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Fibrin glue in coronary artery bypass grafting operations: casting out the Devil with Beelzebub?

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Abstract

Objective: Fibrin sealants are frequently used in aorticcoronary bypass operations. Although they are considered to be clinically safe, we performed a retrospective analysis of our data to examine the possible side effects of Tissucol W® fibrin sealant, namely the acute thrombosis of grafts and native coronary arteries resulting in severe myocardial damage and patient deaths. Methods: The data of 2716 patients (2001 male, 715 female) who received an aorticcoronary bypass operation from November 1995 to December 1999 were studied retrospectively. Two groups (group 1: received Tissucol W®, group 2: no sealant used) were compared with respect to an a priori selected set of demographic and clinical variables and with respect to their effect on the outcome using bivariate tabulation. Multiple exploratory assessments of factors possibly related to fatal outcome were done by multiple logistic regression. Results: Nine hundred ninety patients (group 1) received Tissucol W®, 1726 patients (group 2) did not receive it. Mean patient age was 64 ± 9.1 years. Group 1 had a higher risk of death (7.8% vs 2.8%, p < 0.001). The peak values of creatine kinase >500 and creatine kinase-myocardial band >50 were higher in group 1 than in group 2, p < 0.001. Adjusted odds ratios for the risk of fatal outcome were: 2.01 for the use of Tissucol W®, 6.35 for postoperative cardiopulmonary resuscitation, 4.55 for postoperative aortocoronary reoperation. Conclusion: In our analysis an increased risk of myocardial injury or even death was found in coronary artery bypass grafting patients when Tissucol W® fibrin sealant was used intraoperatively.

Keywords: Coronary disease; Revascularization; Fibrin sealant; Early graft occlusion; Myocardial infarction

1. Introduction

Fibrin has been used experimentally since the beginning of the 20th century. During the Second World War, fibrin sealants were used to stop bleeding caused by war injuries. Commercially available fibrin sealants have been available for more than 20 years in both experimental and clinical studies. They are considered to be effective in controlling intraoperative bleeding. They are also considered to be clinically safe although there are many safety concerns regarding the antigenicity of bovine thrombin or aprotinin employed in fibrin sealants.

Nearly all of the different commercially available fibrin sealants use either bovine thrombin or human thrombin derived from pooled plasma (Table 1). The fibrinogen used in these sealants is likewise derived from pooled plasma.

When applied, Tissucol W® forms a white, non-transparent clot, which is comparatively strong and elastic. The clot structure has been described as relatively thick, branching fibrin threads, which are hardly distinguishable from plasma clots. Although most reports demonstrate the clinical safety of fibrin sealants, there are clinical observations showing a transient increase in MAP and SVR in patients where fibrin sealant had been applied topically to the surface of the pericardium. It has been postulated that the application of fibrin sealant directly to the surface of the heart might lead to vasospasm of coronary grafts or even the native coronary circulation [1]. From animal experiments with pigs it is further known that the intravenous application of 60 IU thrombin/kg leads to a rapid decline in MAP causing all pigs to die. Subsequent necropsy revealed extensive pre mortem clotting in the bovine thrombin group [2].

In clinical studies, adverse immunological reactions were observed early [3]. In addition there are several reports...
about episodes of hypotension associated with fibrin sealant administration [4]. Sudden deaths immediately following fibrin sealant application [5] are reported as well. Severe anaphylactic reactions [6] and coagulation disorders [7] are also known and are usually attributed to the bovine thrombin used in the sealant. Experiences from pediatric cardiac surgery describe a variety of complications associated with fibrin sealants. Low cardiac output and sudden asystole [6] have been reported after the first use of the fibrin sealant and the repeated use of fibrin sealants in pediatric reoperations led to major complications [8].

In 1998 we were confronted with an increased early graft occlusion rate in our department. At the time we did not have an explanation for it and undertook an investigation at great effort to find the reason. After considering many possible causes for the graft failure we noticed that all patients suffering from early graft occlusion received Tissucol® fibrin sealant at the end of the operation. We decided to analyze the patients retrospectively to get a more conclusive answer as to the possible adverse role fibrin sealants could play in aortocoronary bypass surgery. The results of this analysis are presented here.

2. Methods

2.1. Fibrin sealant used

In all procedures there was only Tissucol® fibrin sealant (Immuno, Austria) used. The thrombin concentration per ml of the sealant is 250 U/ml (after 1:1 mixture with the fibronectin solution) per unit used. The bovine aprotinin level used in the sealant for a 3 ml application is 4500 KIU [9]. Since the exact number of units used during an aortocoronary procedure was not clearly documented we only considered the mere use of fibrin sealant.

