The use of Tachosil® surgical patch or fibrin glue in coronary artery surgery does not affect quality of anastomosis or provoke postoperative adhesions in pigs

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Abstract

Objective: Fibrin glue products and collagen surgical patches (TachoSil®) coated with coagulation factors I and IIa are increasingly being used to prevent oozing from distal or proximal coronary anastomosis. Furthermore, an increasing number of patients are being operated upon anti-platelet therapy. These patients often exhibit diffuse bleeding. Especially in an off-pump scenario surgeons refrain from placing additional stitches in order to avoid an impairment of the graft. In these situations, a biological glue can help resolve this dilemma. It is, however, assumed that these products may exert negative effects on the anastomosis. For obvious reasons a systematic histological assessment in humans is impossible. Therefore, a chronic, large animal model was developed to study the fate of these products on a coronary anastomosis. Methods: In 15 pigs receiving off-pump coronary artery bypass graft of the left mammary artery to the left anterior descending coronary artery, three groups were defined. Group A served as control. In group B the anastomosis was covered with 1 ml fibrin glue; in group C TachoSil® coverage was performed. Bypass flow (BF) was measured using a Doppler probe. After 3 months the pigs were sacrificed and the anastomoses were evaluated macroscopically and by means of light microscopy regarding patency and fibrosis. Results: In group A, all five animals survived, three of the five anastomoses were patent and the mean BF was 26 ml min⁻¹. In group B, three of the five animals survived, all anastomoses were patent. The BF was 21 ml min⁻¹. In group C, all five animals survived, four of the five anastomoses were patent and BF was 21 ml min⁻¹. Macroscopic and histological evaluation showed no differences between the groups. Remnants of TachoSil® or fibrin glue were not observed. Conclusions: In the chronic course, no evidence of adverse effects of TachoSil® or fibrin glue was noted. Both agents can therefore be used safely in clinical practice for haemostypic or positioning purposes.

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1. Introduction

Haemostasis plays a particularly important role in coronary bypass surgery. In case of an oozing anastomosis the performing surgeon would often want to refrain from applying additional sutures to avoid jeopardising the patency of the coronary anastomosis. This is especially true in times where an increasing number of patients are operated upon under anti-platelet therapy. In these patients even a meticulously performed anastomosis can show some oozing without necessarily demanding a potentially hazardous suture. In addition, an increasing number of patients are operated in an off-pump coronary artery bypass (OPCAB) scenario. In beating-heart surgery, every additional placed suture is difficult and potentially hazardous. In these situations a biological adhesive may help resolve this dilemma. A multitude of fibrin products with or without a prefabricated fleece have been developed. One of these is TachoSil® (Nycomed, Konstanz, Germany) [1]. This ready-to-use surgical patch consists of an absorbable collagen sponge coated on one side with human fibrinogen and thrombin, thus enabling sealing and haemostatic coverage. It has already been shown that TachoSil® just as well as its predecessor products TachoComb® and TachoCombi® H effectively reduces blood loss and can lead to haemostasis in a wide variety of surgical fields [2–6]. Thus far, numerous reports from visceral and thoracic surgeons have indicated only minor postoperative adhesions or even an entire absence of such following the use of TachoSil® or TachoComb® [7–10]. It is often assumed that fibrin glue or TachoSil® itself may negatively affect the anastomosis. Although considered
entirely as biological, the fate of this coated collagen sponge or of fibrin glue and their effects on the adjacent tissue (which could include potentially endangering the patency of the graft) have not been systematically addressed in cardiac surgery. For obvious reasons a systematic histological assessment of potentially adverse effects in humans is not possible. The aim of this study was to evaluate the chronic effects of TachoSil® and fibrin glue on the surrounding tissue structures, formation of adhesions, and morphological impact on the anastomosis itself. The selected surgical setting was a regularly sewn anastomosis of the left internal thoracic artery to the left anterior descending coronary artery (LAD) in OPCAB technique in pigs that was either covered with a Tachosil® patch, 1ml of fibrin glue or no sealant at all.

2. Material and methods

All experiments performed in this study were approved by the Animal Care Committee of the Brandenburg State and carried out at the Surgical Training Centre in Groß-Doelln, Germany. All animals received humane care in compliance with the 1996 ‘Guide for the Care and Use of Laboratory Animals.’

