Potential interest of a new absorbable collagen membrane in the prevention of adhesions in paediatric cardiac surgery: A feasibility study

Xavier Armoiry\textsuperscript{a,b,c}, Marie Viprey\textsuperscript{a}, Hélène Constant\textsuperscript{a}, Gilles Aulagner\textsuperscript{a,c}, Adeline S. Roux\textsuperscript{d}, Laure Huot\textsuperscript{b,d,e,f}, François Roubertie\textsuperscript{g}, Jean Ninet\textsuperscript{g}, Roland Henaine\textsuperscript{g,h,*}

\textsuperscript{a} Hospices Civils de Lyon, Groupement Hospitalier Est, Service Pharmaceutique, Bron, France
\textsuperscript{b} Hospices Civils de Lyon, Délégation à la Recherche Clinique et à l’Innovation, Cellule Innovation, Lyon, France
\textsuperscript{c} Université Claude-Bernard Lyon-1, UMR-CNRS 5510/MATEIS, Lyon, France
\textsuperscript{d} Hospices Civils de Lyon, Pôle Information Médicale Évaluation Recherche, Unité de Recherche Clinique, Lyon, France
\textsuperscript{e} Université de Lyon, 69007 Lyon, France
\textsuperscript{f} Université Lyon-1, EAM 4128 Santé Individu Société, 69003 Lyon, France
\textsuperscript{g} Hospices Civils de Lyon, Groupement Hospitalier Est, Hôpital Cardiologique Louis-Pradel, Service de Chirurgie Cardiaque, Bron, France
\textsuperscript{h} Inserm U1060, UCBL1, CarMeN, n° 5, Cardioprotection, Lyon, France

Received 5 October 2012; received in revised form 27 April 2013; accepted 6 May 2013
Available online 29 July 2013

KEYWORDS
Biomaterials;
Paediatric;
Cardiac reoperation;
Surgery;
Complications;

Summary

Background. — Open-heart surgery can result in adhesions, which can complicate resternotomy.
Aims. — To document the occurrence of adhesions after the use of a new collagen membrane; to evaluate its tolerability; and to compare surgical parameters with control patients.
Methods. — Paediatric patients who underwent cardiac surgery with the collagen membrane (Cova\textsuperscript{TM} CARD; Biom’up, Saint Priest, France) were analysed retrospectively for levels of adhesion and tolerability. The times of dissection and intervention and the transfusion of packed red
Results. — From January 2010 to December 2011, 36 patients received a collagen membrane. Nineteen re-interventions were performed, after a mean of 169 days. No grade 3 adhesions were observed and no tolerability problems were reported. During re-interventions after more than 30 days, the propensity score-adjusted durations of dissection and the total process for patients with and without a collagen membrane were 32 vs 41 minutes and 151 vs 182 minutes, respectively (not significant). The mean quantities of red blood cells and biological glue administered in the two groups were 98 vs 139 mL and 1.2 vs 0.5 mL, respectively (not significant).

Conclusions. — This feasibility study shows the potential use of the new membrane in paediatric patients, both in terms of prevention from severe adherence and tolerability. This is the first study of this membrane in humans. A prospective, controlled study is necessary to provide strong evidence of its efficiency.

© 2013 Elsevier Masson SAS. All rights reserved.

Background

Cardiac reoperations are increasingly common, especially among paediatric patients with cardiac disease. Approximately 10% of cardiac operations involve repeat sternotomies [1]. There is a risk of re-entry injury due to the presence of adhesions that can obscure the cardiac anatomy [2]. The surgical trauma to the pericardiac mesothelium during open-heart surgery can result in a decrease in fibrinolytic activity and the formation of adhesions at the intervention sites [3]. Therefore, re-interventions may be complicated by the development of dense, fibrous retrosternal or pericardiac adhesions. As a consequence, re-sternotomies can be dangerous and surgery is complicated because the surgeon needs to use sharp instruments that might damage the tissues and cause potentially serious iatrogenic haemorrhagic events [1,2,4–7]. Adverse events related to reoperation can lead to poor patient outcome and higher cost [8].

These complications of reoperations have prompted experimental studies to prevent or decrease adhesion formation and thus decrease the risks associated with reoperation.

Here, we describe our clinical experience of the use of a new collagen membrane which aims to prevent surgical adhesions.

Methods

Study type

This single-centre, retrospective cohort study evaluated a group of patients treated with a collagen membrane, and
compared this group to a historic cohort of patients not treated with a membrane.

**Objectives**

Our main objectives were to evaluate: (1) the occurrence of adhesions during surgical re-interventions with collagen membrane and (2) the tolerability and the morbidity related to the presence of adhesions after the use of the collagen membrane. Our secondary objectives were to evaluate and compare the duration of dissection, the total duration of re-intervention and the volumes of packed red blood cells (RBC) and biological glue used during surgical re-interventions among those treated with and without collagen membrane.

