

Preliminary study with SprayShield™ Adhesion Barrier System in the prevention of abdominal adhesions

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Abstract

Introduction: Peritoneal adhesions, the fibrotic bands that form between the surfaces in the peritoneal cavity following surgery, still pose a difficult clinical challenge.

Aim: To evaluate the SprayShield™ Adhesion Barrier System (PEG ester amine solution and a buffer solution) in reducing post-operative adhesion formation.

Material and methods: This was a prospective, multi-center, randomized, single blind study. A total of 11 subjects diagnosed with ulcerative colitis (UC) or familial adenomatous polyposis (FAP) were randomized: 8 to the SprayShield™ arm and 3 to the control arm. SprayShield™ was applied on the viscera directly under the midline peritoneal incision and at the site of ileostomy. During the follow-up surgery, the incidence, extent, and severity of post-operative adhesion formation were evaluated, as well as the time required to mobilize the ileal loop.

Results: In patients who received SprayShield™ the time required to mobilize the ileal loop at the ileostomy closure was slightly shorter and the incidence and severity of adhesions were somewhat lower vs. control subjects (NS).

Conclusions: SprayShield™ was found to be easy to use, safe, and quick to apply, and performed well in adherence and conformity. The incidence and severity of adhesions were lower for SprayShield™ subjects vs. control subjects, but due to the limited number of patients there are not enough data to confirm the effectiveness of the SprayShield™ Adhesion Barrier System in prevention of adhesions.

Key words: adhesions, adhesion prevention, laparotomy, ileostomy.

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Introduction

Peritoneal adhesions, the fibrotic bands that form between the surfaces in the peritoneal cavity following surgery, still pose a difficult clinical challenge. They cause significant morbidity and can result in organ dysfunction and chronic pain syndromes. Estimates of the workload for the treatment of adhesion-related disorders have put the annual cost in the USA at around USD \$1.3 billion [1]. Adhesions seem to be also one of the most important reasons for technical problems in laparoscopic surgery [2-4].

The pathophysiology of adhesion formation is believed to revolve around the events that follow the inflammation elicited by acute tissue injury. A number of cellular and molecular events mediating the inflammatory process result in the deposition of fibrin around these areas of tissue trauma. Inadequate subsequent fibrinolysis results in the infiltration of this fibrin network by fibroblasts and the deposition of more permanent connective tissue, leading to adhesion formation [5, 6]. When peritoneal tissue has been traumatized, fibrin deposition is evident within 12 h. New mesothelium begins to develop between 2 and 3 days after the initial injury. Re-epithelialization is normally complete within 7-9 days.

The current approach to adhesion prophylaxis primarily involves creating mechanical barriers that inhibit the deposition of fibrin networks between tissue planes. As described above, these fibrin networks can potentially result in the formation of dense, permanent adhesions between tissues. The barrier approach to adhesion prevention is the application of absorbable or non-absorbable materials that create a temporary mechanical barrier during the critical window (a period of hours to days) of post-inflammatory fibrin deposition [7].

Many strategies have been attempted to prevent the formation of adhesions resulting from intraoperative tissue manipulation and injury, as well as postoperative oozing. An expected ideal anti-adhesion material should be effective in prevention or reduction of adhesion formation, not impair wound and anastomosis healing, be safe for patients, be easy to administer, and be cost-effective. Different agents have been used in both experimental and clinical studies, such as polyvinylpyrrolidone [8], α -lipoic acid [9], methylene blue [10], carboxymethyl cellulose and oral vitamin E [11], melatonin [12], agar films [13], sodium hyaluronate [14], carboxymethyl cellulose [15, 16], N-acetyl-l-cys-

teine [17], bioabsorbable nanofibrous poly(lactide-co-glycolide)-based membranes [18] and many others. However, most of the study results have no practical implications and only a few agents progress to clinical trials. There are still a very limited number of officially registered products in surgical practice to prevent postoperative adhesions. The majority of adhesion barrier products are film based and they do not conform or adhere to the target adhesiogenic areas.

