Adhesion Prevention in General Surgery: A Next-Generation PEG Based Adhesion Barrier

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Abstract

Study Objective. Evaluation of SprayShield™ Adhesion Barrier System efficacy in the rat cecum and porcine abdominal sidewall adhesion model.


Setting. Independent research facility, University research facility

Patients. Rats and virgin female pigs.

Interventions. Rat Model: Following cecum and sidewall injury animals are randomized to either SprayShield™ Adhesion Barrier application or control (10 per group). Adhesion evaluation at 14 days. Porcine Model: Following open bilateral pericolic gutter sidewall and uterine horn injuries, midline incisions were closed and animals randomized to either control, or to laparoscopic SprayShield™ adhesion barrier or SprayGel™ application. Adhesion evaluation at 10-14 days.

Measurements and Main Results. Rat Model: Adhesion incidence: Control = 80%, SprayShield™ adhesion barrier = 10% (p = 0.0017). Adhesion extent: Control = 2.0 + 0.4, SprayShield™ adhesion barrier = 0.1 + 0.1 (p < 0.008), Adhesion severity: Control = 1.6 + 0.27, SprayShield™ adhesion barrier = 0.1 + 0.1 (p < 0.008). Porcine Model: SprayShield™ adhesion barrier reduced adhesion area to injured sidewalls 83% relative to control (p < 0.014), and 64% relative to SprayGel™. In addition, SprayShield™ adhesion barrier reduced adhesion incidence by 50%, and adhesion severity by 26%, relative to Control.

Conclusion. While both hydrogel products performed better than controls, the SprayShield™ Adhesion Barrier System, as a next-generation, sprayable, adhesion prevention product, appears to have distinct advantages over SprayGel™ adhesion barrier.

There is little question that adhesion formation remains one of the most common and costly of complications following surgery. A recent “call for action” was issued regarding the prevention of adhesions, stating they are now the most frequent complication of abdominopelvic surgery, and that surgeons should make the prevention of adhesions more of a priority (Parker et al., 2007).

Of patients undergoing lower abdominal surgery in Scotland in 1986, 32.6% of patients were readmitted a mean of 2.2 times in the subsequent ten years for a potential adhesion-related problem, while 7.3% of readmissions were directly related to adhesion formation (Parker et al., 2001).

Other researchers found that within two years of intestinal surgery 17 percent of patients had obstructions, while 3.1 percent required adhesiolysis surgery. Similarly, within two years of rectum, rectosigmoid, and perirectal tissue surgery, 15.3 percent of patients had obstructions, while 5.1 percent required adhesiolysis surgeries (Beck et al., 1999).

Re-operations in patients with previous abdominal surgery found adhesions 83% of the time. Also, the division of adhesions in these patients increased surgical time an average of 16 minutes, relative to patients with no prior surgery (Beck et al., 2000).

To address this need for easy to use abdominopelvic adhesion prevention, the SprayGel™ Adhesion Barrier was granted CE Mark in 2001 for use in the abdominal or pelvic cavity after laparoscopic or open surgical procedures. SprayGel™ is a polyethylene glycol (PEG) based hydrogel that polymerizes within seconds of spraying on tissue. SprayGel™ contains methylene blue which assists in hydrogel visualization during application. The ability of SprayGel™ to prevent adhesions has been demonstrated in a porcine model of gynecological surgery (Ferland, et al., 2001), and clinically in patients following open and laparoscopic myomectomies (Mettler, et al., 2004).

Recently a next-generation sprayable adhesion barrier, SprayShield™ Adhesion Barrier System, has been developed by the same manufacturer as SprayGel™. SprayShield™ adhesion barrier differs from SprayGel™ in several aspects. Unlike SprayGel™ which is formed via a PEG ester – PEG amine reaction, SprayShield™ adhesion barrier is formed via a PEG ester – trilysine reaction. Trilysine is a low molecular weight synthesis product of L-lysine, a naturally occurring and essential amino acid. Relative to the SprayGel™, the change to trilysine allows for easier preparation, as only one vial requires reconstitution. Also, as the PEG powder vial is reconstituted with the trilysine solution, the final gel formed will typically be better mixed and reacted, and thus more adherent than SprayGel™. As expected, excellent tissue adherence is a critical feature for site-specific adhesion barriers. Another functional difference is a change in the SprayShield™ adhesion barrier ester linkage. While SprayGel™ takes up to 20 days to completely hydrolyze in 37°C PBS, SprayShield™ adhesion barrier is completely hydrolyzed within 7 days. This shorter persistence is more in line with published reports on the optimal persistence of effective adhesion prevention products (Cheong et al., 2001).
50% of traumatized area. Adhesion severity was scored as 0) No adhesions; 1) Mild adhesions, easily dissected; 2) Moderate adhesions, blunt dissection required; and 3) Dense adhesions, sharp dissection required.

