

Comparison of the efficacy of seprafilm, interceed, adept, preclude membrane and spraygel in a rat model

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Abstract

Objective. To compare the efficacy of five adhesions barrier products with a control group in a rat model.

Methods. In this randomized controlled animal study, standardized lesions on parietal peritoneum of rats were created by sandpaper and three interrupted sutures. Afterwards, the lesions were treated with Seprafilm, Interceed, Preclude membrane, Adept, SprayGel or no barrier. The resulting adhesions were examined 21 days postoperatively. Adhesion quantity was assessed using a fully quantitative score calculated as the summated width of individual adhesions divided by the width of the traumatized area. **Results.** Compared to the control group, only SprayGel revealed a statistically significant reduction in adhesion quantity. There were also no statistically significant differences between groups. **Conclusion.** The promising efficacy of SprayGel (95% decrease in adhesion quantity) warrants the further evaluation of this product in larger human trials.

Keywords: adhesion, barrier, prophylaxis, rat

Introduction

Adhesions following abdominopelvic surgical interventions are well-known causes of increased morbidity (pelvic pain, infertility, intestinal obstruction etc.) and mortality at early and late postoperative period^(1,2). In addition, the total cost of adhesion dependent medical situations occupies considerable fractions in countries' health budgets⁽³⁾.

In 1989 Food and Drug Administration (FDA) approved the usage of adhesion preventing devices in gynecologic surgeries. Since that time, with the developments in technology, an increasing number of adhesion prevention products for complementing optimal surgical techniques are becoming available in the market⁽⁴⁾. Nevertheless, adhesion formation still remains the leading cause of failed surgical therapy in the peritoneal cavity⁽⁵⁾.

Seprafilm® (Genzyme BV, Naarden, Netherlands), a solid adhesion barrier based on hyaluronic acid and carboxymethylcellulose⁽⁶⁾; Adept® (ML Laboratories, Leicester, United Kingdom), an isotonic solution of 5% icodextrin⁽⁷⁾; Interceed® (Gynecare, Somerville, NJ), a sheet of oxidized regenerated cellulose⁽⁸⁾; SprayGel® (Confluent Surgical Waltham, MA), two sprayable polyethylene glycol solutions that form a gel when coming into contact⁽⁹⁾; Preclude® membrane (WF Gore, Flagstaff, AZ), expanded polytetrafluoroethylene⁽¹⁰⁾ are some of the examples of adhesion barriers. We performed this study to compare the efficiency of these agents with in adhesion prophylaxis on an experimental animal model.

Methods

The protocol of this randomized controlled animal study was approved by the Ethics Committee of Ege University.

Wistar rats with a weight range of 230 to 270 g were housed under laboratory conditions (temperature 21°C±2°C, humidity 55%±10%, 12:12h light-dark cycle). All operations were performed by the same surgeon. The animals were anesthetized with ketamine (100 mg/kg) and xylazine (5 mg/kg) according to standard protocols. After ventral incision over a length of 5 cm, a 3 x 0.5 cm area on the surface of the right side of the parietal peritoneum was abraded for one minute using sandpaper, which was previously described by Whang et al⁽¹¹⁾. Then three interrupted sutures (3-0 Vicryl; Ethicon) were placed over the traumatized area by 1 cm intervals in order to increase the severity of tissue damage. According to the approval of Ethics Committee; 42 Wistar rats were included in our study. There were five study groups (Seprafilm, Adept, Interceed, SprayGel, Preclude Membrane) and a control group. Each group consisted of 7 Wistar rats. Seprafilm and Interceed were applied direct over the traumatized area as 4x2 cm patches. A 4x2 cm patch of Preclude Membrane was also applied over the traumatized area by teeing separate sutures (5-0 Prolene; Ethicon) on each corner. Adept 7.5 mL was instilled intraperitoneally before the last throw of the abdominal closure. The volume of 7.5 mL was chosen on the basis of previous studies, which had indicated optimal results for volumes greater than 20 mL/kg body weight and to account for some postoperative leakage from the laparotomy wound⁽¹²⁾. The two precursor solutions of SprayGel were sprayed directly into the traumatized area using the manufacturer's application kit, which was also applied in a previous study by Rajab et al.⁽¹³⁾ (Figure 1). Upon contact, they formed a viscous gel of approximately 2 mm thickness, completely covering the traumatized area. Finally, no treatment was applied to the rats on control group.

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Following adhesion prophylaxis the midline incision was closed in two separate layers with absorbable sutures (3-0 Vicryl Rapide, Ethicon). Postoperatively, the animals received analgesia with subcutaneous buprenorphine (0.05 mg/kg) and were observed daily in the laboratory of animal facility. At the 21st day of the operation, animals were scarified using CO₂. Adhesion quantity was assessed using a fully quantitative score calculated as the summated width of individual adhesions divided by the width of the traumatized area⁽¹⁴⁾. In both cases, the assessor was blinded to the nature of the adhesion barrier used.

Test groups' data were compared statistically with those of control using a Kruskal-Wallis test, and also the differences between groups were evaluated by Mann-Whitney U test. A p value <0.005 was considered statistically significant.

Results

All animals survived until postoperative day 21 (necropsy day). On re-laparotomy, ground glassy appearance of peritoneum was detected in all subjects. There were no residues of materials in animals treated with Seprafilm, Interceed, SprayGel and Adept. As expected, any amount of Preclude membrane were absorbed (Figure 2).

All of the rats in Adept and control groups had adhesions. On the other hand, the number of adhesion-free rats in SprayGel and Seprafilm groups was 5 and 3, respectively. Only one rat in both Interceed and Gore-Tex groups did not have any adhesions.