2.2. Indications for usage of fibrin glue

Fibrin glue is used mainly to stop bleeding on the epicardial surface or for graft fixation. Since the indications for the use of the fibrin sealent were not clearly stipulated in the operation records of most of the cases, we only considered whether or not Tissucol® was administered during the procedure.

2.3. Patients

We performed 2716 isolated or combined coronary artery bypass operations from November 1995 to December 2000 at the Heart Clinic of the University Munich at Augustinum. This clinic is a direct dependent of the Department of Cardiac Surgery of the university hospital Grosshadern and is run by the University of Munich.

2.4. Operative technique

All procedures were done either on the beating heart or by use of the extracorporeal circulation with standard surgical techniques, i.e., after ITN sternotomy was performed simultaneously to saphenectomy, cardiac arrest was initiated either by cold blood cardioplegia (Koehler, Austria) or by HTK-solution (Custodiol®), Dr Franz Köhler Chemie, Alsbach-Hähnlein, Germany). Peripheral anastomoses were done using Prolene 7/0 sutures, central anastomoses using Prolene 6/0 sutures. To perform the peripheral anastomoses the heart was either held by an assistant or fixed with two semielastic gauze bandages [10]. The operations were done by eight different fully qualified cardiac surgeons or by residents under the assistance of the qualified surgeons. Overall, the operations were performed by 15 different surgeons. The intensive care unit was run by the same anesthesiologist throughout the observation period.

After the operation the patients were transferred to a specialized intensive care unit adjacent to the OR. Immediately upon arrival blood values for routine laboratory parameters were taken. Creatine kinase (CK) and creatine kinase-myocardial band (CK-MB) values were routinely obtained immediately after the operation and 6 h thereafter. Additional measurements were taken daily for the duration of the patient’s stay on the intensive care unit. If there were clinical necessities or an abnormal increase of the values immediately postoperatively other values were taken on a 6 h basis continuously until a decrease was established. Electrocardiogram was monitored continuously while the patients were in the intensive care unit and rhythm disorders were recorded. In accordance with the guidelines of the German Society for Thoracic and Cardiovascular Surgery we only considered CK values over 500 and CK MB values over 50 to be of significance. Intra aortic counterpulsation was used whenever there was a hemodynamic impairment, which could not be solved by drug administration.

2.5. Data analysis

All patients’ records of this study were analyzed retrospectively. The data were retrieved from the database of the Department of Cardiac Surgery of the University of Munich. In the first step, all records of patients being operated from November 1995 to December 1999 were selected. Laboratory values were compared to values in the database of the Department of Clinical Chemistry of the hospital of the University of Munich. This was necessary because our own database did not contain all CK and CK-MB values for the years 1995 and 1996. Data missing (CK and CK-MB values) in our records were retrieved from the Department of Clinical Chemistry. Finally, the analysis database was saved on March...
The aim of the exploratory analysis was to specify the risk of fibrin glue on postoperative mortality (outcome). Postoperative mortality was defined as patient death within 30 days after an operation. The two groups (group 1: Tissucol® fibrin glue used vs group 2: not used) were compared with respect to an a priori selected set of demographic and clinical variables (Table 2) as well as with perioperative variables and events (Table 3). Bivariate tabulation was also done in order to assess these variables, if considered relevant for the outcome, as well as the usage of fibrin glue with respect to their effect on the outcome (Table 4).

All bivariate tabulations, whether stratified for fibrin glue usage or for outcome, are based on descriptive statistics appropriate to the measurement scale of each variable. Additionally, chi-square tests as well as Mann–Whitney U-tests were performed for dichotomous and ordinal as well as continuous variables, respectively. Due to the exploratory rather than confirmatory use of these tests, p-values were not adjusted with respect to a multiple alpha level.

Multiple exploratory assessments of the factors possibly related to fatal outcome were done by means of multiple logistic regression. Since it was not known which factors contributed to postoperative fatality, a stepwise analysis was performed; starting with the full main effects model, using the variables contained in Table 5 as well as surgeon details (dummy-coded). The local alpha level at each backward selection stage was set at 5%. All analyses were done with SPSS for Windows, Version 10.

To explore potential effects of the additive EuroScore on the results of the final multiple logistic regression model estimates, additional data required to calculate this score were retrieved from the patient records. The calculation of the additive EuroScore was, due to the limited data available, based on age, sex, extracardiac arteriopathy, neurological dysfunction disease, previous cardiac surgery, serum creatinine, recent myocardial infarct, pulmonary hypertension, emergency and other than isolated CABG. No case with active endocarditis, surgery on thoracic aorta, and postinfarct septal rupture occurred in the sample.

