the one of most frequent complications in abdominal surgery [1]. Incidence reports differ from 20 to 93 percent [2], according to type of surgery, entry techniques, operating times and concomitant diseases. Multiple adhesiogenic entities have been described, amongst which are desiccation, CO_2-insufflation, traumatic tissue handling, coagulation and diseases like endometriosis or pelvic inflammatory disease. They arise from an imbalance between fibrin production and fibrinolysis during the healing process after the surgical trauma, and their presence implies a high risk of complications in further surgeries, affecting the patient's quality of life and the budget of the health system. Affected patients showed an increased morbidity and mortality [3] with a higher incidence of intensive care admission, longer hospital stays and a higher incidence of bowel resections [4]. Additionally, it is well known that adhesions tend to reformate after laparoscopic adhesiolysis in 55-100% of cases [2].

Nevertheless at this time good evidence about the best option to handle with peritoneal adhesions, and methods to assess their efficacy are lacking. Therefore, prevention of adhesions is a significant unmet need in surgical therapeutics [5]. Investigation in this field had led to the development and use of different substances capable of reducing the postoperative formation of adhesions. Then the decision to use these products is based on consensus which encourages surgeons to assume effective steps to prevent adhesions [6], and are especially recommended in "high-risk of adhesions" procedures, regardless of open or laparoscopic surgery [7]. Of course, patients should be informed about the risks of adhesion formation and prevention strategies.

For the purpose to support the surgeon's decision and to give an accurate counselling to patients in regard the type of agent to be used, we realized a review on the safety and efficacy of available Antiadhesion Agents (AA). Again, remembering that the first step in adhesions prophylaxis is based on a meticulous surgical technique, and adherence to general microsurgical rules [3], an issue that is of ultimate interest in gynecology and fertility surgery.

Available Antiadhesion Agents

An antiadhesion agent is any natural or synthetic substance capable of interfering the adhesions formation process between adjacent anatomic structures normally not attached to each other [4]. To reach its goal, the agent should act during the

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first seven days of peritoneal healing, or staying long enough during this critical period of adhesion development, leading to a minor incidence, extension and severity of adhesions, and their associated disorders.

Factors that need to be considered before using an AA are not only safety, usability and clinical outcome but also its cost/effectiveness ratio. In the SCAR study [7], costs of adhesion-related pathology have been modeled by measuring adhesion-related readmission within the first 3 years after surgery, with or without the use of an AA. To be cost-effective, products that cost €130 or €300 need to demonstrate a 26% or 60% reduction of adhesion-related readmissions, respectively. Concluding that healthcare systems could save overall costs by using an AA with a reasonable cost-effectiveness ratio.

Modern products - films, powder, gels and fluids - comply with most of the desirable characteristics required to produce an effective barrier between adjacent tissues (Table 1), but surgeons continue using Ringer's solution, that does not fulfill the requirements to be a very effective AA [3].

TABLE 1
DESIRABLE CHARACTERISTICS OF AN ANTIADHESION AGENT

Adequate intraperitoneal disposition to stay in the peritoneal cavity for the healing process.
Effective surface division.
No degradation or loss of efficacy in wet or bloody environment.
Being resorbed and metabolized with minimal inflammatory response.
Has no negative effect on wound healing.
Restriction of bacterial growth.
Good cost/effectiveness ratio

Nevertheless, evidence of safety and effectivity of AA is limited as a consequence of paucity and the quality of studies. Most of them are observational, not controlled, and non-head to head trials.

Other products are no longer used because they show no clear clinical benefits, like antibiotics, non-steroidal anti-inflammatory drugs, corticosteroids and fibrinolytic drugs. In case of SurgiWrap ® (polylactide: copolymer of 70:30 Poly [L-lactide-co-D,L lactide]), a polymer film designed to be sutured between adjuncting structures and with an extended resorption time of up to 6 months, there is no evidence about its safety and efficacy. Preclude ®, (Gore-Tex. Expanded Polytetrafluoroethylene, PTFE), a non-resorbable mechanical barrier that should be removed in a second surgery, is rarely used in Europe [7].