**Evaluation criteria**

As there is no specific classification for the severity of adhesions in cardiopaediatric surgery, adhesions among patients in the collagen membrane group were graded according to the levels of adhesion described by Lodge et al. [9] (Table 1). No record of adhesion severity in the control arm was available, as we only started using this classification scheme after the introduction of the collagen membrane.

Adhesions among collagen membrane recipients were also characterized by the risk zone of their occurrence, as described in Table 1. Zone A is the first zone encountered during re-intervention. Resternotomy in a patient with adhesions in zone A is accompanied by the risks of damaging the heart or any other structure that can stick to the sternum. This can be fatal, as the ECC has not yet been implemented, and the patient may die from haemorrhagic shock, especially as access to a femoro-femoral ECC is impossible in young children. Adhesions in zone B can affect the second stage of surgery, which begins once the sternal retractor is in place and the structures needed to start the ECC (aorta and right atrium) are dissected. This step is somewhat less dangerous because the wound can be more easily controlled as the heart is better exposed. The morbidity related to the presence of adhesions was assessed as any complication related to the presence of adhesions mentioned in the medical charts, regardless of the severity.

The evaluation of adhesion grade was not blinded. Potential undesirable effects related to the collagen membrane, such as inflammatory or allergic reactions, were collected in order to evaluate its tolerability.

As adhesions were not recorded in the control arm, the following objective parameters were retrieved for comparison between the groups. The duration of dissection of the re-intervention was the time between the first surgical incision and the start of ECC. The volume of RBC was assessed, taking into account all administration of RBC during the procedure. The volume of biological glue used during re-intervention was the total amount of Tissucol® (Baxter, Deerfield, USA).

**Study membrane and procedure**

The study membrane is a resorbable, malleable porcine collagen membrane called Cova™ CARD (Biom’up, Saint Priest, France) (Fig. 1), which acts as a barrier between the heart and the surrounding tissues. It also promotes tissue regeneration [10,11]. It is a class III device that obtained a CE approval in 2009. The membrane is available in two sizes (30 × 40 mm and 40 × 60 mm), according to the weight of the child. The membrane has to be moisturized for a few minutes in a physiological serum to make it more flexible. It can be cut as necessary, in order to be able to place it on delicate structures; and can be fixed with sutures. It is applied next to the right atrium, the aorta and the sternum, before the sternal closure.

**Selection criteria for the collagen membrane group**

Patients in the collagen membrane group were those who had received the collagen membrane during January 2010 to December 2011 during surgery for a congenital cardiopathy requiring repeat scheduled open-heart surgery with a first re-intervention scheduled less than 24 months after the first intervention with median sternotomy and requiring ECC.

**Selection criteria for the control population**

Control patients were those who had an initial intervention using an approach with median sternotomy during 2009; had a re-intervention performed by the same cardiac surgeon as the re-interventions performed in the membrane group; had a re-intervention occurring more than 30 days after the original procedure that was performed using an approach with median sternotomy and requiring ECC. In all control patients, the pericardium was not closed after the first procedure.

**Data collection and analysis**

Baseline parameters are presented as means and standard deviations (SDs) for quantitative variables and numbers

### Table 1 Description of the levels of adhesion and adhesion risk zones.

<table>
<thead>
<tr>
<th>Level of adhesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Absence of adhesion</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Low adhesion (possibility to lyse it with the finger)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate adhesion (possibility to lyse it with scissors)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>High adhesion requiring the use of an electrical bistoury in order to perform the dissection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adhesion risk zone</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anatomic structures located in the sternotomy zone</td>
</tr>
<tr>
<td>B</td>
<td>Necessary mediastinum elements for the installation of ECC (ascending aorta, superior vena cava, part of the right atrium)</td>
</tr>
</tbody>
</table>

ECC: extracorporeal circulation.
(percentages) for qualitative variables. To adjust for baseline characteristics between the two groups, we estimated propensity scores using a logistic regression model (gender, age at initial surgery, delay of re-intervention, age at re-intervention and weight at revision surgery). We then compared re-intervention parameters using linear models with a covariate adjustment on these propensity scores. Adjusted means with 95% confidence intervals (CIs) are presented.

Results

Use of the collagen membrane

From January 2010 to December 2011, 36 children (25 boys; 11 girls) with congenital cardiopathy received a collagen membrane after a first cardiac surgery and were included in this study. Among them, two received a second membrane after a second surgery and one patient received a total of four membranes after four surgeries performed during the observation period. In total, 41 collagen membranes were implanted during 41 surgeries. The mean age of the patients at the time of the first intervention was 13.8 ± 33.7 months (range: 0.1—200 months).

