The Effects of Hydrophilic Polyethylene Glycol-Based Adhesion Barrier Use to Prevent Intra-abdominal Adhesions in Intra-abdominal Sepsis Model

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Abstract Postoperative adhesion formation is still an important cause of morbidity and mortality. Hydrophilic polyethylene glycol-based adhesion barrier (SprayGel™, Confluent Surgical, Inc., Waltham, MA) is reported to prevent adhesion formation after gynecologic surgery. This study aims to determine the effectiveness of SprayGel™ on adhesion formation after laparotomy in an experimental septic peritonitis model. Wistar albino male rats with weights of 250–350 g were used in this study. Forty rats were grouped into four groups: group I (control), laparotomy and sham operation; group II, laparotomy and cecal ligation puncture (CLP); group III (SprayGel™), laparotomy, sham operation, and SprayGel™; group IV (CLP + SprayGel™), laparotomy, CLP, and SprayGel™. Intra-abdominal sepsis was achieved by perforating the cecum with a 26-gauge needle in selected groups. All animals were sacrificed after 10 days. The results were evaluated according to the score systems of Nair and Knightly. Kruskal–Wallis variance analysis was used for statistical analysis. There were significant differences for the development of adhesion between groups II (CLP) and III–IV (SprayGel™ – CLP + SprayGel™) ($p < 0.02$). Mortality and wound infection rates were significantly lower in the SprayGel™ treatment groups compared to control groups. Intraperitoneal administration of SprayGel™ significantly decreased the intraperitoneal

adhesion formation, and it reduced mortality and wound infection as well.

Keywords Peritoneal adhesions · Intra-abdominal sepsis · Hydrophilic polyethylene glycol (HPG) · Bioabsorbable barrier · SprayGel™

Introduction

Postoperative adhesion formation is a well-known complication of surgery [1]. It is seen in more than 90 % of patients undergoing laparotomy for various reasons [2–5]. Ischemia at suture sites, infection, presence of a foreign body, and mechanical trauma from retractors and tissue handling are the major underlying etiologic factors [6, 7].

The treatment of adhesion-related complications increases health care costs and reduces life quality of the patients because of the repeated hospitalization and afflictions from conservative treatment or adhesiolysis. For example, the economic impact in the USA in 1994 was significant with a direct cost of \$1.33 billion for all hospitalizations during which adhesiolysis was performed [8].

Careful surgical technique, minimal tissue trauma, and good hemostasis, known as the principles of Halsted, have an important role in the prevention of postoperative adhesions [9]. However, taking all these measures could not completely prevent the formation of adhesions. Unfortunately, no single method, which is universally accepted for the prevention of adhesions, could be determined until now, despite many experimental and clinical studies.

There is growing literature to support the use of hydrophilic polyethylene glycol (HPG)-based agents to reduce

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postoperative adhesion formation in several animal models and clinical settings especially in gynecologic surgeries [10–15]. Intra-abdominal infection is a potent stimulus of peritoneal inflammation, which leads to severe adhesion formation. The present study aimed to assess the efficacy of HPG-based agent, SprayGel™, in an intra-abdominal sepsis model.

Materials and Methods

In this study, we needed 40 rats that could stay alive during the experiment. For that purpose, 53 male Wistar albino rats with a median weight of 280 g (range, 250–350) were used. The animal protocol was approved by the Ankara University Ethical Committee. All animals had free access to food and water ad libitum and were handled in accordance with the guidelines for the care and use of laboratory animals. The ready-to-use kit containing HPG was supplied by Optimus Medical, İstanbul, Turkey.

Operative Procedure

First Operation Rats were anesthetized with a cocktail of ketamine (Ketalar®, Parke-Davis, Eczacıbaşı) (80 mg/kg) and xylazine (Rompun®, Bayer) (8 mg/kg) given intraperitoneally. The abdominal area was shaved and prepared for aseptic surgery. A midline laparotomy was performed with a small (3–3.5 cm) incision. Forty rats were divided into four groups: group I (control) undergoing laparotomy and sham operation; group II (CLP) undergoing laparotomy and CLP; group III (SprayGel™) undergoing laparotomy, sham operation, and SprayGel™; and group IV (CLP+SprayGel™) undergoing laparotomy, CLP, and SprayGel™ (Fig. 1). Sham animals underwent manipulation of the cecum and division of the vascular plane between the cecum and terminal ileum. In the infectious groups, sepsis was induced by cecal ligation and multiple puncture (CLP), as described

Fig. 1 Application of SprayGel™ to the intra-abdominal area after CLP

elsewhere [16]. Briefly, the cecum was exteriorized and then filled with feces by milking stool backward from the ascending colon. A ligature was placed around the cecum below the ileocecal valve, maintaining the bowel continuity with 3-0 silk suture. The cecum was then punctured at multiple locations with a 26-gauge needle. The cecum was gently squeezed to extrude feces and to ensure that the puncture holes did not close. The entire abdominal cavity was contaminated with this fecal inoculum. In the SprayGel™ groups, SprayGel™ was applied to the cecum and sidewall surfaces. The abdominal incisions were then closed with 4-0 nylon sutures.