Table 1 shows adhesion quantity for adhesion barriers. 54% of traumatized area was covered with adhesions in



Figure 1. Implementation of SprayGel using manufacturer's application kit



Figure 2. View of Preclude membrane and adhesions on re-laparotomy

Table 1 Adhesion quantity

Treatment group (N=42)	Fraction of the traumatised area covered by adhesions (Mean \pm Standard deviation)	Median (Min-Max)
Control (N=7)	0.54 \pm 0.33	0.45 (0.22 – 0.92)
Seprafilm (N=7)	0.11 \pm 0.11	0.12 (0.00 – 0.30)
Interceed (N=7)	0.23 \pm 0.12	0.22 (0.00 – 0.38)
Gore – Tex (N=7)	0.21 \pm 0.10	0.22 (0.00 – 0.30)
Adept (N=7)	0.55 \pm 0.09	0.60 (0.44 – 0.66)
SprayGel *** (N=7)	0.03 \pm 0.05	0.00 (0.00 – 0.12)

***statistically significant versus control ($p < 0.005$), (Kruskal - Wallis test)

control group; whereas 11% in Seprafilm, 23% in Interceed, 21% in Gore-Tex, 55% in Adept and 3% in SprayGel. Compared with control group, only SprayGel revealed a statistically significant reduction in adhesion quantity. Also there was no significant difference between study groups.

Discussion

Peritoneal adhesions are a worldwide problem and may develop following any type of pelvic or abdominal surgery. They may involve female reproductive organs, leading to infertility, deep dyspareunia, bowel obstruction and chronic pelvic pains⁽¹⁵⁾.

Seprafilm, a solid sheet of biodegradable carboxymethylcellulose and hyaluronic acid, is one of the most studied and used adhesion prevention therapies. Randomized, controlled, human trials comprising greater than 5,000 total patients show that Seprafilm has some efficacy in reducing the incidence, severity, extent, and/or area of abdominal adhesions. On the other side, there are also data indicating that Seprafilm had no efficacy in adhesion, prevention versus controls⁽¹⁶⁾. It was also reported that Interceed, a sheet of oxidized regenerated cellulose that typically biodegrades in 1 to 2 weeks, reduced the incidence, extent and severity of postoperative pelvic adhesions but did not completely prevent them⁽¹⁷⁾. However, this reduction did not reach statistical significance when compared to untreated individuals in human studies⁽¹⁸⁾. In our study, compared to the control group, Seprafilm and Interceed revealed an 80% and a 60% decrease in adhesion quantity, respectively. To us, although not significant, this is an important finding to support using Seprafilm or Interceed as an adhesion barrier.

Beneath this mostly investigated adhesion barriers, some new products were introduced to the market. Gore-Tex surgical membrane, constructed of expanded polytetrafluoroethylene (Preclude®, WL Gore), is a nonabsorbable barrier, and produced in thin sheets (0.1 mm), with an average pore size of less than 1 μ m. It is sutured to the tissue so that it overlaps the incision by at least 1 cm. In a randomized trial, ePTFE decreased postmyomectomy and pelvic sidewall adhesions^(19,20). In our study, like In-

terceed, we found a 60% decrease in adhesion quantity with Gore-Tex. Beneath this similar benefit comparing to other barriers, this product has a big handling limitation. Non-dissolvableness results in the necessity of the removal with a second surgical intervention. This situation puts the patient at risk for more adhesions or complications of surgery.

Adept (4% icodextrin solution) is a non-viscous, iso-osmotic, clear solution that has been proven safe and effective as an anti-adhesion device in preclinical and preliminary clinical studies^(6,21). In the United States, Adept is only approved for laparoscopic gynecological surgery⁽²²⁾. In a multicentral comparative, randomised study about Adept in gynecologic laparoscopy, no difference were manifested in the scoring of post-operative adhesion severity and extent⁽²³⁾. Nevertheless another prospective, randomized investigation about postlaparotomic adhesive small bowel obstruction revealed that Adept did not assure any statistically significant difference in the adhesion severity score and in the need of surgery for adhesive small bowel obstruction⁽²⁴⁾. We also did not find any difference in the adhesion quantity with Adept. The main reason of this unpromising result could be the incompatibility of icodextrin solution for laparotomic procedures.

SprayGel consists of two synthetic liquid (sprayable polyethylene glycol) precursors that, when mix together, rapidly cross-link to form a solid, biocompatible hydrogel *in situ*⁽²⁵⁾. It was shown to reduce the incidence of adhesions by 64.7% in a second-look laparoscopy for gynecologic conditions⁽²⁶⁾. Besides this, it was also reported that there were no controlled trials support use in humans⁽²⁷⁾.

Conclusion

In this animal study, we found that SprayGel usage made a statistically significant reduction in peritoneal adhesion quantity compared with adhesion affliction in the control group.

Trials about postoperative adhesion prophylaxis are frequently supervised to the literature. Vast majority are about the benefit of a single product, whereas direct comparisons between these

agents are lacking. We performed this animal study to evaluate and to compare the efficacy of Seprafilm, Interceed, Adept, Preclude Membrane and SprayGel in adhesion prophylaxis. According to the approval of the Ethics Committee of our university, we could only include 7 rats in each group. We determined a significant adhesion reduction only with the usage of SprayGel. There was also no difference between groups in terms of the decrease in adhesion quantity. Despite the little number of included subjects of the study, the promising efficacy of SprayGel (95% decrease in adhesion quantity) warrant the further evaluation of this product in larger human trials. ■

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