Icodextrin 4% solution (Adept ®), exhibits major efficacy against adhesion re-formation after a laparoscopic adhesiolysis, than Ringer's lactate solution (49% vs. 38%), being more effective in infertile patients (55% vs.33%) [8].

In the metaanalysis made by [9], the use of auto-crosslinked hyaluronan gel (Hyalobarrier gel ®) showed a reduced incidence of postoperative abdominal and intrauterine adhesions compared to standard surgery when used after laparoscopic myomectomy (OR 0.248, 95% CI 0.098 to 0.628) and hysteroscopic surgery (OR 0.408, 95% CI 0.217 to 0.766).

In a recent Cochrane review of 18 randomized controlled trials of AA with a total of 1262 women undergoing gynecological surgery [10], it was found that there is no effect of AA on pain or fertility outcome in women of reproductive age, though no adverse effects were reported. They also encountered that some AA could have stronger anti adhesion effects than no treatment after pelvic surgery.

Agents of oxidized regenerated cellulose (Interceed ®) reduce the incidence of de novo adhesions after laparoscopy (OR 0.50; 95% CI 0.30 to 0.83), but not after laparotomy (OR 0.72; 95% CI 0.42 to 1.25). Regarding re-formed adhesions, it shows a reduction after laparoscopy (OR 0.38; 95% CI 0.27 to 0.55), and laparotomy (0.17; 95% CI 0.07 to 0.41). Expanded polytetrafluoroethylene (Gore-Tex ®) also reduces de novo adhesions (OR 0.17; 95% CI 0.03 to 0.94).

But no difference in adhesion prevention was found between both the previous mentioned products (RR 0.36; 95% CI 0.13 to 1.01). Specifically in this review [10], sodium hyaluronate and carboxymethylcellulose (Seprafilm ®) shows lower adhesion scores versus no treatment (0.49; 95% CI 0.53 to 0.45). Expanded polytetrafluoroethylene (Gore-Tex ®) reduces de novo adhesions (OR 0.17; 95% CI 0.03 to 0.94). Oxidized regenerated cellulose (Interceed ®) reduces the incidence of de novo adhesions after laparoscopy (OR 0.50; 95% CI 0.30 to 0.83), but not after laparotomy (OR 0.72; 95% CI

0.42 to 1.25); yet it shows a reduction of re-formed adhesions after laparoscopy (OR 0.38; 95% CI 0.27 to 0.55), and laparotomy (0.17; 95% CI 0.07 to 0.41). However, no difference in adhesion prevention was found between Interceed and Gore-Tex ®) (RR 0.36; 95% CI 0.13 to 1.01). On the contrary, the use of Fibrin sheet ® after myomectomy shows no difference in the incidence of de novo adhesions (OR 1.20; 95% CI 0.42 to 3.41), or in the adhesions score (MD 0.14; 95% CI -0.67 to 0.39). According to our objective, in Table 2 the differences between a broad of safe and effective AA are summarized, giving the reader understructure in the decision-making process facing a high-risk of adhesion formation procedure, as defined in the Preoperative and Perioperative Adhesion Risk Score designed by the Angel group [11]. Adequately counselled high risk patients could obtain not only clinical benefit from the use of an AA, but their previous identification makes the use of an AA economically justifiable, and diminishes the possibility for lawsuits against physicians [12].