Aim

This study evaluated a sprayable adhesion barrier to determine if its application benefits of being site specific and adhering and conforming to irregular and complex adhesiogenic surfaces would translate into a clinical benefit. The anticipated benefit to the subject after receiving SprayShield during abdominal surgery is a reduction of the incidence, and/or severity, and/or extent of postoperative adhesion formation along the midline incision. This is anticipated to result in a decrease in morbidity, in complications associated with postoperative adhesions, and in the overall risk related to any future abdominal surgery.

Material and methods

A total of 30 subjects were to be randomized using a 2 : 1 treatment to control scheme at up to 10 investigational sites in the European Union. The sample size determination was not based on formal statistical considerations. This post-market study was performed to monitor the safety profile of the product and for data gathering purposes. The results will be analyzed and may be used to support the study design for a pivotal trial. Due to the small sample size and the resulting low statistical power, no formal statistical hypothesis tests will be performed. All data collected in this study will be documented using summary tables and subject data listings. Summary tables will be presented by treatment group (SprayShield and control). Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

This multi-center, randomized, single blind study was performed to collect and evaluate preliminary clinical data on the SprayShield™ Adhesion Barrier System for the reduction of postoperative adhesion formation in comparison to good surgical technique

alone (without any type of adhesion barrier). The primary effectiveness endpoint was the incidence of adhesions, defined as the proportion of subjects presenting at the follow-up surgery (10–12 weeks) with one or more adhesions to the midline incision regardless of extent and/or severity. Secondary effectiveness endpoints included severity of adhesions, extent of adhesion involvement, and loop mobilization time.

SprayShield™ Adhesion Barrier System Description

The SprayShield™ Adhesion Barrier System is CE Mark approved in the European Union. It consists of two solutions, a PEG ester amine solution and a buffer solution (referred to as the “blue” and clear precursors, respectively). The PEG powder is a 10,000 Da PEG succinimidyl succinate (4 arm 10K PEG SS). The PEG molecule has electrophilic end groups activated with esters of N-hydroxysuccinimide (NHS). Trilysine amine is a low molecular weight cross-linker with nucleophilic amine end groups. The PEG ester – trilysine amine reaction is strongly pH dependent.

When sprayed, the PEG ester and trilysine amine start to rapidly cross-link due to the increase in pH as a result of mixing with the borate solution. The result of this reaction is a biocompatible absorbable hydrogel *in situ*. The *in situ* polymerization occurs very rapidly (within seconds) with no heat involved and no external energy source required (i.e., light source). When the sprayed liquids mix on the tissue, they polymerize to form a flexible barrier that is adherent to tissue. The formed hydrogel remains intact for approximately 2 to 7 days. During this period the adhesion barrier undergoes hydrolysis similar to absorbable synthetic sutures where it is absorbed into the circulatory system and is excreted through the kidneys.

Patients

Subjects who were diagnosed with ulcerative colitis or familial polyposis and required multistage surgery for treatment of either of these disorders were eligible. Randomization took place after creation of the diverting loop ileostomy and just prior to closure of the abdominal incision. The randomization envelope was opened to disclose the treatment assignment to either SprayShield™ treatment or control treatment (good surgical technique alone with no adhesion barrier of any kind). The subjects were blinded to their treatment status.

Surgical procedure

Prior to randomization, subjects had to have undergone a restorative proctocolectomy with ileal J-pouch-anal anastomosis with diverting loop ileostomy. Randomization to the SprayShield™ treatment group or control group took place at the end of the operation. In SprayShield™ treated subjects, Spray Shield™ was applied on the viscera directly under the midline peritoneal incision and at the site of ileostomy using an air-assisted sprayer. The blue color of SprayShield™ was helpful in visual control of the correct administration on the surface of the viscera (Photos 1 and 2). Control group subjects received good surgical technique without the use of SprayShield™. Approximately 10–12 weeks after surgery, the subjects underwent follow-up surgery to close the loop ileostomy. During the follow-up surgery the adhesions were observed and scored.

Adhesion analysis

The incidence, extent, and severity of post-operative adhesion formation to the midline incision and throughout the abdomen from the previous surgery were evaluated. To improve the evaluation of the adhesions a balloon trocar was used in some cases. An evaluator who was blinded to the treatment status of the subjects performed the evaluation of the midline incision at both first and follow-up surgery.

