Abstract

We sought to evaluate the utility and safety of CoSeal® Surgical Sealant (Baxter) for the prevention of cardiac adhesions in children. Seven cardiac surgery centers in Europe recruited consecutive pediatric patients requiring primary sternotomy for staged repair of congenital heart defects. Exclusion criteria included immune system disorder, unplanned reoperation, or reoperation within three months of primary repair. CoSeal was sprayed onto the surface of the heart at the end of surgery. Evaluation of adhesions took place at first reoperation. Data on safety, duration of surgery, and ease of CoSeal use were also collected. Seventy-nine pediatric patients were recruited between February 2005 and September 2007. Of these, 76 underwent major surgery to repair a wide range of congenital heart defects. Thirty-six patients underwent reoperation >3 months after primary repair, and were included in the efficacy analysis. Mean adhesions score was 8.3 (standard deviation [S.D.] 2.4; range 7–16). Six adverse events (5 serious) were possibly/definitely attributed to CoSeal. CoSeal’s ease of use at primary operation was graded by surgeons as 12.1 mm (S.D. 9.8) on a visual analog scale of 0 (‘very easy’) to 100 mm (‘very difficult’). Results of this prospective uncontrolled trial justify further investigation in a randomized, controlled trial.

Keywords: Congenital heart defect; Cardiac surgical procedure; Pericardial adhesions; Repeat sternotomy; Surgical sealant; CoSeal®

1. Introduction

Each year, thousands of children undergo complex cardiac surgeries for the repair of congenital heart defects. Among the many complications that characterize these challenging forms of surgery, the formation of cardiac adhesions remains prominent. Cardiac adhesions present a major problem to surgeons upon sternal re-entry to carry out staged cardiac repair [1–6]. Estimates of the incidence of injury to cardiac structures upon resternotomy in patients with adhesions on the large vessels range from 0.7% [4] to 10% [7] of operations.

Various strategies to prevent or reduce the formation of adhesions have been explored, largely at the preclinical level [8], but more recently at a clinical level, e.g. Lodge et al. observed a reduction in severe adhesion formation with the use of a biodegradable barrier film vs. controls in infants undergoing staged cardiac operations [9]. Promising research indicates that surgical sealants, frequently used in cardiac surgery to control anastomotic bleeding, may also have a role in inhibiting the formation of cardiac adhesions [10]. CoSeal® Surgical Sealant (Angiotech Biomaterials Corp, Palo Alto, CA, USA; manufactured and distributed by Baxter Healthcare, Deerfield, IL, USA) is approved in the USA, Canada, Europe, and select countries for sealing suture lines along arterial and venous reconstructions. In Europe, Australia and some countries in Latin America and the Asia Pacific, CoSeal is also approved for use in patients undergoing cardiac surgery to reduce the incidence and severity of postsurgical adhesion formation.

In early 2004, we began to use CoSeal in patients scheduled for staged cardiac surgery. Following favorable initial experience [11], we collaborated with other institutions to design an observational study in order to evaluate the utility and safety of CoSeal for the prevention of cardiac adhesions.
adhesions in staged surgical procedures in children with congenital cardiac malformations.

2. Materials and methods

2.1. Centers and patients

Seven pediatric cardiac surgery centers in Europe using CoSeal in routine practice were asked to recruit ten consecutive pediatric patients requiring primary sternotomy for the staged repair of congenital heart defects. Written informed consent was sought from the patient’s legal guardian.

Exclusion criteria included immune system disorder or immunodeficiency; known hypersensitivity to components in CoSeal; use of any other anti-adhesion product during surgery; and participation in another clinical trial within 30 days prior to surgery. In order to allow adequate time for adhesions to form, patients who underwent reoperation prior to planned stage 2 repair at >3 months post-primary surgery were excluded from the efficacy analysis.

2.2. Materials

CoSeal Surgical Sealant is composed of two synthetic polyethylene glycols (PEGs), a dilute hydrogen chloride solution and a sodium phosphate/sodium carbonate solution, provided in kits of 2, 4 and 8 ml. After mixing, the two PEG solutions polymerize to form a hydrogel that must be used within 2 h.

Prior to sternal closure, CoSeal was sprayed in a thin homogeneous layer in the mediastinum, covering the visible surface of the heart and great vessels. Application was via a product-specific gas-driven spray device (CoSeal® Air Enhanced Spray Applicator, Baxter, Deerfield, IL, USA). Initially, patients received 2 ml product. Following the occurrence of an adverse event possibly related to product overdose, the protocol was amended in January 2006 so that patients weighing <3 kg received 1 ml product, 3–10 kg received 1–2 ml, and >10 kg received 2–4 ml CoSeal (see Results).