TABLE 2
PRACTICAL ISSUES TO CONSIDER BEFORE USE OF ANTIADHESION AGENTS

Type	Product	Active Substance	Reported Effectivity	Clinical Remarks
Film	Interceed ® (Gynecare, Ethicon)	Oxidized regenerated cellulose membrane.	De novo adhesions after laparoscopy (OR 0.50; 95% CI 0.30 to 0.83); Re-formed adhesions after laparoscopy (OR 0.38; 95% CI 0.27 to 0.55), and laparotomy (0.17; 95% CI 0.07 to 0.41).	Meticulous hemostasis is necessary before application. Adheres to the injured site after slight moistening. Resorbable within 4 weeks
Film	Seprafilm ® (Genzyme)	Hyaluronate-carboxymethyl cellulose.	De novo adhesions (0.49; 95% CI 0.53 to 0.45)	Its effect is not impaired by local blood loss. Because of its fragility, the laparoscopic handling could be difficult.
Film	Gore-Tex ® (W.L. Gore and Associates Inc)	Expanded polytetrafluoroethylene	De novo adhesions (OR 0.17; 95% CI 0.03 to 0.94).	Non-absorbable Requires to be sutured with continuous permanent suture.
Gel	SprayShield/Spray Gel ® (Covidien Bio-Surgery)	Synthetic polyethilene glycol.	De novo adhesions (0.49; 95% CI 0.53 to 0.45)	Generates an adherent layer after tissue contact. Spray Gel ®, differs in the use of methylene blue, to visualize its application. Resorbable within 5-7 days
Gel	Hyalobarrier Gel Endo ® (Nordic Group)	Auto-cross linked ester of hyaluronic acid	Abdominal adhesions (OR 0.248, 95% CI 0.098, 0.628). Intrauterine adhesions (OR 0.408, 95% CI 0.217 to 0.766).	Does not induce inflammatory reaction. It is easy to allocate it in the abdominal cavity and abdominal wall Resorbable within 7 days.
Gel	Intercoat/Oxiplex/AP ® (FzioMedObispo.)	Synthetic polyethylene glycol and carboxymethyl cellulose	Pilot studies show no superiority than standard surgery.	A viscoelastic gel To be used in abdominal and in spinal surgery. Resorbable within 5-7 days.
Powder and Gel	4DryField PH ® (PlantTec Medical)	Plant based-polysaccharides	75% - 89% adhesion reduction	Certified for hemostasis and preventing adhesions As powder, can be applied directly to bleeding or oozing surfaces, and forms a coagulum. By adding water or NaCl 0,9 transforms into a gel for adhesion prevention.
Broad-coverage fluid agent	Adept ® (Baxter Healthcare)	Icodextrin 4% solution (1-4 linked glucose polymer)	49% - 55% adhesion reduction	It is filled into the abdominal cavity after the surgery (1000 ml), producing hydroflotation. Could produce labial swelling, which dissipates within a few days. As it is based on corn starch, allergies to maltose, isomaltose and cornstarch based polymers or a glycogen storage disease are a contraindication. Resorbable within 4 days

Safety Issues About Antiadhesion Agents

Prior to use any product, surgeons should be aware of particular handling and application specifications provided by the producer in order to prevent complications, iatrogenic or product's misuse. Below we present the most relevant safety issues of agents frequently used in the gynecological surgery.

Seprafilm ® has not been evaluated in pregnant women; therefore contraception should be used in the first cycle after application. Its combination with other AA has not been tested, as well as the use in the presence of abdominal infection or

malignancy. In bowel surgery, it should not be used around anastomoses, since the rate of anastomotic leakage and leakage related events could be increased. Gynecare Interceed ®, an absorbable adhesion barrier is contraindicated in the presence of abdominal infection; a single layer should be applied, as multiple layers alter its rate of absorption.

The SprayShield Adhesion Barrier System ® should be used within one hour after preparing the blue precursor and not be applied on active bleeding; the gel should not be applied between tissue layers, and surfaces should be irrigated after its application. Cauterization or any electronic energy should not be used during its application.

4DryField ® PH can be applied directly on bleeding or oozing surfaces for hemostasis or as an antiadhesion barrier by adding water or NaCl 0.09%. It has no known contraindications to date. After application, elevation of CRP levels, leukocytosis and fever can occur.

Adept ® should not be used in laparotomic procedures or in patients with allergies to cornstarch, maltose or isomaltose intolerance or a glycogen storage disease. Wound complications, vulvar edema and subcutaneous fluid collection have been reported after laparoscopic leakage of Adept through port incisions. Severe postoperative wound dehiscence and cutaneous fistula formation have been reported when used in presence of abdominopelvic infection.