Porcine Abdominopelvic Adhesion Study

The objective of this study was to evaluate the adhesion prevention efficacy of laparoscopically applied SprayShield™ adhesion barrier and SprayGel™ adhesion barrier verses Control in a porcine abdominal sidewall injury model. A total of 18 virgin female hogs (33.2–39.4 kg) were evaluated in this model first proposed by Ferland et al (2001). Using aseptic technique, animals received adhesiogenic injuries via laparotomy, followed by subsequent laparoscopic treatment. A single midline abdominal incision was created, animals were placed in Trendelenburg position, and the bladder was aspirated. Dry surgical gauze, towels and retractors were used to facilitate adhesion formation. The parietal peritoneum of the pericolic gutter was then sharply excised to expose an area about 5 cm x 4 cm on the pelvic sidewall. Monopolar electrocautery (Valley lab Force 2, 35 watts coag) was used to score the exposed muscle (Figure 1). Following the injury of one sidewall, the corresponding uterine horn was transected at its midpoint with electrocautery and end-to-end re-anastomosed using two interrupted 3-0 braided polyester sutures. The same injuries were then performed on the contra lateral pericolic gutter and uterine horn, and the cavity was rinsed with several hundred ml saline that was suctioned out. Trocars were then placed, and the laparotomy was closed in layers with continuous braided 0 polyester suture. Following laparotomy closure the abdomen was insufflated to 10 mmHg with CO2, and animals were randomized to receive either SprayShield™ adhesion barrier (n=8), SprayGel™ adhesion barrier (n=7), or good surgical technique (Control, n=3). Animals randomized to SprayShield™ adhesion barrier or SprayGel™ treatment had the hydrogel laparoscopically applied via a 5 mm port to the injured areas of the peritoneal sidewalls and uterine horns using the air assisted applicator (Figure 2). All treated sites were rinsed with saline, and excess saline

MATERIALS AND METHODS

All surgical procedures were conducted in accordance with the regulations and with the approval of the Animal Care and Use Committees.

Rat Cecum Adhesion Study

The objective of this study was to evaluate the SprayShield™ Adhesion Barrier System as compared to surgical control (no treatment) on adhesion development after surgical injury of the cecum and abdominal wall of rats.

Using aseptic techniques, a total of twenty rats received caudal ventral midline incisions, followed by cecum exteriorization. An approximate 2 cm² area of serosa of the lateral side of the cecum was abraded using dry sterile gauze until petechial hemorrhage was observed, and a 2 x 1 cm portion of the corresponding sidewall was abraded with a #10 scalpel blade to the point of muscle disruption. The surgeons were blinded to the treatment assignment until completion of the injury procedures.

Following injury animals were randomized to receive SprayShield™ adhesion barrier on the injured cecum and sidewall, or to remain as controls with no further treatment. All SprayShield™ adhesion barrier and Control animal abdomens were rinsed with 5ml sterile saline, and animals had the muscle layer and skin closed separately using 4-0 PDS suture.

All animals were returned to their cages and monitored daily for general health. Body weights were recorded at pretreatment and at termination at 14 days.

At termination animals were euthanized with CO2 inhalation, the peritoneal cavity was opened, and the viscera examined by a blinded reviewer for adverse changes. Adhesions between the cecum and sidewall were assessed for number, and extent per the following: 0) No adhesions; 1) Adhesions up to 25% of traumatized area; 2) 25-50% of traumatized area; and 3) > 50% of traumatized area. Adhesion severity was scored as 0) No adhesions; 1) Mild adhesions, easily dissected; 2) Moderate adhesions, blunt dissection required; and 3) Dense adhesions, sharp dissection required.

Another difference is the colorant used that allows for visualization during application. SprayShield™ adhesion barrier contains FD&C Blue #1, compared to methylene blue in SprayGel™. While methylene blue is frequently used in gynecological procedures, there are reports of sensitization (Keller, et al. 2007). The objective of the changes was to take a product with proven safety and efficacy, and make it easier to prepare, and even more efficacious with potential superior mechanical bonding to underlying adhesiogenic tissues and a faster absorption rate.

This report details the evaluation of SprayShield™ adhesion barrier in the rat cecum adhesion model, and the comparison of SprayShield™ adhesion barrier and SprayGel™ adhesion prevention efficacy in a clinically relevant porcine model of abdominal surgery.