The final hospital reports of the deceased patients in both groups were screened to evaluate the rate of documented early graft occlusions (seen during re-exploration, autopsy or coronary angiography).

The lethality rate for the years 2001—2003 was calculated later on to see a possible effect of the non-use of Tissucol® (within that period there was no procedural change and the operations were done by the same surgeons).
### Table 5
Bivariate relationship of risk factors and outcome (% or mean ± SD).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Outcome</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male</td>
<td>Exitus</td>
<td>69.0</td>
</tr>
<tr>
<td>Patient age &gt;70 years</td>
<td>Exitus</td>
<td>54.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Outcome</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>Exitus</td>
<td>7.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Exitus</td>
<td>30.2</td>
</tr>
<tr>
<td>Elective reoperation</td>
<td>Exitus</td>
<td>11.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operative procedure</th>
<th>Outcome</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrin glue used</td>
<td>Exitus</td>
<td>61.1</td>
</tr>
<tr>
<td>Number of vein grafts</td>
<td>Exitus</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Use of 1 or more mammary arteries</td>
<td>Exitus</td>
<td>74.6</td>
</tr>
<tr>
<td>CABG* and AVR* or AAA*</td>
<td>Exitus</td>
<td>17.5</td>
</tr>
<tr>
<td>CABG and carotis desobliteration</td>
<td>Exitus</td>
<td>4.8</td>
</tr>
<tr>
<td>Aortic cross clamp time &gt;90 min</td>
<td>Exitus</td>
<td>32.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perioperative complications</th>
<th>Outcome</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative re-operation</td>
<td>Exitus</td>
<td>38.1</td>
</tr>
<tr>
<td>CPR**</td>
<td>Exitus</td>
<td>14.3</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>Exitus</td>
<td>13.5</td>
</tr>
<tr>
<td>Angiography</td>
<td>Exitus</td>
<td>9.5</td>
</tr>
<tr>
<td>Delayed or missing R-progression</td>
<td>Exitus</td>
<td>10.3</td>
</tr>
<tr>
<td>ST-elevation</td>
<td>Exitus</td>
<td>25.4</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>Exitus</td>
<td>15.1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Exitus</td>
<td>21.4</td>
</tr>
</tbody>
</table>

* Coronary artery bypass grafting.
** Aortic valve replacement.
* Aorta ascenders replacement.
* Cardiopulmonary resuscitation.

### 2.6. History of the paper
After having finished the study in March 2002, Baxter Inc., Heidelberg, Germany and the Paul Ehrlich Institut, Langen, Germany were informed about the results. A first manuscript of this paper in addition to a CD-ROM containing all relevant data of this study was given to the Paul-Ehrlich-Institut. Additionally, we reported the possible influence of Tissucol® on the deaths of 54 patients to the Paul-Ehrlich-Institut. Subsequently the validity of our data was evaluated by a board commission of the Ludwig-Maximilians-University Munich and the Paul-Ehrlich-Institut. The Paul-Ehrlich-Institut organized another retrospective study at the University of Hannover. The use of Tissucol® in aortocoronary procedures was officially forbidden by the Ludwig-Maximilians-University Munich in 2002. In November 2004 the validity of the data was approved by the Paul-Ehrlich-Institut and the board commission of the Ludwig-Maximilians-University Munich. Publication of the data was recommended by all involved authorities. In 2006 the editorial letter from the German Society of Thorax and Cardiovascular Surgery was finished and the paper was sent in for publication. The product description has meanwhile been changed, stating, that special care should be taken when using Tissucol® in aortocoronary bypass operations. The usage of Tissucol® in aortocoronary operations at the Ludwig-Maximilians-University Munich was drastically reduced in 2001 and completely prohibited by the Ludwig-Maximilians-University Munich in May 2002.

### 3. Results
A total of 2732 patients (1202 male, 720 female) were operated on. Sixteen patients (11 male, 5 female) were excluded from the analysis due to missing data. Ten patients had multiple operations. If the reoperation took place within the first 30 days, only the first operation was counted. Otherwise the second one was counted. Thus 2716 patients (2011 male, 715 female) were included in the study. Nine hundred and ninety patients (group 1) were intraoperatively treated with Tissucol® fibrin sealant, 1726 patients did not receive any adhesive sealant (group 2). Patients who received Tissucol® fibrin sealant had a higher risk of dying within the first 30 days postoperatively (7.8% vs 2.8%).