Research Agenda

New substances and new devices are under investigation, though research studies on adhesion preventing agents are difficult to undertake, but they are essential to have a better understanding of their superiority and impact on clinical outcomes. The alpha linked disaccharide sprayable gel (Adblock Gel ®, Terumo Europe NV) forms a visible opaque hydrogel barrier which is metabolized within 10 days. It has demonstrated its safety after laparoscopic myomectomy in a randomized, controlled, multicentric, first-in-human clinical trial with women of reproductive age wishing to get pregnant. Its effectivity on adhesion prevention still pending [13]. The thermosensitive hydrogel PCEC (Poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone), is a polymer that at body temperature could convert into a hydrogel. Investigations on animals showed its ability to adhere to wounds and to prevent adhesions. It is gradually metabolized within 7-9 days by transformation into a viscous fluid, which is reabsorbed within 12 days [14].

Other products have been used lately in abdominal surgery, like the Synthetic polyethylene glycol and carboxymethyl cellulose gel (Intercoat/Oxiplex/AP ® FzioMedObispo). It has been initially used after spinal surgery with no superiority on clinical outcomes than surgery alone. In a mouse model study, this gel decreased adhesion formation following bowel manipulation or bipolar coagulation of opposing lesions (p <0.0001) [15]. While in a small prospective double-bind, randomized, controlled pilot study in women, there were no statically significant differences between cases (1/26, 4%) and controls (3/26; 14%.) for reducing intrauterine adhesions after hysteroscopic treatment because of retained products of conception [16].

Coseal ® (Baxter Healthcare Corporation) is a polyethylene glycol ester fluid that is long used in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage. First studies have shown its ability to prevent postsurgical adhesions after abdominopelvic surgery [7]. It should not be used in pregnant women, children, inside blood vessels, as a replacement for sutures, staples or other closing devices. The surface used should also not be greater than 16 mm per patient.

Further experiments are aimed to change the peritoneal conditions during laparoscopy while avoiding unfavorable side effects of N_2O, named "Full conditioning" [17]. In this concept, acute inflammation is reduced by using 1) a specific mixture of gases (86% CO_2, 10% N_2O and 4% O_2) to insufflate the peritoneum, 2) cooling and humidification of the peritoneal cavity and 3) using heparinized solution to rinse together with an application of 5 mg of dexamethasone. In a translational randomized, controlled study, of patients with endometriosis (n = 44), the combination of Full conditioning with Hyaluronic acid gel (Hyalobarrier ®) resulted in less area, density and severity of adhesions (p <0.0001), as well as less postoperative pain and faster clinical recovery (p <0.0001) than patients following standard laparoscopy with humidified CO_2. The long term benefits of this combination could be a step forward in adhesions prophylaxis.

CONCLUSION

Postoperative peritoneal adhesions are an issue of major concern for surgeons and patients who suffer its consequences, or do not find a solution after an adhesiolysis. Therefore, patients need to be informed on the risks of adhesions and measures to prevent them. And surgeons should choose the antiadhesion agent most suitable to the underlying disease, type of surgery and extension of surgical trauma. Although none of the available agents or surgical strategies could prevent adhesions at all. More research is needed in this field.

REFERENCES

[1] R. L. DeWilde and G. Trew, "Postoperative abdominal adhesions and their prevention in gynaecological surgery: Expert consensus position," *Gynecological Surgery,* vol. 4, no. 3, pp. 161-168, 2007.

[2] A. Hirschelmann, G. Tchartchian, M. Wallwiener, A. Hackethal and R. L. De Wilde, "A review of the problematic adhesion prophylaxis in gynaecological surgery," *Archives of Gynecology and Obstetrics,* vol. 285, no. 4, pp. 1089-1097, 2012.

[3] M. Wallwiener, P. R. Koninckx, A. Hackethal, H. Brolmann, P. Lundorff, M. Mara, ... and R. L. De Wilde, "A European survey on awareness of post-surgical adhesions among gynaecological surgeons," *Gynecological Surgery,* vol. 11, no. 2, pp. 105-112, 2014.

[4] S. Rimbach, M. Korell, H. R. Tinneberg and R. L. De Wilde, "Adhesions and their prevention in gynecological surgery: Location determination and current consensus based on the results of four workshops," *Obstetrics and Gynecology,* vol. 64, no. 9, pp. 891-899, 2004.

