An Absorbable Hydrogel Spray Reduces Postoperative Mediastinal Adhesions After Congenital Heart Surgery

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Background. **Adhesions encountered during reoperative cardiac surgery can prolong operative time and increase operative risk. The purpose of this clinical study was to investigate the antiadhesion property of a synthetic bioabsorbable polymer spray after cardiac reoperations in infants.**

Methods. **A prospective randomized double-blinded study was designed. Forty infants requiring staged cardiac operations were randomly allocated to a study group (n = 20) or a control group (n = 20). The appropriate volume of the polymer was sprayed onto the mediastinal surfaces before chest closure after the first surgical procedure in the study group. At reoperation, adhesions were evaluated by a blinded investigator following a 5-grade scoring system. Five predetermined anatomic areas were scored. Incision to extracorporeal circulation time was also analyzed.**

Results. **In all, 40 subjects were enrolled into the study. Four babies died before the second operation. Three others were missed for reevaluation. The control group (n = 16) had longer incision to extracorporeal circulation time (38 ± 10 minutes) than the study group (n = 17; 23 ± 6 minutes; $p < 0.001$). The control subjects had significantly more severe adhesions than the study group at all five mediastinal areas: (1) retrosternal ($p < 0.001$); (2) base of the heart (large vessels [$p < 0.05$]); (3) right side ($p < 0.01$); (4) left side ($p < 0.02$); and (5) diaphragmatic side of the mediastinum ($p < 0.001$).**

Conclusions. **The use of synthetic bioabsorbable polymer sealant spray at the end of primary pediatric cardiac surgery reduces the intensity of mediastinal adhesions and the reentry time in infants undergoing repeat median sternotomy.**

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Surgical trauma to the pericardium and epicardium during open heart operations typically results in the formation of dense fibrovascular adhesions between the epicardium, the sternum, and the surrounding structures [1]. These adhesions may lead to heart constriction, right ventricular dysfunction, and even to coronary bypass graft occlusion [2–4]. During resternotomy, dense adhesions frequently contribute to increased surgical time, and they may lead to serious injury of the heart, lungs, or great vessels [5]. Postoperative surgical bleeding, transfusions, and hospital length of stay may all be increased [1, 2, 6].

There is a clear need for an easy to use, safe, and effective antiadhesive. A variety of strategies ranging from the installation of solutions into the pericardium to the use of biological and synthetic patches to reduce postoperative adhesions have been investigated in both animals and humans [7]. Reports of such techniques either failed to capture surgical attention, lacked clinical relevance, or were cumbersome in application. Several recent animal studies and clinical trials have evaluated a commercially available biocompatible polyethylene glycol polymer with impressive antiadhesive outcomes [8–10]. In Europe, where this synthetic bioabsorbable polymer spray gained early approval for use in patients undergoing cardiac surgery, an observational study was designed around children who were undergoing staged surgical correction for congenital heart defects. Dense and vascular adhesions were largely prevented in seven sites evaluated at reoperation. Eighty-five percent of the observed adhesions were classified as "filmy and avascular" [11].

A retrospective chart review of children at our institution who required staged cardiac surgeries suggested to us that those who had had the biocompatible polyethylene glycol polymer product lightly sprayed onto the heart and mediastinal tissues before sternal closure had at reoperation thin, filmy, and reduced adhesion formation. There was a noticeable contrast to the moderate or dense fibrous adhesions observed among patients who had not received the product (our unpublished data). The results of both the European observational study and our own institutional retrospective chart review prompted the design of this prospective randomized study.

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Material and Methods

This is a single-institution study. Approval was obtained from the Institutional Review Board of Loma Linda University Children's Hospital. Study subjects were identified by diagnosis and by the anticipated need for staged surgery through a median sternotomy. The second sternotomy was anticipated to occur within 2 to 8 months of the initial operation. Subjects were randomly assigned just before their initial surgery to either a study group (polyethylene glycol polymer treatment) or to a control group (no treatment). Otherwise, no other retrosternal product was used.

Surgical Procedure

The surgical procedure was performed as planned by the operating surgeon. For the experimental study group, the product (hydrogel spray) was selected and prepared. The primary surgical procedure was completed. The sternotomy wound was left open and prepared for delayed primary closure. All subjects had intentionally delayed chest closure. Before chest closure, the heart and mediastinum of the study group subjects were sprayed with the hydrogel product. The amount of product used was based on the patient's weight (Table 1). Closures were usually accomplished between the second and fourth postoperative day. Standard sternal wound closure was performed. Control group subjects where closed routinely without use of the product spray.