There were 3 categories of the evaluation:

- Severity of adhesions was categorized as filmy thickness, avascular; moderate thickness, limited vascularity; and dense thickness, vascularised. The corresponding numeric severity ratings are 1, 2, and 3. Subjects without adhesions were assigned a severity rating of 0.
- Extent of adhesion involvement was defined as the proportion of the total length of the initial midline incision associated with any adhesion at the time of the follow-up surgery, as determined by dividing the length of the incision associated with adhesions (cm) by the overall initial midline incision length (cm).
- Mobilization time was defined as the time (min) required to incise and mobilize the ileal loop in preparation for reanastomosis for ileostomy closure.

Additionally, the incidence and severity of adhesions not involving the midline incision were summarized.

Safety evaluation

Safety was assessed based on documentation and evaluation of adverse events, monitoring of vital

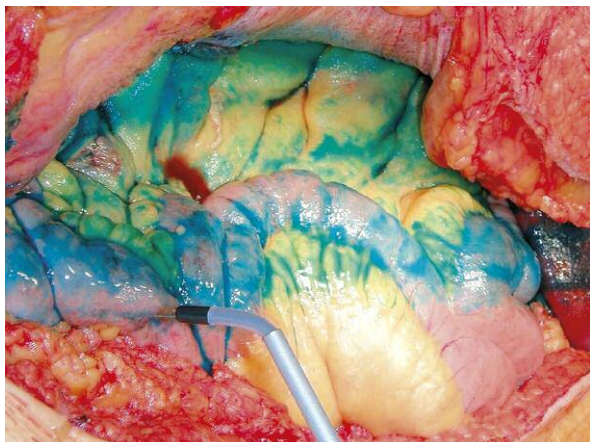


Photo 1. Administration of SprayShield™ on the surface of the viscera



Photo 2. Abdominal cavity after administration of SprayShield™. The blue color was helpful in visual control of the correct administration on the surface of the viscera

signs and physical examinations, and quantitative laboratory tests. Any laboratory evaluations that were determined to be both outside the normal range for the institution involved and clinically significant (based on the investigator's assessment) were documented as adverse events. For each reported adverse event, the investigator was required to determine if there was a relationship between the study treatment and the event. The relationship could be rated as "no relationship," "possible relationship", "definite relationship", or "unknown/impossible to determine."

Results

A total of 30 subjects were initially to be randomized using a 2 : 1 treatment to control scheme. However, the study was terminated early after a total of 11 subjects were randomized intra-operatively at four sites (Figure 1) following confirmation of eligibility due to funding constraints. The sponsor's decision to terminate the study was purely a business decision and is in no way related to the product's safety or efficacy. Eight subjects were randomized to the SprayShield™ treatment arm and three to the control arm according to a computer generated randomization list to achieve a balanced enrollment at each investigational site (Figure 1).

Prevention of adhesions with the SprayShield™ Adhesion Barrier System

The results summarizing the occurrence of midline incision adhesions, adhesions associated with ileostomy, maximum adhesion severity, extent of

adhesion involvement, as well as procedure time and mobilization time of the reversal of the loop ileostomy are shown in Tables I and II.

The results from the small number of subjects enrolled in the study did not show any significant difference between SprayShield™ and control groups.

Of note, the incidence and maximum severity of adhesions involving the midline were somewhat lower for subjects who received SprayShield™ versus control subjects. In the SprayShield™ group adhesions occurred in 37.5% of subjects, while in the control group they occurred in 66.7% of subjects. The mean severity of adhesions was 0.9 in the SprayShield™ group and 1.3 in the control group.

Additionally, the time required to mobilize the ileal loop at the ileostomy closure visit was slightly shorter for subjects who received SprayShield™ compared to control subjects who received good surgical technique alone (41.0 min vs. 43.3 min).

On the other hand, the number of subjects with occurrence of adhesions associated with ileostomy was higher for subjects who received SprayShield™ compared to control subjects (75% vs. 65.7%). The total time for reversal ileostomy in the SprayShield™ group was 100.6 min, which was longer than the reversal ileostomy in the control group (89 min).