Second Operation Ten days after the first operation, rats were again anesthetized by ketamine and xylazine. The abdomen was reopened, and the peritoneal cavity was examined. Adhesions, mortalities, and wound infections were evaluated. Rats were sacrificed with aortic dissection.

Adhesion Evaluation

A blinded observer evaluated formation of adhesions between the sidewall and cecum by using the following two adhesion scoring systems. Score A was graded according to Nair et al. [17]: grade 0 = no adhesions; grade 1 = between viscera or between visceral viscus and abdominal wall (one band); grade 2 = between viscera or between visceral viscus and abdominal wall (two bands); grade 3 = between viscera or between visceral viscus and abdominal wall (more than two bands) or multiple intestinal adhesions without adhesion to the abdominal wall; and grade 4 = adhesion of the viscera directly to the abdominal wall (number of bands or size not important). Score B was graded according to Knightly et al. [18]: grade 0 = no adhesions; grade 1 = a single, thin, easily separable adhesion; grade 2 = less extensive but weak adhesions that stood traction poorly; grade 3 = numerous extensive visceral adhesions that involved the parietal extensions; grade 4 = numerous extensive dense adhesions that involved the adjacent mesentery, intestine, and omentum, extending to the abdominal wall.

Statistical Analysis

Kruskal–Wallis variance analysis was used for the comparison of adhesion scores between groups. Sidak-corrected Mann–Whitney *U* test was used for the pairwise comparisons among groups. A value of $p < 0.02$ was considered to be statistically significant. In addition, rates of mortality and wound infection were recorded.

Results

Adhesion scores according to both Nair et al. and Knightly et al. are shown in Table 1. Significantly more dense adhesions were found in group II (CLP) compared to groups III (SprayGel™) and IV (CLP + SprayGel™) according to both Nair and Knightly adhesion scales (Table 2). The use of SprayGel™ reduced the adhesion scores in the infectious group (Fig. 2). Both scoring systems revealed similar results in each group and showed a good correlation.

The effects of adhesion barriers on mortality and wound infection are shown in Table 3. Some of the animals died due to sepsis within the first fifth postoperative day. A large number of deaths occurred in the infectious groups [6 of 16 in the CLP group (II), 4 of 14 in the CLP + SprayGel™ group (IV)], whereas there was only one mortality in the SprayGel™ group (III) and two in the sham group (I). However, statistical analysis could not be applied because the expected frequency for the cells was less than five.

Wound infection has been found in only three rats (out of 40) that could survive the period of experiment. There were two rats in the CLP group (II) and one in the CLP + SprayGel™ group (IV). Statistical analysis could not be applied in this section either seeing as the expected frequency for the cells was less than five.

Discussion

Postoperative adhesions are the underlying etiology in 40 % of all cases of intestinal obstruction, which involve the small bowel in approximately 60–70 % of the cases [19, 20]. Adhesions involving the ovaries or fallopian tubes are also responsible for 15–20 % of female infertility [10]. Other adhesion-related complications include chronic pelvic pain, ureteral obstruction, and voiding dysfunction. Intraperitoneal adhesions can also limit

Table 1 Adhesion scores according to Nair and Knightly

	Group I (sham)	Group II (CLP)	Group III (SprayGel™)	Group IV (CLP + SprayGel™)
Nair 0	4	1	7	5
Knightly 0	4	1	7	5
Nair 1	2	2	3	4
Knightly 1	2	2	3	3
Nair 2	3	4	0	1
Knightly 2	3	3	0	2
Nair 3	1	2	0	0
Knightly 3	1	3	0	0
Nair 4	0	1	0	0
Knightly 4	0	1	0	0

Table 2 Adhesion scores and comparison of groups according to both Nair and Knightly adhesion scoring systems

Groups	Nair		Knightly	
	Mean ± SD	Med (min; max)	Mean ± SD	Med (min; max)
1	1.10±1.10	1.00 (0.0; 3.0)	1.10±1.10	1.00 (0.0; 3.0)
2	2.00±1.15	2.00 (0.0; 4.0)	2.10±1.19	2.00 (0.0; 4.0)
3	0.30±0.48	0.00 (0.0; 1.0)	0.30±0.48	0.00 (0.0; 1.0)
4	0.60±0.69	0.50 (0.0; 2.0)	0.70±0.82	0.50 (0.0; 2.0)
<i>p</i> values				
1–2	0.123	0.089		
1–3	0.123	0.123		
1–4	0.353	0.481		
2–3	0.001	0.001		
2–4	0.007	0.011		
3–4	0.393	0.353		

SD standard deviation, *min* minimum, *max* maximum, *med* median)

the effectiveness of intraperitoneal therapeutic agents used in cancer treatment [21].

Inadvertent enterotomy is a frightening complication of adhesiotomy during abdominal reoperation. Krabben et al. reported inadvertent enterotomy in 19 % of 270 reoperations for adhesiotomy. These patients had significantly more postoperative complications and underwent urgent relaparotomies. They reported a higher rate of admission to the intensive care unit, more parenteral nutrition usage, and a longer postoperative hospital stay [22]. Preventing the postoperative adhesion is important for all these complications.