Sternotomy for the subsequent staged operation was conducted in a routine reoperative manner. An assistant surgeon or a physician assistant who was blinded to the subject's group assignment graded the adhesions at five surgical sites using the predefined scale (Table 2). Only the areas involved in the surgical procedure were evaluated and graded. The time from incision to extracorporeal circulation was recorded to reflect any potential delay imposed by lysis of adhesions. Adverse untoward events such as cardiac or large vessel injury were recorded. The subjects were assessed for complications and wound healing for 30 days after the second-stage operation. Follow-up of the enrolled patients was completed on all but the subjects who died or were lost to follow-up before the second surgery.

Investigational Product

Bioabsorbable polyethylene glycol (PEG) polymer is a commercially available surgical sealant composed of two synthetic PEGs in a dilute hydrogen chloride solution, and a sodium phosphate/sodium carbonate solution (CoSeal Surgical Sealant; Baxter Healthcare, Deerfield, IL). The product components are provided in kits of 2 mL, 4 mL, or 8 mL volume. With mixing, the two PEG solutions polymerize to form a hydrogel that adheres to the surface of tissues.

Based on our initial experience, this product should be sprayed just before sternal closure and after surgical hemostasis so that the product is not diluted or washed away with hemorrhage and irrigation. It was lightly sprayed in a thin homogenous layer in the mediastinum. All the visible surfaces of the heart, the great vessels, the diaphragmatic surface, and the lateral sides of the pericardial space were covered. Application was with a product-specific gas-driven spray device (Air Enhanced Spray Applicator; Baxter Healthcare). Infants received 1 or 2 mL of the product based on the subject's weight (Table 1). Subjects weighing less than 3 kg received 1 mL. Infants weighing 3 to 10 kg received 2 mL.

Table 1. Volume of Product Used Based on Patient Weight

Weight	Volume Sprayed
<3 kg	1 mL
3–10 kg	2 mL
>10 kg	4 mL

Outcome Measures

This was a prospective randomized double-blind study evaluation of adhesions observed at a staged reoperation. Evaluation of adhesions was performed by blinded assistant investigators. The primary outcome measure was the quality and intensity of adhesions at five predefined sites: retrosternal area; base of the heart including the great vessels; right and left lateral surfaces; and diaphragmatic surface of the heart. Adhesions were recorded on a 0 to 4 scale based on predetermined criteria (Table 2). The time from incision to extracorporeal circulation was recorded. Secondary outcomes included postoperative mediastinal bleeding and drainage, hospital length of stay, and the use of blood products.

Statistical Methods

Descriptive statistics are presented as mean and standard deviation for the quantitative variables. Counts and percentage were used for the qualitative variables. An independent Student's t test was used to compare weight at surgery and months to second surgery between the experimental and control groups. We used χ^2 testing to assess the association of sex and ventricle type of the experimental group and control group. When assumptions of χ^2 were not met, we used Fisher's exact test. For data analysis, IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY) was used. Alpha was set at a level of 0.05.

Results

Between December 2011 and July 2015, a total of 40 patients was prospectively randomly allocated to either the control group or the experimental group. The two groups of subjects were comparable in terms of age, sex, diagnoses, and blood utilization (Table 3). Four subjects, 2 in each group, died before the second operation. Deaths were unrelated to the study. Three subjects either had their second operation in another institution or were overlooked for evaluation at the second-stage operation; hence, they were eliminated. The operations were performed by three surgeons. The same surgeon performed both the first and second operations.

Table 2. Grading System Used for Scoring Adhesion Severity

Adhesion Grade	Description
0	No adhesions
1	Filmy, avascular
2	Requiring blunt dissection only
3	Moderate, requiring sharp or electrocautery dissection
4	Severe, requiring extensive sharp electrocautery dissection
NE	Not evaluated

In the control group, 5 babies underwent a systemic-to-pulmonary shunt procedure off pump compared with 6 babies in the study group. One control baby underwent pulmonary artery banding. The rest, 10 control and 11 study patients, underwent Norwood or Norwood equivalent operations on cardiopulmonary bypass.

The control group (n = 16) had longer incision-to-extracorporeal circulation time than the experimental group (n = 17; Table 4). Control subjects had significantly ($p < 0.05$) more intense adhesions than the experimental group at the five mediastinal areas examined (Table 5). Evaluation of specific areas was dependent on whether dissection of the area was included in the second stage operation. There was no significant difference between the two groups in terms of postoperative bleeding or hospital length of stay. Postoperative drainage, age, sex, diagnosis, blood utilization, hospital length of stay, and mortality were not different between the two groups.