All surgical procedures were carried out under sterile conditions. Fifteen approximately 3-month-old pigs received OPCAB grafting of the left internal mammary artery (LIMA) as a pedicle to the LAD. Group A served as control. In group B the anastomosis was covered with 1 ml fibrin glue (Beriplast®, ZLB Behring, Bern, Switzerland), in group C a fibrin-coated collagen fleece coverage (TachoSil®, Nycomed, Linz, Austria) was performed. The animals were divided into three groups. Group A consisted of five animals with a mean weight of 50.4 ± 7.3 kg, group B included 51 animals, with mean weight 6 ± 5.9 kg, and group C included 52 animals with mean weight 7 ± 3.5 kg (p = 0.884). Bypass flow (BF) to evaluate graft patency was measured using a Doppler probe (Medi-Stim Inc., Oslo, Norway); flow measurement was registered only when the PI (pulse index) suggested adequate measurements. The animals were assigned to their groups sequentially; randomisation was not performed.

Each animal underwent OPCAB of a pedicled LIMA to the LAD; they were pre-anaesthetised with an intramuscular cocktail of ketamine (2—4 mg kg⁻¹). The animals were then shaved and disinfected in common surgical practice; the operating field was covered with disposable sterile sheets. OPCAB was performed after sternotomy and electrical preparation of the LIMA. Before clamping of the LIMA, 10 000 units of IV heparin were administered. The coronary anastomosis was facilitated with the Estec stabiliser (Estec Corporation, Danville, CA, USA) and an intracoronary shunt (Fumedica, Muri, Switzerland) in standard technique using a 7/0 Prolene (Ethicon Inc., Somerville, NJ, USA) continuous running suture. Further, the LIMA was fixedated with two 5/0 Prolene stay sutures. Following anastomosis, blood flow was re-established and patency controlled using a Doppler probe (Medi-Stim Inc., Oslo, Norway). The sternum was closed using three standard sternotomy wires (Serag Wiessner, Naila, Germany). The animals were then allowed to recover.

2.1. Postoperative care

The arterial femoral cannula was removed at the end of the operation when the animals were in a haemodynamically stable condition. During recovery, oxygen saturation and ECG were continuously monitored. When the animals were able to breathe spontaneously, mechanical ventilation was discontinued. The endotracheal tube and ear vein cannula were removed when they were no longer tolerated, and the animals were moved to a temperature-controlled recovery kennel. Here the animals had free access to water during the first 12 h postoperatively and thereafter also to food. For pain management, intramuscular application of metamizol was sufficient in all cases. After a survival period of 3 months the animals were sedated with ketamine. A marginal ear vein was cannulated for administration of systemic heparin and euthanasia solution (T-61, Intervet, Boxmeer, the Netherlands). Later the chest was opened, the heart excised and the anastomoses were recovered and immediately placed in a fixative solution of formalin and then processed for histological sectioning.

2.2. Histological examination

The paraffin sections were cut at 7—11 μm thickness and stained with haematoxylin–eosin, Azan and Masson–Goldner. The areas of interest were first identified at 10× magnification. Then detailed analyses were performed at 20, 40 or 100× magnification. The pathologist was blinded to which groups the slides belonged to.

2.3. Statistical analysis

Statistical analysis was performed with SPSS 15.0 software. Data is expressed as the mean ± standard deviation (SD). Demographic data as well as target parameters were analysed for significant differences among the three groups. Comparisons of numerical values were performed with a one-way analysis of variance (ANOVA). Descriptive statistical analysis with categorical data was performed by cross-tabulation applying the chi-square test (Pearson’s test). A probability of p-value <0.05 was considered statistically significant (Table 1).
Table 1
Mean values ± SD of characteristics and outcomes.