The mean patient age was 64 ± 9.1 years. Table 2 shows the demographic and clinical description of our patients. A higher percentage of the patients in group 1 suffered from pulmonary hypertension, whereas a higher percentage of patients in group 2 suffered from hypercholesterolemia. The other comonitant diseases showed no differences at the local 5% alpha level.

Table 3 displays perioperative data. Aortic cross clamp time and bypass time were higher in group 1. Mammary arteries were used more often in group 2. There was almost no difference regarding the average number of vein grafts used. The perioperative need for cardiopulmonary resuscitation, and for the circulatory support via the IABP was elevated in group 1, as was the risk of suffering from perioperative ventricular fibrillation.

Table 4 shows the overall outcome (mortality) of both groups as well as CK and CK-MB peak values as important signs for myocardial damage. Mortality was higher in group 1 compared to group 2 ($p < 0.001$). Also the peak values of the CK >500 and CK-MB >50 were higher in group 1 than in group 2.

Table 5 shows the bivariate relationships of risk factors and outcome (mortality). The use of mammary arteries, the percentages of perioperative arterial and ventricular fibrillation, perioperative resuscitation, patient age over 70 years, aortic cross clamp time over 90 min, intraoperative application of fibrin glue and the need for perioperative coronary angiographies were higher in the non-survivors when compared to the survivors at a local alpha level of 5% each. This was also true for CABG operations combined with either aortic valve replacements or replacements of the ascending aorta as well as CABG operations combined with carotis desobliterations. The rate was higher in the survivor group, only in respect to the use of mammary arteries.

### Table 6
Adjusted odds ratios and 95% confidence intervals

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of fibrin glue</td>
<td>2.01</td>
<td>1.34</td>
</tr>
<tr>
<td>Patient age &gt;70 years</td>
<td>2.71</td>
<td>1.83</td>
</tr>
<tr>
<td>Aortic cross clamp time &gt;90 min</td>
<td>2.02</td>
<td>1.32</td>
</tr>
<tr>
<td>Postoperative ventricular fibrillation</td>
<td>3.95</td>
<td>1.62</td>
</tr>
<tr>
<td>Postoperative angiography</td>
<td>2.90</td>
<td>1.30</td>
</tr>
<tr>
<td>Postoperative CPR*</td>
<td>6.35</td>
<td>2.58</td>
</tr>
<tr>
<td>Perioperative reoperation</td>
<td>4.55</td>
<td>2.89</td>
</tr>
</tbody>
</table>

Nagelkerke $R^2 = 0.221$. $p$-values corresponding to the effect estimates were $<0.01$.

* Cardiopulmonary resuscitation.
The results of the multiple logistic regression analysis are contained in Table 6. As expected, fatal outcome was associated with serious perioperative events. After adjusting for the other factors in the multiple main effects model, the risk of a fatal outcome after the intraoperative use of fibrin glue was about twice as high in group 1 as in group 2.

The model containing all variables from Table 6 plus the EuroScore increased the effect of fibrin glue only slightly from 2.01 to 2.06. The EuroScore effect in this model was 1.18 (95% confidence interval: 1.07–1.30), with median values of 3 (interquartile range 1–5) and 3 (interquartile range 1–4) in the group where Tissucol® was used and not used, respectively, and 4 (interquartile range 3–6) and 3 (interquartile range 1–4) in those patients who died and who survived, respectively.

There were documented early grafts occlusions in 23 deceased patients in group 1 and in 6 deceased patients of group 2.

From 2001 to 2003, 1701 aortocoronary operations were performed with an overall lethality rate of 2.1%. The lethality rate after the complete stop of Tissucol® was 1.7% (2002 and 2003).

4. Discussion

Fibrin sealants are used today in many surgical disciplines. Their routine usage has hardly ever been questioned. If queries do arise they usually consider the possible anti- genicity of thrombin and aprotinin and possible immunological side effects. There are only case reports of severe hemodynamic impairment after the use of fibrin sealants, mainly from pediatric experiences. The pathomechanisms relevant to cardiac surgery discussed thus far include allergic reactions and possible spasms of grafts and coronary arteries. There has not yet been a prospective or retrospective study for the evaluation of hemodynamic impairment after the use of fibrin sealants during an aortic bypass operation. Our statistics clearly show an increased risk for CABG patients to suffer myocardial injury (increased CK and CK-MB values) or even to die when Tissucol® fibrin sealant was used perioperatively.