Dissection Time

Dissection time was defined as the time from skin incision to the time of initiating cardiopulmonary bypass. This time included dissection of both the retrosternal area and the base of the heart, and it included cannulation time. There was a significant difference in this time between the control group (37.79 minutes) and the experimental group (23.44 minutes, $p < 0.001$; Table 4).

Table 3. Subject Characteristics (n = 30)

Characteristics	Values	p Value
Weight at surgery, kg	3.8 ± 0.5	>0.35[a]
Months to second surgery	8.1 ± 3.5	>0.05[a]
Control group	14 (46.7)	
Experimental group	16 (53.3)	
Sex		>0.49[b]
Female	13 (43.3)	
Male	17 (56.7)	
Ventricle		>0.57[c]
NSV	8 (26.7)	
SV	22 (73.3)	

[a] Independent Student's *t* test. [b] By χ^2 test. [c] Fisher's exact test.

Values are mean ± SD or n (%).

NSV = non-single ventricle; SV = single ventricle.

Table 4. Mean Differences

Variable	Number of Patients	Mean ± SD	p Value
Incision to ECC, minutes			<0.001[a]
Control group	14	37.79 ± 10.445	
Experimental group	16	23.44 ± 6.366	
Mediastinal drainage, cc			<0.95
Control group	13	106.38 ± 78.539	
Experimental group	14	108.64 ± 116.449	
Hospital stay, days			<0.38
Control group	12	4.75 ± 2.832	
Experimental group	14	6.29 ± 5.269	

[a] Significant at an alpha of 0.05.

ECC = extracorporeal circulation.

Wound Infection or Dehiscence

Three of the experimental group subjects had serouslike wound discharge. One control subject had superficial wound separation. There were no major wound infections. No untoward injury occurred at the time of the second operation in either group. No emergency extracorporeal circulation was required.

Comment

Patients with congenital cardiac disease are now living longer after their primary corrective or palliative operations. This prolonged survival correlates with more repeat sternotomies either for enhanced reoperations or for transplantation. Repeat sternotomies in the face of dense adhesion formation between the sternum and the epicardium pose a surgical challenge and the threat of injury to the myocardium, great vessels, and even the lungs. Inadvertent injury to any of these structures adds to the morbidity and mortality risks of the operation.

Preventing adhesions is a goal for which every surgeon strives. A good antiadhesion product is one that completely prevents dense adhesions, is easy to apply, and is associated with minimal side effects. Several studies have been conducted with the aim to reduce postoperative adhesions after cardiac surgery to facilitate reoperation and reduce risks. Most experimental animal studies have been limited by small numbers and short intervals between operations. However, when Seeger and colleagues [12] evaluated data after a longer interval, they observed positive results with a PEG polymer. Currently, many products are marketed with an eye to reducing postoperative adhesions. These can be classified into five groups: (1) prosthetic membranes like polytetrafluoroethylene membrane, polyethelene film, and Dacron mesh; (2) xenograft membranes like bovine pericardium; (3) solutions containing pharmacologic agents, such as hydrophilic polymer solution, hyaluronic acid coating

Table 5. Adhesion Differences

Adhesions Location and Grade	Control Group	Experimental Group	*p* Value
Retrosternal	(n = 14)	(n = 16)	<0.01[a]
No adhesions	0 (0.0)	5 (31.3)	
Filmy and avascular	0 (0.0)	6 (37.5)	
Filmy requiring blunt dissection	0 (0.0)	3 (18.8)	
Filmy, noncohesive requiring blunt and sharp dissection	11 (78.6)	1 (6.3)	
Dense and cohesive requiring extensive sharp dissection	3 (21.4)	1 (6.3)	
Left lateral	(n = 8)	(n = 12)	<0.05
No adhesions	0 (0.0)	1 (8.3)	
Filmy and avascular	0 (0.0)	6 (50.0)	
Filmy requiring blunt dissection	0 (0.0)	1 (8.3)	
Filmy, noncohesive requiring blunt and sharp dissection	7 (87.5)	4 (33.3)	
Dense and cohesive requiring extensive sharp dissection	1 (12.5)	0 (0.0)	
Diaphragm	(n = 2)	(n = 7)	<0.01[a]
Filmy and avascular	0 (0.0)	6 (85.7)	
Filmy requiring blunt dissection	0 (0.0)	1 (14.3)	
Filmy, non-cohesive requiring blunt and sharp dissection	2 (100.0)	0 (0.0)	
Right lateral	(n = 13)	(n = 16)	<0.02[a]
No adhesions	0 (0.0)	1 (6.3)	
Filmy and avascular	0 (0.0)	4 (25.0)	
Filmy requiring blunt dissection	1 (7.7)	8 (50.0)	
Filmy, noncohesive requiring blunt and sharp dissection	7 (53.8)	3 (18.8)	
Dense and cohesive requiring extensive sharp dissection	5 (38.5)	0 (0.0)	
Arterial base	(n = 14)	(n = 16)	<0.01[a]
No adhesions	0 (0.0)	2 (12.5)	
Filmy and avascular	0 (0.0)	7 (43.8)	
Filmy requiring blunt dissection	1 (7.1)	4 (25.0)	
Filmy, noncohesive requiring blunt and sharp dissection	8 (57.1)	3 (18.8)	
Dense and cohesive requiring extensive sharp dissection	5 (35.7)	0 (0.0)	