Figure 1: Sidewall injury in one pericolic gutter via laparotomy. Resection of peritoneum followed by cautery scoring of the underlying muscle.
was suctioned out. Animals randomized to Control had 10 minutes of insufflation followed by rinsing of injured sites with saline, with removal of excess saline.

![Image](image-url)

**Figure 2:** Laparoscopic adhesion barrier application to the injured sidewall site. The blue colorant in the hydrogel assists in visualization during open and laparoscopic procedures.

Following the appropriate treatment the abdomen was deinsufflated, trocars were removed, and trocar sites were sutured closed with 3-0 braided synthetic suture. Animals were recovered, monitored and group housed.

Animals were evaluated for adhesion formation 10-14 days following surgery. Following euthanasia, a reviewer blinded to the randomization scheme performed a laparotomy and identified all adhesion attachment sites to the injured abdominal sidewalls. The injured area was defined as the area inside a 1 cm border around the left and right injured sidewall defects. The dimensions of the adhesion attachment sites were measured, and the adhesion severity at each site was scored as; 0: no adhesion, 1: filmy, generally avascular adhesion, 2: dense, vascular adhesion, and 3: cohesive adhesion with distinct organ planes indistinguishable.

**STATISTICS**

For the rat study, statistical significance between test and control group adhesion incidence was determined using the Chi Square test. Differences in the extent and severity of adhesion formation scores were assessed using the Wilcoxon signed-rank test for nonparametric data.

For the porcine study statistical significance of adhesion area and severity was determined using the Student T-test and the Wilcoxon Two Sample test.

A result of p<0.05 was considered to be statistically significant.

**RESULTS**

**Rat Cecum Adhesion Study**

Surgery proceeded uneventfully; with the exception of two anesthesia deaths (animals were replaced). In animals randomized to SprayShield™ adhesion barrier the average volume of hydrogel applied was 3.3 ml. Following surgery there were no unexpected clinical findings or changes in body weights.

At harvest adhesions were present in 8/10 (80%) of the surgical control animals, with the average extent and severity scores being 2.0 + 0.4 and 1.6 + 0.27, respectively (+ SE). In contrast, only 1/10 (10%) of the SprayShield™ adhesion barrier treated rats had adhesions, with the average extent and severity scores being 0.1 + 0.1 and 0.1 + 0.1, respectively. The one SprayShield™ adhesion barrier animal with an adhesion had a mild adhesion adhered to less than 25% of the cecum. The differences between the SprayShield™ adhesion barrier and control group adhesion incidence (p = 0.0017), adhesion extent (p < 0.008) and adhesion severity (p < 0.008) were all statistically significant (Figure 3). At necropsy no hydrogel was observed in any of the SprayShield™ adhesion barrier treated rats.

**Figure 3:** Percent of control and SprayShield™ adhesion barrier treated rats with adhesions (top), along with average adhesion extent and severity scores (bottom). Differences in adhesion incidence, extent and severity were all statistically significant.
Porcine Abdominopelvic Adhesion Study

Aside from three animals that developed postoperative hernias (1 animal from each group), all animals were found to be healthy throughout the postoperative period. Hernias were found to be due to inadequate fascia closure at the time of the initial surgery.

In the control animals, 100% (6/6) of the injured sidewalls had adhesions, while SprayShield™ adhesion barrier and SprayGel™ had 8/16 (50%) and 5/14 (36%) of sidewalls with adhesions, respectively.

Regarding adhesion area, the average adhesion area for the control group was 11.0 ± 0.3 cm² (+ SE). In contrast the average adhesion area for the SprayShield™ adhesion barrier and SprayGel™ groups was 1.9 ± 0.8 and 5.2 ± 2.8 cm² (Figure 4). This represents a decrease in adhesion area of 83% for SprayShield™ adhesion barrier treated animals (p < 0.014), and 53% in SprayGel™ treated animals (p = NS). Compared to SprayGel™ treated sidewalls, the SprayShield™ adhesion barrier treated sidewalls had 64% less adhesion area (p = 0.09). No SprayShield™ adhesion barrier treated animals had residual gel present at harvest, while one animal in the SprayGel™ group had gel present on one sidewall 13 days following surgery.

The average adhesion severity score in control animals was found to be 2.4 ± 0.2, while the average severity score in the SprayShield™ adhesion barrier and SprayGel™ groups was 1.8 ± 0.2 and 1.8 ± 0.4 (p = NS).

DISCUSSION

The rat cecum sidewall study found that SprayShield™ adhesion barrier application significantly reduced adhesion incidence, extent and severity compared to surgical control. As the average SprayShield™ adhesion barrier rat dose was 3.3 ml, and the average rat weight at surgery was 0.36 kg, the SprayShield™ adhesion barrier dose represented 63 times the expected human dose (10 ml in a 70 kg patient). Despite the high dosing relative to man, there were no adverse effects of SprayShield™ adhesion barrier treatment on rat health or weight gain. This observation speaks to the compatibility of the primarily water and PEG SprayShield™ adhesion barrier composition.