Nineteen re-interventions were undertaken during the observation period on a total of 14 patients, of whom two had two re-interventions and one had four re-interventions. No re-intervention was due to an undesirable event related to the initially implanted anti-adhesion membrane. Re-interventions occurred within a mean delay after initial surgery of 169 ± 166 days (range: 3—558 days). Twelve re-interventions (63%) occurred after a delay of more than 30 days.

The adhesion levels for the 19 re-interventions performed after the installation of the collagen membranes are shown in Fig. 2. In risk zone A (sternotomy zone), regardless of the re-intervention delay, no grade 2/3 adhesion was observed and 89% of patients had no adhesion (Fig. 2A). Beyond a re-intervention delay of 30 days, 17% of patients had grade 1 adhesions. In risk zone B (ECC zone), there were some grade 1/2 adhesions, but no severe adhesions (grade 3) (Fig. 2B). Beyond a re-intervention delay of 30 days, the

![Figure 1. Cova™ CARD before implantation.](image)

![Figure 2. Adhesion levels observed in the membrane cohort according to the delay of re-intervention in (A) risk zone A (sternotomy zone) and (B) risk zone B (ECC zone). ECC: extracorporeal circulation.)](image)
rates of grade 1 and grade 2 adhesions were 42% and 25%, respectively. Tolerance of the membrane was good as no serious or minor undesirable effects were observed, in terms of infection, allergy, intolerance, inflammatory signs or secondary vascular rupture. There were no complications due to the presence of adhesions during the re-interventions performed in the membrane group; and no haemorrhagic accidents were recorded.

Comparison with historical controls

Thirteen patients met the selection criteria for the control population; none of these patients benefited from a specific preventative measure of surgical adhesions. Demographic characteristics for these patients are shown in Table 2, along with data for the 12 patients from the membrane group who underwent re-intervention after a delay of more than 30 days. Although the number of patients in each group is limited, patient characteristics were similar. However, the aetiologies were heterogeneous (Table 3). The occurrence of surgical adhesions was not related to the underlying cardiac pathology, but only related to the injury of tissues resulting from the surgical approach due to a resternotomy.

The durations of the dissection and the total re-intervention were not significantly different between the groups (Table 4). RBC and biological glue use were also not significantly different between the groups, but numerically more RBC was used in the control group (Table 4). In both groups, no aorta scars or haemorrhagic events related to adhesions were reported. In the membrane group, durations of dissection were not related to the degree of adhesions (Table 5).

Discussion

In this exploratory study, which evaluated and compared the Cova™ CARD cohort to a historic cohort of patients who did not benefit from any techniques of adhesion, there were no grade 3 adhesions in the membrane group. The good tolerability of this membrane, which has a European Economic Community grading, was also confirmed.

Strategies for reducing re-entry injury vary greatly between centres and operators, with therapeutic options varying between no prevention measures to partial closure of the pericardium or the installation of an anti-adhesion device or expanded polytetrafluoroethylene (ePTFE) [12,13].

The use of Seprafilm® membrane (Genzyme, Cambridge, Mass, USA), composed of carboxymethyl cellulose and hyaluronic acid, has been shown to reduce the grade of adhesions and the duration of dissection in patients...
More recently, the Repel CV® membrane (SyntheMed, Iselin, USA), made from polylactic acid, has been shown to reduce the occurrence of severe adhesions compared to a control group, and the bioresorbable device appeared to be safe [9]. However, there are two main disadvantages of these membranes, namely their composition and their lack of mechanical resistance. Despite its efficacy in preventing pericardial adhesions, the Repel CV® device has been associated with inflammatory reactions due to polylactic acid [15]. Seprafilm®’s biological composition does not allow it to be applied onto wet sutures, which is a common situation in cardiac surgery. Also, sutures can easily be displaced or broken by heart beats [16]. Furthermore, the resorption of its main component does not involve naturally present endogenous enzymes (like collagenases), but occurs by hydrolysis, which causes the release of non-metabolized fragments into the mediastinal cavity [15].