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight at Operation (kg)</th>
<th>Operation time (min)</th>
<th>Blood loss (ml)</th>
<th>Patency (+/-)</th>
<th>Survival</th>
<th>Blood flow (ml min⁻¹) anastomosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (control)</td>
<td>50.4 ± 7.3</td>
<td>92 ± 15.2</td>
<td>140 ± 41.8</td>
<td>3/5</td>
<td>5/5</td>
<td>25.2 ± 9.7</td>
</tr>
<tr>
<td>B (fibrin glue)</td>
<td>51.6 ± 5.9</td>
<td>104.2 ± 15.9</td>
<td>148 ± 32.7</td>
<td>3/3</td>
<td>3/5</td>
<td>20.7 ± 9.4</td>
</tr>
<tr>
<td>C (TachoSil®)</td>
<td>54.2 ± 3.5</td>
<td>99.4 ± 21.3</td>
<td>118 ± 54.1</td>
<td>4/5</td>
<td>5/5</td>
<td>21.93 ± 8.1</td>
</tr>
<tr>
<td>(p)</td>
<td>0.884</td>
<td>0.565</td>
<td>0.549</td>
<td>0.420</td>
<td></td>
<td>0.538</td>
</tr>
</tbody>
</table>

3. Results

3.1. Clinical course

Of the 15 pigs operated, 13 survived the operation and the 3-month postoperative period uneventfully. The two intra-operative deaths (group B) were due to ventricular fibrillation (VF) that occurred before the use of fibrin glue. In both cases, VF occurred after opening of the mammary artery following anastomosis. The ECG showed ST-elevation, indicating that the VF was probably due to ischaemia. Resuscitation was tried but was not successful. Later, the anastomoses of the dead animals were examined and found to be patent; however, a stenosis could not be ruled out. Since no Doppler flow was measured in these cases, competitive flow could not be demonstrated but was possible. In groups A and C, all five animals survived while in group B only three survived. The pigs thrived and gained weight normally, regardless of the group. The intra-operative course of all the surviving pigs was uneventful. The mean operation time was 92 ± 15.2 min in group A, 104.2 ± 15.9 min in group B and 99.4 ± 21.3 min in group C \((p = 0.565)\). The mean blood loss was 140 ± 41.8 ml in group A, 148 ± 32.7 ml in group B and 118 ± 54.1 ml in group C \((p = 0.549)\). Blood flow of the mammary artery after anastomosis with the LAD was sufficient in all cases. The mean blood flow in group A was 25.2 ± 9.7 ml min⁻¹, in group B 20.7 ± 9.45 ml min⁻¹ and in group C 21.2 ± 4.3 ml min⁻¹. There was no statistical difference \((p = 0.538)\). All animals had an uneventful postoperative course and were sacrificed 3 months postoperatively. There was no wound infection present after sternotomy. None of the animals suffered from fever or showed any other signs of infections in the postoperative period.

3.2. Autopsy

At autopsy, all animals showed perfectly healed sternotomies, and there were no local reactions or inflammatory signs in the treatment areas of the pericardium. In all cases there were marked pericardial adhesions regardless of the anastomotic coating. There was a subjective notion that the animals in which patency of the anastomosis was not achieved the adhesions were more severe. In group A, three of five anastomoses were open; in group B, all anastomoses of the three surviving pigs were patent; and in group C, four of five anastomoses were patent. Statistical analysis of the patency among the three groups was performed with the chi-square test (Pearson’s test) and showed no significant differences \((p = 0.42)\).

3.3. Histological findings

Histological studies confirmed the patency of the LIMA to LAD grafts in most cases. There was no histological evidence of intimal hyperplasia or stenosis due to a perigraft reaction to either of the sealants used (group C TachoSil® or group B fibrin glue). There was, however, some fibroblastic in-growth around the anastomotic sites and evident scar tissue to the surrounding areas. Among the three groups there was no difference in the histological aspect of a patent anastomoses. In obliterated anastomoses there was a strong evidence of scar tissue and pronounced activity of predominately fibroblasts. No remnants of either TachoSil® or fibrin glue were identified (Figs. 1–3).