[5] M. P. Diamond, S. D. Wexner, G. S. Dizereg, M. Korell, O. Zmora, H. Van Goor and M. Kamar, "Review article: Adhesion prevention and reduction: Current status and future recommendations of a multinational interdisciplinary consensus conference," *Surgical Innovation,* vol. 17, no. 3, pp. 183-188, 2010.

[6] R. L. De Wilde, H. Brolmann, P. R. Koninckx, P. Lundorff, A. M. Lower, ... and M. Wallwiener, "Prevention of adhesions in gynaecological surgery: The 2012 European field guideline," *Gynecological Surgery,* vol. 9, pp. 365-368, 2012.

[7] R. L. DeWilde and G. Trew, "Postoperative abdominal adhesions and their prevention in gynaecological surgery: Expert consensus position," *Gynecological Surgery,* vol. 4, no. 3, pp. 161-168, 2007.

[8] C. B. Brown, A. A. Luciano, D. Martin, E. Peers and A. Scrimgeour, "Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: A double-blind, randomized, controlled study," *Fertility and Sterility,* vol. 88, no. 5, pp. 1413-1426, 2007.

[9] V. Mais, M. G. Cirronis, M. Peiretti, G. Ferrucci, E. Cossu and G. B. Melis, "Efficacy of auto-crosslinked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy: A systematic review and meta-analysis of randomized controlled trials," *European Journal of Obstetrics & Gynecology and Reproductive Biology,* vol. 160, no. 1, pp. 1-5, 2012.

[10] G. Ahmad, H. O'Flynn, A. Hindocha and A. Watson, "Barrier agents for adhesion prevention after gynaecological surgery," *The Cochrane Library,* 2015.

[11] P. Lundorff, H. Brolmann, P. R. Koninckx, M. Mara, A. Wattiez, M. Wallwiener, ... and R. L. De Wilde, "Predicting formation of adhesions after gynaecological surgery: Development of a risk score," *Archives of Gynecology and Obstetrics,* vol. 292, no. 4, pp. 931-938, 2015.

[12] A. Hirschelmann, C. W. Wallwiener, M. Wallwiener, D. Weyhe, G. Tchartchian, A. Hackethal and R. L. De Wilde, "Is patient education about adhesions a requirement in abdominopelvic surgery?" *Geburtshilfe und Frauenheilkunde,* vol. 72, no. 04, pp. 299-304, 2012.

[13] C. Cezar, M. Korell, G. Tchartchian, N. Ziegler, K. Senshu, A. Herrmann, ... and R. L. De Wilde, "How to avoid risks for patients in minimal-access trials: Avoiding complications in clinical first-in-human studies by example of the ADBEE study," *Best Practice & Research Clinical Obstetrics & Gynaecology,* vol. 35, pp. 84-96, 2016.

[14] X. Gao, X. Deng, X. Wei, H. Shi, F. Wang, T. Ye, ... and C. Gong, "Novel thermosensitive hydrogel for preventing formation of abdominal adhesions," *International Journal of Nanomedicine,* vol. 8, pp. 2453-2463, 2013.

[15] R. Schonman, R. Corona, A. Bastidas, C. De Cicco, K. Mailova and P. R. Koninckx, "Intercoat gel (oxiplex): Efficacy, safety, and tissue response in a laparoscopic mouse model," *Journal of Minimally Invasive Gynecology,* vol. 16, no. 2, pp. 188-194, 2009.

[16] N. Fuchs, N. Smorgick, I. B. Ami, Z. Vaknin, Y. Tovbin, R. Halperin and M. Pansky, "Intercoat (Oxiplex/AP gel) for preventing intrauterine adhesions after operative hysteroscopy for suspected retained products of conception: Double-blind, prospective, randomized pilot study," *Journal of Minimally Invasive Gynecology,* vol. 21, no. 1, pp. 126-130, 2014.

[17] P. R. Koninckx, V. Gomel, A. Ussia and L. Adamyan, "Role of the peritoneal cavity in the prevention of postoperative adhesions, pain, and fatigue," *Fertility and Sterility,* vol. 106, no. 5, pp. 998-1010, 2016.

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