[a] Significant at an alpha of 0.05.

Values are n (%).

solution, and solutions with fibrinolytic drugs; (4) bioresorbable films made of PEGs and polylactic acid; and (5) bioresorbable spray made of PEGs.

Bioresorbable materials have an advantage based on their ability to prevent dense adhesion formation, without triggering a strong foreign body response [13–19]. Nonabsorbable membranes can result in formation of a fibrous capsule. This capsule is not transparent, and can predispose to infection and late calcifications [19–24]. Solutions have been shown to reduce adhesions but they were associated with postoperative bruising, bleeding, and swelling [25]. Bioresorbable films can prevent adhesions in the retrosternal area. These films run the risk of dislodging owing to cardiac movement, which defeats their purpose. Thicker films may take a longer time to biodegrade, resulting in more pericardial inflammation and subsequent adhesion formation [26].

Bioresorbable spray has several advantages. It is applied directly on the heart and all mediastinal surfaces and does not shift or move. It swells up to four times its original volume, which separates the different surfaces, thereby reducing adhesion formation. It degrades macroscopically in 7 days and microscopically in 30 days. These characteristics, coupled with ease of use, make it an attractive option for the reduction of postoperative adhesions in heart surgery.

Currently, there is no PEG-based hydrogel product that is approved for use in the United States specifically for the prevention of adhesions after cardiac surgery. The product used in this study is marketed as a surgical sealant. Its use for the prevention or reduction of postoperative adhesions is currently off label. Nevertheless, this material appears to be effective when used as an antiadhesive. Sprayed lightly and evenly on all cardiac and mediastinal surfaces, the polymer hydrogel adheres almost instantaneously, and appears to reduce the amount and intensity of postoperative adhesion formation without interfering with wound healing in surrounding surfaces, and holding it in place during early wound healing. This effect was shown in three animal studies and one observational study of pediatric cardiac surgery [27–29]. This is the first prospective randomized study.

It seems essential to use the appropriate volume of polymer, and to spray it lightly and evenly in the retrosternal area. The material will expand by a factor of

approximately four as it initially gels during the first hours and days after chest closure. Too much product, and it will appear under the sternum on echocardiography and could be misrepresented as a blood clot and a sign of cardiac tamponade. Indeed, there is potential to produce an iatrogenic form of cardiac tamponade if the hydrogel is used too generously. The product should be applied to a hemostatic surface, with even distribution. To help gentle and homogeneous distribution of the spray, a low pressure is recommended. The fact it is sprayed directly on the heart and mediastinum makes it unique among options for the prevention of postoperative adhesions. The present study did not evaluate this product as a surgical sealant.

Of note, hydrogel sprayed into the sternum and soft subcutaneous tissue of the incision may drain out of the wound as a yellowish drainage fluid, giving a false impression of wound dehiscence or infection. That occurred frequently during our earliest use of the product and before beginning this prospective study. Wound disruption, however, was rare. This postoperative wound drainage issue was sorted out before the present study, simply by reducing the volume of hydrogel utilization. That is why a calculated volume of the product based on the size of infant was used during this study. This observation is based on unpublished retrospective experience. The sternum and incisional soft tissues should be protected with dry gauze during spraying of the polymer. Overall, the use of this hydrogel product proved to be safe and effective. Catastrophic cardiac injury due to resternotomy is a rare event. Therefore, it did not factor into the outcomes of this small study. The product did significantly reduce reentry operative time, although variability in surgical techniques was not controlled in this study.

Study Limitations

This is a small study, and a multicenter study is recommended. Although the evaluators of the adhesions were blinded as to which group the patient was in, the surgeon performing the second operation was aware of which group his patient belonged to at reentry. That might have affected the reentry time.

Conclusion

Polyethylene glycol polymer when lightly sprayed on the heart and mediastinal tissues after cardiac surgery produced a significant reduction in adhesions after median sternotomy. When used as outlined, the product appears to be safe, effective, and easy to apply.

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