We had several cases with acute thrombosis of the bypass grafts after Tissucol® was applied in proximity to the anastomoses with the coronary arteries or the aorta ascenders. Immediate embolectomy showed a fresh fibrin clot in the lumen of the grafts in each case. We noticed acute thrombosis of the central parts of three saphenous vein grafts when the fibrin sealant was applied in proximity to the central anastomoses. When fibrin sealants are used in an aortocoronary bypass operation, an immediate clotting of the sealant is required in order to prevent thrombin from penetrating the bypass graft or the coronary artery wall; otherwise there is a risk of myocardial edema or thrombosis of native coronary arteries or bypass grafts caused by transmural diffusion of free thrombin. A prolonged clotting time of the sealant leaves the sealant mobile and allows it to penetrate the anastomoses and reach the blood before it clots. Thromboembolic complications could be the possible consequences [11]. In our experience the immediate clotting of the sealants is unfortunately the exception. Normally it takes a few minutes to achieve a stable sealant at the site of bleeding. Even if there is no anastomosis in close proximity to the applied sealant there might still be a considerable diffusion of thrombin through the wall of bypass grafts leading to early graft occlusion or in the native coronary arteries leading to myocardial ischemia. Animal studies have demonstrated the destruction of muscle flaps when thrombin was applied to the free flaps [12]. A further uncertainty in clinical settings is the fact that the release of thrombin from a Tissucol® clot is two times greater when the sealant is applied sequentially with a syringe rather than when Duploject application is performed [13]. Since both Tissucol® components are frozen and have to be thawed before use there will always be the possibility of a more or less sequential application even when Duploject application is used. Further uncertainties for the unwanted thrombin release are dependant on the efficiency of the mixing of the sealant preparation, the clot porosity and the binding of the thrombin to the clot. Depending on the amount of diffusion, there may be an immediate release of thrombin out of the fibrin clot in the wall of the respective bypass grafts or in the peripheral microcirculation. In addition there may be a delayed release upon fibrinolysis [14]. Thrombin has further been shown to enhance the adhesion of platelets to human aortic endothelial cells [15] and it was suggested that this adhesion might play an important role in the formation of microthrombi after circulatory disturbance [16]. Besides early graft occlusion, the result would once more be myocardial edema and myocardial ischemia. In aortocoronary surgery even minor embolizations in the microcirculation may lead to myocardial infarction. In each of the following, the age of the patient, the fact that it was an aorto coronary reoperation, and the intraoperative use of Tissucol® fibrin sealant showed there was a positive correlation with increased values of CK and CK-MB. With the exception of the positive correlation with the fibrin sealant all other correlations have been described previously [17]. The risk of dying within 30 days after an aortocoronary bypass operation was approximately twice as high for patients who received Tissucol® fibrin glue intraoperatively than it was for those who did not receive it. This ratio was independent of the respective surgeon. Tissucol® fibrin sealant seems to raise the perioperative risk of patients to suffer a myocardial infarction or an early graft occlusion. Considering this and the fact that fibrin sealants containing high concentrations of thrombin are commonly used during aortocoronary procedures, we think that even the well-known benefits of these sealants such as control of bleeding do not justify their unrestricted use in aortocoronary bypass surgery anymore. This thought is further justified since most incidences of unexpected hemodynamic deterioration within our patients who received Tissucol® happened within the first three days after the operation and this corresponds very well with the half-time of thrombin in Tissucol® of approximately 10 days. In order to achieve a conclusive result as to the advantages and disadvantages of fibrin glue application in cardiac surgery, it would be helpful if our results were validated by data from other cardiac surgical units. The risk of a treatment and selection bias should be reduced by doing so. To find a conclusive answer to the clinical safety of fibrin sealants, one has to consider that
the multiple risk assessment undertaken in the present retrospective analysis was done in an exploratory manner. Independent confirmatory analysis of the multiple model identified here is mandatory. Such analysis must be done using an independent data set. From a methodological point of view such a replication should not be done by retrospective analysis but by a randomized clinical trial. Only then, confusion (e.g., by implicit indication) can be avoided in a conclusive way. There may, however, be serious ethical concerns in doing so especially considering the significant drop in lethality we experienced after not using Tissucol® in aortocoronary procedures at all. Based on the present findings we suspect that the increased risk of fatality associated with the use of fibrin glue will be confirmed.

Although we only used Tissucol® fibrin sealant, the same considerations are probably valid for most other commercially available fibrin sealants, which contain significant thrombin concentrations (Table 1). We suggest however, independent to further studies, that manufacturers not only endeavor to reduce the amount of thrombin to lower the risk of embolization and intravascular thrombosis but also that the entire production is maintained in an autologous system to reduce the immunological risks involved. We further conclude that the use of fibrin sealants in aortocoronary procedures should be restricted to the treatment of otherwise not controllable bleeding until further confirmatory analysis must be done for its unrestricted use in future patients.

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References

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