2.3. Outcome measures

Evaluation of adhesions took place at first planned reoperation. The primary outcome measure was the severity of adhesions at seven predefined sites (Table 1). Data on safety, duration of surgery, and ease of CoSeal use were also collected, with assessments taking place during primary surgery, at ~1 month following primary surgery, at planned reoperation and 1 month following reoperation.

Collection of data was monitored by a medically-qualified representative from Baxter, in order to check for protocol adherence and completeness of data collection. Case report data were processed by an independent Clinical Research Organization, funded by Baxter BioScience Europe. Data were entered by double entry and computerized checks were performed.

2.4. Statistical analysis

The safety population comprised all patients undergoing primary repair. The efficacy population comprised patients who underwent reoperation as planned after at least three months following primary surgery. Descriptive statistics are provided. We included a prespecified analysis of patients undergoing cardiopulmonary bypass vs. those not requiring cardiopulmonary bypass.

2.5. Ethics

As this was an observational study of an approved medical device routinely used in surgical practice, ethics approval was not required in Italy or France. For the UK center, ethics approval was obtained from the relevant authorities prior to study commencement. Written informed consent was obtained from parents/guardians to allow anonymous data management.

3. Results

3.1. Patients

Recruiting centers were located in Italy (5), France (1), and the UK (1). A total of 79 children were enrolled between 24 February 2005 and 25 August 2007, with centers contributing a mean of 11.3 patients (standard deviation [S.D.] 7.8; range 2–25). At the time of database lock on 11 April 2008, 76 patients had undergone primary surgery with application of CoSeal, and 43 of these had undergone staged reoperation. Of these 43, 36 had undergone reoperation in accordance with the predefined >3 months period, 7 underwent reoperation prior to this.

Of the 76 patients, 3 (1 female, 2 males) were over 18 years of age. The mean age of the 73 pediatric patients was 14.9 months (S.D. 29.1; range 0–130). Of these, 40 were male (55%); mean height was 63.6 cm (S.D. 23.6;

Table 1

| Primary and secondary outcome measures in children undergoing staged surgical repair with application of CoSeal after first operation |

The primary outcome measure was quantified at reoperation as follows:

- Severity of adhesions at 7 predefined sites – pericardial or retrosternal, inferior or diaphragmatic region, right lateral or arterial region, region around great vessels – graded at each site as 1 = filmy and avascular; 2 = dense/vascular; or 3 = cohesive.●
- An adhesion score for each patient was derived from the sum of adhesion severity scores at each site, ranging from 0 (free of adhesions) to 21 (cohesive adhesions at all 7 sites).

Secondary outcome measures included:
- Incidence of adverse events and serious adverse events.
- Ease of use of CoSeal – graded by lead surgeon via a visual analog scale (VAS; ranging from 0 [very easy] to 100 mm [very difficult]).
- Type and duration of operation and reoperation.
- Quality of cutaneous wound healing (normal or delayed).

●This ranking system was already in common practice at the participating institutions.
range 40–131); mean weight was 6.6 kg (S.D. 6.5; range 1.9–34.0). As shown in Table 2, a broad range of heart malformations was evident, with the most common being single ventricle pathology in 29 patients (38%).

### 3.2. Primary operation

All 76 patients underwent median sternotomy and cardio-pulmonary bypass was used in 31 operations (41%), with surgical procedure staged in 65 (86%) of patients. The most frequent types of surgical procedure were Blalock–Taussig shunt in 23 cases (30%), bidirectional cavopulmonary anastomosis in 13 cases (17%), and pulmonary artery banding in 13 cases (17%). Mean operating time was 3.9 h (S.D. 1.8; range 1–10).

The mean volume of CoSeal used was 2.4 ml (S.D. 0.8; range 1–4). Using bodyweight-adjusted quantities, 4 patients received 1 ml, 54 received 2 ml, 5 received 3 ml and 13 received 4 ml. Over 76% of patients received the recommended quantity of CoSeal. Lead surgeons rated the ease of use of CoSeal as 12.1 mm (S.D. 9.8; range 0–51 on aVAS of 0–100 mm).

#### 3.3. Follow-up after primary operation

Within the first month following primary surgery, 24 of 76 patients (32%) developed 31 adverse events, principally postoperative complications characteristic of this form of surgery (e.g. bleeding, infection, seroma, desaturation, pleural effusion, cardiac arrest, low cardiac output, cardiac tamponade), with 17 events classified as serious. The most common adverse events were bleeding (6 cases), chest infection (4 cases), cardiac arrest and shunt occlusion (3 cases each), and pleural effusion and seroma (2 cases each).