Safety and adverse events

In all investigational centers five mild adverse events (leukocytosis, impaired healing, urinary tract infection, surgical skin tear, hepatic enzyme increased)

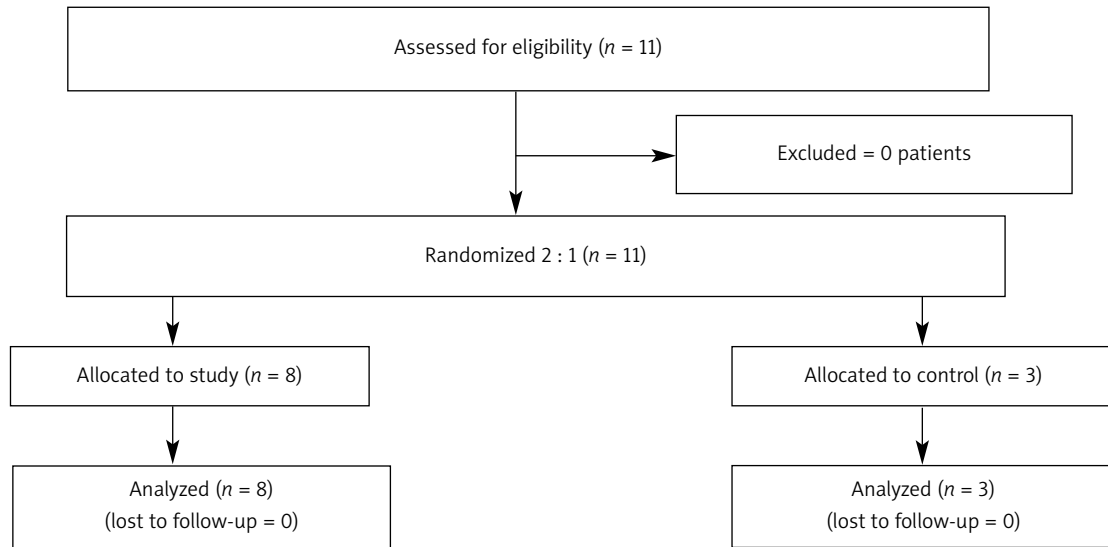


Figure 1. Flowchart representing the course double-blinded randomized study

Table I. Occurrence, description, and severity of midline adhesions in the SprayShield™ and control groups. Table I summarizes the number of subjects from each arm who experienced midline adhesions when evaluated at the ileostomy closure visit 10–12 weeks following surgery. Adhesion severity was rated as either 0, 1, 2, or 3, as previously described. The extent of adhesion involvement was defined as the length of the incision associated with adhesions (cm) divided by the length of the initial midline incision (cm) multiplied by 100

Parameter	Statistic	SprayShield (N = 8)	Control (N = 3)	Value of <i>p</i>
Midline incision adhesions	<i>n</i>	8	3	0.5455
No	<i>n</i> (%)	5 (62.5)	1 (33.3)	
Yes	<i>n</i> (%)	3 (37.5)	2 (66.7)	
Maximum adhesion severity	<i>n</i>	8	3	0.9091
0 – No	<i>n</i> (%)	5 (62.5)	1 (33.3)	
1 – Filmy thickness	<i>n</i> (%)	0 (0.0)	0 (0.0)	
2 – Moderate thickness	<i>n</i> (%)	2 (25.0)	2 (66.7)	
3 – Dense thickness	<i>n</i> (%)	1 (12.5)	0 (0.0)	
Maximum adhesion severity (rating)	<i>n</i>	8	3	0.9091
Mean (SD)		0.9 (1.2)	1.3 (1.2)	
Median		0.0	2.0	
Min, max		0, 3	0, 2	
Extent of adhesion involvement [%]	<i>n</i>	1	2	> 0.9999
Mean (SD)		66.7	76.3 (33.5)	
Median		66.7	76.3	
Min, max		67, 67	53, 100	

Table II. Occurrence, description, and severity of ileostomy associated adhesions in the SprayShield™ and control groups. Table II summarizes the number of subjects from each arm who experienced ileostomy associated adhesions when evaluated at the ileostomy closure visit 10–12 weeks following surgery. Adhesion severity was rated as either 0, 1, 2, or 3, as previously described. The loop ileostomy mobilization time and total loop ileostomy reversal procedure times were both measured in minutes