In this context, no recommendation has yet been established to guide the clinician in choosing a technique to prevent adhesions. As soon as it was commercialized, the Cova™ CARD device raised significant interest among pediatric cardiac surgeons, due to its ease of use and handling. The Cova™ CARD membrane was first evaluated for cardiac surgery through a pre-clinical model conducted on 16 sheep, which underwent sternotomy followed by scarification of the heart [10]. Three approaches were compared: pericardium left open or installation of a hyaluronic acid and carboxymethylcellulose or Cova™ CARD before closure. Explanted hearts were evaluated for inflammatory response and fibrosis. The Cova™ CARD membrane was nearly completely absorbed within 4 months and was replaced by loosely adherent tissue. No inflammatory reaction was seen, and fibrosis was minimal. A composite score (tightness of adhesions, inflammation and fibrosis) was significantly lower in the Cova™ CARD than in the Seprafilm® group [10]. A second study involved 18 sheep that underwent sternotomy and an ECC of 30 minutes [11]. Three options were tested: pericardium left open or use of an ePTFE or Cova™ CARD membrane. Four months after surgery, the best adhesion score was obtained in the Cova™ CARD group. However, the presence of the collagen membrane allowed the re-epithelialization of the heart [11]. Despite its CE approval, no clinical studies on the Cova™ CARD membrane had been published when it was commercialized. Therefore, we evaluated its potential impact in pediatric cardiac surgery. Our study is the first reported experience on Cova™ CARD membrane in congenital cardiopathy surgeries. Our results confirm its potential benefit in preventing severe adhesions as no grade 3 adhesions were reported, regardless of the delay of re-intervention after initial surgery and the risk zone. The absence of severe adhesion in the sternotomy zone is particularly satisfactory considering that, as stated by the French National Authority for Health, the complications related to re-opening the sternum in the presence of adhesions between the sternum and the heart can be life-threatening [17].

No significant differences were found for the duration of dissection or the total duration of surgery between the membrane and control groups. Also, there was no link between dissection time and level of adhesions in the membrane group. However, these results should be interpreted with caution due to the low number of patients evaluated. In a randomized study by Lodge et al. [9], which reported significantly less severe adhesions with the Repel CV® membrane compared with no barrier, there was no difference in the duration of dissection between the groups, although there was a small, but significant increase in the duration of dissection with severe versus no severe adhesions. Intuitively, the presence of adhesions that complicate surgery would be expected to increase the time for the dissection of tissues before the installation of ECC. However, if there are strong adhesions, the surgeon may choose to clear the necessary elements quickly, then start ECC, and finish the dissection

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of re-intervention parameters between the two populations.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Membrane group (n = 12)</td>
</tr>
<tr>
<td>Duration of dissectionb (minutes)</td>
<td>32 (24–40)</td>
</tr>
<tr>
<td>Total duration of re-interventionc (minutes)</td>
<td>151 (120–183)</td>
</tr>
<tr>
<td>Volume of RBC transfused at revision surgeryd (mL)</td>
<td>98 (20–177)</td>
</tr>
<tr>
<td>Volume of biological glue used at the revision surgeryd (mL)</td>
<td>1.2 (0.2–2.2)</td>
</tr>
</tbody>
</table>

Data are expressed as adjusted mean (95% confidence interval).

a P-values were obtained using linear regression analysis, adjusted for propensity scores (estimated from logistic regression with baseline characteristics; C score = 0.821).
b Data are missing for one patient in each group.
c Data are missing for two patients in the membrane group and five patients in the control group.
d Data are missing for one patient in the control group.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Time of dissection according to the level of adhesion in the membrane group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of adhesion</td>
<td>Duration of dissection (minutes)</td>
</tr>
<tr>
<td>Zone A: 0; zone B: 0 (n = 4)</td>
<td>33 ± 9</td>
</tr>
<tr>
<td>Zone A: 0; zone B: 1 (n = 4)</td>
<td>37 ± 16</td>
</tr>
<tr>
<td>Zone A: 0; zone B: 2 (n = 1)</td>
<td>28</td>
</tr>
<tr>
<td>Zone A: 1; zone B: 2 (n = 2)</td>
<td>32 ± 1</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.
under ECC, which therefore does not increase the time of dissection, which was defined as the time from first incision to start of ECC. A better parameter may be the complete time of intervention, but only if the same types of interventions by the same surgeon are compared, which would require a much higher number of patients.

There were no significant differences between the groups in terms of consumption of medical resources (RBC and biological glue), which is consistent with the absence of any haemorrhagic wounds or other preoperation undesired events in the two groups. However, these criteria are potentially useful for future studies, considering the risk of haemorrhagic complications associated with the presence of adhesions.

It should be noted that only considering such criteria may be restrictive. In fact, the presence of major adhesions may sometimes compel the surgeon to use other approaches [18].

The major limitations of this study were the non-randomization of patients, the low number of patients, the monocentric aspect of the study and the use of historical randomization of patients, the low number of patients. A high level of proof study on a higher number of patients is to be carried out in order to further evaluate its efficiency in the prevention of adhesions.

Conclusions

The Cova™ CARD membrane was used with good tolerability in this first human clinical study including 36 paediatric patients. A high level of proof study on a higher number of patients is to be carried out in order to further evaluate its efficiency in the prevention of adhesions.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

We are grateful to Mrs Jennifer Kayal for her assistance with translation.

References