A total of six adverse events were classified as possibly or definitely related to study product. One case each of cardiac tamponade (serious), pericardial effusion, and mediastinitis (serious) were classified as ‘possibly related’. One case each of cardiac tamponade, superior vena cava occlusion, and cardiac fibrillation were all classified as serious adverse events ‘definitely related’ to study product.

The two cases of cardiac tamponade (necesitating re-entry) arose within the first operations, and were attributed to the capacity of the product to swell to four times its volume within 24 h after application. This led us to amend the protocol (January 2006) to optimize volume of CoSeal in accordance with body weight (see Methods), after which no more cases of cardiac tamponade arose. Three patients died (shunt occlusion; sudden death; cardiac arrest). These events were classified as unrelated to study product. Overall, 80% of adverse events resolved without sequelae.

Cutaneous wound healing appeared to be excellent, with 70 of 76 patients (92%) experiencing normal wound healing.

#### 3.4. Staged reoperation

For the 36 children who underwent staged reoperation at >3 months following primary surgery, the mean interval between primary operation and reoperation was 8 months (S.D. 4.5; range 3–24). Mean age was 8.5 months (S.D. 22.3; range 0–89); 20 were male (56%), mean weight was 4.8 kg (S.D. 5.0; range 1.9–25.0); mean height was 55.6 cm (S.D. 20.0; range 40–130). The most common forms of reoperation were bidirectional cavopulmonary anastomosis (12 patients) and pulmonary artery banding (12 patients). The mean operating time was 3.5 h (S.D. 1.8; range 1–10).

As shown in Fig. 1, at reoperation all 36 (100%) of patients had developed adhesions at one or more of the seven

<table>
<thead>
<tr>
<th>Type of congenital heart defect</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Aortic coarctation – ventricular septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Aortic incompetence</td>
<td>1</td>
</tr>
<tr>
<td>Atroventricular septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Congenital heart block</td>
<td>2</td>
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<tr>
<td>Congenitally correct transposition of great artery</td>
<td>1</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>5</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>8</td>
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<tr>
<td>Pulmonary atresia – intact ventricular septum</td>
<td>4</td>
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<tr>
<td>Pulmonary atresia – ventricular septal defect</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary incompetence</td>
<td>2</td>
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<tr>
<td>Pulmonary stenosis</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary vein obstruction</td>
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</tr>
<tr>
<td>Single ventricle pathology</td>
<td>29</td>
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<tr>
<td>Subaortic stenosis</td>
<td>1</td>
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<tr>
<td>Transposition of great vessels</td>
<td>2</td>
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<tr>
<td>Transposition of great vessels – ventricular septal defect</td>
<td>2</td>
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<tr>
<td>Ventricular septal defect</td>
<td>3</td>
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*Verified by site investigator.
from three countries were involved in this prospective study, embracing a broad range of congenital heart defects and surgical procedures used to correct them, thereby enhancing the generalizability of the findings.

Regarding the safety of CoSeal following primary operation in 76 patients, only 6 of the 31 recorded adverse events were classed as possibly or definitely related to the application of CoSeal, 5 of these ‘serious’. The two cases of cardiac tamponade arose early in the study and were attributed to the known capacity of CoSeal to swell to four times its volume after application, which led to an amendment to the study protocol, with no cases of tamponade arising afterwards. The importance of even distribution of product over the heart surface is key to obtaining the best outcome. Cardiac fibrillation triggered by the delivery of cold air from the applicator can easily be avoided by holding the sprayer at least 20 cm from the heart surface, as recommended by the manufacturer. Overall, the safety of CoSeal for prevention of cardiac adhesions was considered to be very good. In addition, surgeon’s ranking of CoSeal’s ease-of-use was very favorable.

Regarding study weaknesses, our investigation lacked controls, and it is hoped that a controlled study will shortly be designed and commenced. On this point, currently the FDA is looking at how such trials might be conducted, given the difficulty of choosing primary and secondary endpoints that embrace benefit and risk, and the inherent difficulties in planning a trial whereby patients who receive the study product may not undergo planned re-operation. In the meantime, in the absence of studies reporting on the use of surgical sealant to reduce the incidence/severity of cardiac adhesions following open heart surgery in children, our observations contribute a body of data that will help guide further research in this much understudied field.

Acknowledgments

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References