Parameter	Statistic	SprayShield (N = 8)	Control (N = 3)	Value of p
Adhesions associated with ileostomy	<i>n</i>	8	3	> 0.9999
No	<i>n</i> (%)	2 (25.0)	1 (33.3)	
Yes	<i>n</i> (%)	6 (75.0)	2 (66.7)	
Maximum adhesion severity	<i>n</i>	8	3	0.9091
0 – No	<i>n</i> (%)	2 (25.0)	1 (33.3)	
1 – Filmy thickness	<i>n</i> (%)	2 (25.0)	2 (66.7)	
2 – Moderate thickness	<i>n</i> (%)	4 (50.0)	0 (0.0)	
3 – Dense thickness	<i>n</i> (%)	0 (0.0)	0 (0.0)	
Reversal of the loop ileostomy – procedure time [min]	<i>n</i>	8	3	0.6303
	Mean (SD)	100.6 (26.5)	89.0 (14.9)	
	Median	101.5	95.0	
	Min, max	65, 141	72, 100	
Reversal of the loop ileostomy – mobilization time [min]	<i>n</i>	8	3	0.5879
	Mean (SD)	41.0 (13.7)	43.3 (2.9)	
	Median	40.0	45.0	
	Min, max	23, 60	40, 45	

and two severe adverse events (dehydration, fasciitis) were reported. Overall, 50.0% of subjects within the SprayShield™ treatment group and 33.3% within the control group experienced at least one adverse event. The differences in these rates were not statistically significant. All adverse events were determined to have no relationship to treatment (SprayShield™ or control) by the investigators and the medical monitor. There were no unanticipated adverse device effects and no deaths reported during the study. There was no evidence of any SprayShield™ remaining at the second look laparoscopy in any of the eight SprayShield™ treated subjects.

Discussion

Adhesion evaluation model

On a molecular level, the factors determining cell proliferation, migration, differentiation, angiogenesis, apoptosis and host defense will all have an impact

on adhesion formation. Several cytokines are continuously produced by macrophages and fibroblasts entrapped within the fibrin meshwork, including TNF- α , IL-1, PDGF, EGF and MCP-1, which in turn recruit leukocytes and increase collagen synthesis. As long as these conditions persist, adhesions will proliferate. The decrease or stop of the inflammation is the key to the effective prevention of adhesions. Adhesion reduction agents can be broadly divided into two categories. The first comprises the pharmacological therapies given around the time of the patient's operation, but they can negatively influence the wound and anastomotic healing. The second encompasses topical products applied directly to the adhesionogenic areas caused by tissue trauma during the operation, such as the SprayShield™ Adhesion Barrier System used in this study. The administration of the product increases the operation time, but provides an opportunity to create a barrier between opposing traumatized tissue planes so they have an

opportunity to heal rather than the opposed fibrin deposits developing into collagen and leading to the formation of adhesions.

Studies of the prevention and reduction of adhesions are mostly experimental, and the number of clinical trials is limited. The main reason there are so few studies is because of the requirement for surgical protocols to include a reoperation for adhesion evaluation at a similar time for all subjects. Additionally, there is a lack of objective evaluation methods for adhesion occurrence and severity to choose from.

Presently there is no widely accepted scoring system for adhesion evaluations. There are some different scores for measurement of adhesion severity, such as the Mazuji 0–5 point score, which is based on problems that occur during the dissection and separation [8]; the Moreno 2–7 point score, based on thickness, types and vascularization of adhesions [19]; or Bigatti's 0–11 point scoring system, which is based on tenacity, density and extent of adhesions [20]. However, these scoring systems are based on the subjective impressions of the surgeon, which is of course a limitation of the described systems. Other methods using biochemical analysis, such as tissue hydroxyproline or malondialdehyde levels, are not widely accepted and cannot reliably be used as a standard procedure in the description of the adhesion's severity [9]. In our study a subjective measurement of the adhesions was also used, but to improve the objectiveness of the study the time of the loop mobilization during re-operation was also measured.

To evaluate the effectiveness of adhesion prevention it is necessary to check the abdominal cavity after the primary procedure. The restorative proctocolectomy with ileal pouch-anal anastomosis with diverting loop ileostomy procedure was used because it typically occurs in two stages. This provides an optimal opportunity to evaluate the effectiveness of the SprayShield™ Adhesion Barrier System following major colorectal surgery without putting subjects at any additional risk. We used this model in our study due to the widely accepted indication for re-operation as the reversal of a loop ileostomy after restorative proctocolectomy, which is also described by other authors [21].