In this study, we found that HPG reduces adhesion formation significantly in a rat CLP model. Use of physical barriers between tissues has long been proposed as a method to prevent postoperative adhesion formation. Wiseman defined the general characteristics of adhesion barrier as follows: it should not interfere with wound healing, not evoke fibrosis, and not promote or potentiate infection, and it should remain effective in the presence of blood, be easy to use in endoscopic procedures, and be absorbable [23].

Fig. 2 Appearance of treatment site without any adhesion

Table 3 Mortality and wound infection rates in groups

Groups	I (control)	II (CLP)	III (SprayGel™)	IV (CLP + SprayGel™)
Mortality	2 (16.7 %)	6 (37.5 %)	1 (9.1 %)	4 (28.6 %)
Wound infection	0	2 (20 %)	0	1 (10 %)

Most barriers developed up to date are liquids, gels, or rigid coats. Liquid solutions easily coat the abdominal and pelvic organs but are often cleared from the site of application before the necessary time of therapeutic efficacy. Gels such as ferric hyaluronate hydrogels coat organs with viscosity. These are slowly cleared solutions, but their adherence to injured tissue is not hard. Film layers such as those made from hyaluronic acid and oxidized regenerated cellulose have a more durable local presence only if they could remain at the site of application without migration. In addition, it may not be easy to use these films in endoscopic procedures. Thus, most presently available adhesion barriers are inadequate for one or more of the characteristics defined by Wiseman [11].

In contrast, the SprayGel™ adhesion barrier possesses most of the key characteristics required for an ideal adhesion barrier. The SprayGel™ adhesion barrier system consists of two synthetic modified polyethylene glycol (PEG) solutions that polymerize rapidly when mixed at the site of application to form an absorbable biocompatible hydrogel. One of the precursor solutions also contains methylene blue, to assist visualization of the SprayGel™ deposition. PEG is a poor substrate for bacteria because of its nonbiological structure. Thus, along with the rapid barrier absorption rate, the barrier material does not lend itself readily to the promotion or potentiation of bacterial infection. The synthetic chemistry has been optimized to react rapidly on the tissue to allow for easy deposition and visualization. Because the material transforms from a liquid to a solid hydrogel, it can tenaciously adhere to wet tissues and protect these tissues through the critical repair period. The SprayGel™ barrier is formulated to remain adherent to the site of application for approximately 5–7 days. From the time of application to the time of absorption, the hydrogel remains adherent to the surface applied. After several days, the adhesion barrier is hydrolyzed into water-soluble PEG molecules, absorbed into the circulatory system, and cleared by renal excretion. The hydrogel barrier itself is more than 90 % water at application. Because of this high water content, the adhesion barrier presents a highly lubricious and biocompatible interface with the surrounding tissue [10, 11, 24].

Intraperitoneal application of SprayGel™ is a simple process and takes only 1–2 min. Material coverage and thickness is simple to calibrate because of the methylene blue added to the hydrogel. Thus, a hydrogel thickness of 1–2 mm could be easily achieved. In the literature, many studies using various models of SprayGel™ have shown that it reduces adhesion formation significantly.

In our study, sepsis was induced by cecal ligation and multiple punctures (CLP) as described elsewhere. We evaluated the adhesions on the tenth postoperative day, which is enough for the development of adhesions according to the literature.

There was a good correlation between the two scoring systems. There was significant difference between the septic group (II) and septic group using SprayGel™ (IV), according to both Nair and Knightly. Although no statistical assessment could be done, positive effects on the mortality and wound infection were observed.

The reducing effect of SprayGel™ on the intra-abdominal adhesions may be explained by its protection effect from surgical trauma on the peritoneal surfaces. Another effect of SprayGel™ is the ability to accelerate tissue healing without causing a very fast formation of connective tissue on the tissues. The fact that maintains its effect throughout the critical healing period makes this mechanism possible. As explained earlier, PEG is a weak source of foodstuff for the bacteria because of its nonbiological structure. SprayGel™ does not potentialize and increase infections. PEG, which is bound to the proteins of many therapeutic agents, makes it possible to clear the carrier proteins from the blood. This ensures a longer therapeutic effect and longer dose intervals as well as reduces the toxicity. Because 90 % of the SprayGel™ contains water, it reduces the tissue reaction, which is observed with other dense materials to a great extent. During application, it does not cause an increase in the temperature. Besides its success in reducing adhesion scores, it has positive effects on wound infections and mortality.

In conclusion, it is important to prevent the development of intra-abdominal adhesions considering its morbidity and mortality. We suggest that it would be useful to conduct an experiment with an HPG-based adhesion barrier agent on pigs besides rat and rabbit models so as to have a better idea about its effect on humans because of pigs' larger and heavier organs. The studies in the literature are predominantly related to the application of this agent after gynecologic surgery. In this study, we found that SprayGel™ solution, which is applied in a rat CLP model, reduced adhesion formation significantly.

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