4. Discussion

The use of glue in a surgical setting has been a long tradition. Even Egyptians 2000 years ago used honey-drenched gauzes to seal wounds [12]. For haemostyptic purposes, first experiments were reported at the beginning of the last century. Here the haemostyptic characteristics of fibrin were first described [13,14]. The fibrin was applied as a powder, with drenched paper or tampons [20]. Fibrinogen and thrombin were first used in the 1940s as tissue glue when nerve ends or skin transplants were glued for bleeding reduction [15,16]. However, back then the fibrinolytic activity in the wound could not be influenced and high concentrations of fibrin solutions were not available. The
Currently the use of surgical sealants such as fibrin glue remains popular among cardiac surgeons, although robust evidence concerning a clear reduction of blood loss and its sequelae such as necessity of blood product substitution, chest tube removal or rethoracotomy for haemorrhage does not exist. The surgeon, however, chooses haemostytic products in an individual situation in order to achieve a dry surgical field and to feel safe at his or her discretion, thereby diminishing operation time. Fibrin glue alone serves many purposes such as sealing of distal or proximal coronary anastomoses or positioning of arterial or venous grafts in order to avoid kinking. However, in some instances, the use of an absorbable fleece in combination with fibrin glue improves local stability of the sealing manoeuvre. In order to facilitate application, prefabricated products such as TachoComb® and consecutively TachoSil® [1,3—5] have been developed.

Many physicians express concerns following the use of fibrin products regarding potentially adverse effects on the morphology of the anastomosis and thus the patency rate. In humans, a systematic appraisal of the morphology is impossible except in those dire cases where a gross and microscopic pathological examination is performed. To our best knowledge, no such study exists elucidating the impact of fibrin glue on coronary anastomoses in these instances. There is however some discussion on the impact of fibrin glue on the outcome of patients after coronary re-vascularisation. Lamm et al. published a paper where the risk of myocardial injury or even death of patients following CABG was significantly higher than in those patients where fibrin glue was not used [21] and therefore suggested that its use should be discontinued. In another study, Goerler et al. arrived at a similar result regarding the outcome if not as distinctive, but the authors pointed out that in their opinion the use of fibrin glue is still safe [22]. Especially the lack of prospective randomisation was criticised. Finally, Cremer wrote an editorial [23] about these studies also criticising the lack of prospective randomisation and that ‘specific information regarding the application of fibrin glue is lacking.’ Especially stating what most of the cardiac surgeons think: ‘...the fact that fibrin glue is used, tells us that there were some problems,’ meaning that the morbidity and mortality in a cohort of cases that do not go smoothly is naturally higher.

Due to these reasons, we performed a large animal study for the purpose of a systematic approach to the chronic course of LIMA to LAD grafts in the presence of fibrin glue. Interestingly, there was no difference in the gross examination or histological evaluation among the three study groups. Therefore, a detrimental effect of either fibrin glue or fibrin glue attached to an absorbable fleece (TachoSil®) on coronary anastomoses could not be shown. At 3 months postoperatively, no remnants or secondary evidence of fibrin glue or fibrin glue with collagen flece were found. Such effects have previously been studied by us for other surgical adhesives based on glutaraldehyde or formaldehyde [11] in a similar animal model. In this study, evidence of pronounced histological changes around the anastomoses was generated. At 3 months postoperatively, remnants of the glutaraldehyde or formaldehyde glue were found and considered to be a significant limitation for their use compared to fibrin glue or TachoSil®. The observation of some authors that TachoSil® can prevent or minimise postoperative adhesions [7—9], as shown for the
peritoneum or the pleura, cannot be shared by the outcome of the present study. There was no evidence of a considerable reduction of postoperative adhesions in the pericardium or at the anastomotic site when using fibrin glue or TachoSil®.

4.1. Limitations of the study

In this large animal study, the observation period did not exceed 3 months. Therefore, potential differences in the further postoperative course cannot be ruled out entirely. However, as an entire absence of collagen or fibrin glue remnants were observed after 3 months, it is rather unlikely that adverse effects depending on these agents occur in the further course. The results seen in pigs cannot be readily extrapolated to humans. In general, however, pigs demonstrate a stronger inflammatory response than humans to any surgical procedure. Furthermore, one may speculate that human coagulation components per se provoke a stronger reaction in pigs than in humans and induce immunological reactions as well. As a potential inflammatory response was obviously below the detectable threshold in this study, a more pronounced adverse reaction in humans is rather unlikely. In addition, since the study was performed with only a small number of animals, further investigation is warranted for stronger statistical evidence.

5. Conclusion

In the chronic course of a coronary anastomosis of the LIMA to the LAD, no evidence of adverse effects of TachoSil® or fibrin glue can be observed. As our study suggests, and in consideration of the already vast clinical experience with both agents, TachoSil® or fibrin glue may be used safely in clinical practice for haemostyptic or positioning purposes, even in the direct vicinity of coronary anastomoses.

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References