To evaluate the extent and severity of abdominal adhesions, observation of the entire abdominal cavity is indicated. In the reversal of a loop ileostomy there is, in most cases, only a very limited range of the peritoneum that can be evaluated due to the small area

within the abdominal cavity. In our study a balloon trocar was used for the abdominal cavity evaluation. The balloon trocar was reported to be helpful for visualization of adhesions in the eight subjects (5 SprayShield™ and 3 control) it was used in.

In the presented study the type of administration, adhesion scoring system and the model of the surgical procedures used to evaluate the adhesions appear to be correct, accepted and useful for investigation of the prevention of adhesions.

Usefulness of the device

For the eight SprayShield™ subjects, all investigators reported that SprayShield™ was easy to use. There were no device malfunctions reported. The median application time for the eight subjects who received SprayShield™ was 8.5 min. The time of application seems to be acceptable and did not prolong the total time of surgery significantly.

The sprayable formulation of SprayShield™ makes the product easy to apply, and more importantly, it can also be used laparoscopically. The stiff and brittle nature of other products, such as HA-CMC (sodium hyaluronate – carboxymethyl cellulose), complicates their use during laparoscopy [14, 15]. In this small open study, SprayShield™ appears to have been more useful in preventing adhesions to the midline incision as opposed to the ileostomy site. The potential reasons for this could be the suture of the peritoneum in the midline, the mechanical trauma caused by the retractors used during the surgery, and the highest stretching forces in the midline after the surgery, leading to microinjury in the regenerative tissue. All these factors can increase the risk of adhesion formation.

Safety of the SprayShield™ Adhesion Barrier System

The overall incidence of adverse events was low, as was anticipated. Only eight adverse events were reported from both treatment groups. No unanticipated adverse device effects or events resulting in death were observed in the study. Four of the adverse events were considered serious but no subject within either group was noted to have a device-related event. These data provide evidence that SprayShield™ may be well tolerated in this patient population. The safety and toleration of adhesion prevention agents are very important for practical

use, and are always an important part of the usefulness evaluation. In some cases there are reports of serious complications correlated with the use of the agents, such as HA-CMC (sodium hyaluronate – carboxymethyl cellulose). Signs of severe inflammation and abscess formation have been reported previously in the literature [23, 24].

Prevention of adhesions by the SprayShield™ Adhesion Barrier System

Many strategies have been attempted to prevent adhesions resulting from intraoperative tissue manipulation and injury, as well as postoperative oozing. Prevention strategies vary from perioperative instillation of colloidal solutions, to both biologic and synthetic barriers, to systemic steroids. Numerous products have been used to help minimize the formation of adhesions. However, none of the barriers has yet achieved sustained success [25, 26].

Anti-adhesion products used in colorectal surgical procedures should possess the ability to prevent or reduce adhesion formation, but not affect normal wound healing or elicit an inflammatory response. The SprayShield™ Adhesion Barrier System possesses these characteristics, and therefore it is considered to be ideally suited for use in patients undergoing laparotomy or laparoscopic abdominopelvic surgery as an adjunct to good surgical technique to reduce the incidence, severity, and extent of post-surgical adhesion formation.

The effectiveness data do not show any statistically significant differences between the SprayShield™ and control groups. These results are not surprising given that the study was not powered to detect statistical significance for the performance endpoints. It is necessary to emphasize that the originally planned study of 30 patients was stopped at 11 patients due to funding constraints, as opposed to safety or lack of clinical effectiveness, which may be inferred if no reason is specified. This post-market study was designed to include only a small number of subjects for data gathering purposes, and contained no formal hypothesis. Data were also collected to monitor the safety profile of the product. The study was not designed to achieve statistical significance.

Conclusions

The results of this study do not present any safety concerns that can be attributed to the use of

SprayShield™ in a clinical setting. SprayShield™ was found to be easy to use and quick to apply, and performed well in adherence and conformity. The very small sample size makes it difficult to detect any real differences between the treatments, if such differences exist. A much larger clinical study that is statistically powered to detect differences of clinical interest is needed to further assess the safety profile and the effectiveness of the SprayShield™ Adhesion Barrier System.

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