Arguably the porcine sidewall model is more clinically relevant than the rat model due to size and scaling issues. In that model SprayShield™ adhesion barrier was shown to reduce adhesion incidence by 50%, and more significantly, adhesion area by 83%, relative to control. Further, SprayShield™ adhesion barrier was found to reduce adhesion area by 64% relative to SprayGel™. This potential improvement in adhesion reduction should be clinically important, as the clinical efficacy of SprayGel™ has been described.

Mettler et al. (2004) evaluated SprayGel™ efficacy and safety in open and laparoscopic myomectomy procedures. Following myomectomies a total of 66 women were randomized to either receive SprayGel™ application, or to remain as controls (good surgical technique only). Adhesion formation was evaluated via a second look laparoscopy between 3 and 16 weeks after surgery. When compared with initial surgery, the mean adhesion tenacity score at second-look laparoscopy was significantly reduced in treatment patients compared with control patients (0.6 vs. 1.7, a 64.7% reduction). Mean adhesion extent score at second-look laparoscopy compared with initial surgery was 4.5 vs. 7.2 cm², mean adhesion incidence score was 0.64 vs. 1.22. The authors concluded that SprayGel™ was safe, well tolerated, and demonstrated efficacy in a population of patients known to be at risk for adhesion formation.

Kruschinski et al. (2006) evaluated the efficacy of SprayGel™ in preventing adhesion reformation during adhesiolysis procedures in patients with adhesion related disorder. Following gasless laparoscopic adhesiolysis, 35 patients received SprayGel™ application, followed by a second-look laparoscopy at Day 7 and, in cases of continued pain, a third-look laparoscopy within 6 months after the initial surgery. The reduction in the adhesion score at Day 7 was 89.8% (90.1% reduction in extent, 89.3% reduction in severity, and 89.9% reduction in grade). Five patients (14.3%) had a third-look laparoscopy within 6 months of the initial surgery, in which four cases of adhesion

![Figure 4: Average adhesion area in injured porcine abdominal sidewalls (top), along with average adhesion severity scores (bottom).](image-url)
reformation were confirmed. However, the scores were reduced compared to the initial surgery, especially in grade (94.2%) and severity (93.2%). The author concluded that SprayGel™ was uniquely effective in improving the success rates of adhesiolysis when combined with gasless laparoscopy and good hemostasis techniques.

Tjandra et al (2008) evaluated whether SprayGel™ application prevented adhesions and facilitated ileostomy closure. A total of 40 patients undergoing closure of loop ileostomy were randomized to have either SprayGel™ application around both limbs of ileostomy for 20 cm (n=19), or to control without adhesion barrier (n=21). Ileostomies were reversed at ten weeks when the extent of peristomal adhesions were scored in blinded manner (each quadrant, range, 1-3: 3 = most severe; total, range, 4-12: 12 = most severe). Compared to the control group, SprayGel™ treated patients had a significant reduction in mean overall adhesion scores (6.11 vs. 9.67; p < 0.0005), in all four-quadrant adhesion scores (p < 0.002), and proportion of patients with dense (scores > 8) adhesions (0.11 vs. 0.71; p < 0.0005). Also, the time taken to mobilize (16.53 vs. 21.67 minutes; p = 0.008) and close ileostomy (35.37 vs. 41.90 minutes; p = 0.008) was significantly reduced. Postoperative complications between the SprayGel™ and control groups were comparable.

As the clinical adhesion prevention efficacy of SprayGel™ adhesion barrier has been demonstrated in laparoscopic and open myomectomies, in adhesiolysis procedures and in ileostomy closures, the additional efficacy of SprayShield™ adhesion barrier, relative to SprayGel™, should result in a safe, easy to use and highly efficacious adhesion prevention product for general surgery.

CONCLUSION

The need for effective, easy to use adhesion prevention strategies in abdominopelvic surgery remains an ongoing clinical need. The SprayShield™ Adhesion Barrier System provides a sprayable, PEG based, adherent and absorbable adhesion barrier that has been shown to significantly reduce adhesions in relevant preclinical models. Relative to SprayGel™, the SprayShield™ Adhesion Barrier enhancements of improved adhesion prevention efficacy, ease of use, FD&C Blue #1 colorant, improved adherence and an absorption rate more in line with the peritoneal healing rates should further extend the safety and efficacy of this hydrogel adhesion prevention platform.

REFERENCES


