Impact of hemostasis and blood loss on outcome after liver surgery

de Boer, Marieke T.

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Fibrin sealant for prevention of resection surface-related complications after liver resection. A randomized controlled trial

Marieke T. de Boer
Joost M. Klaase
Cornelis Verhoef
Ronald M. van Dam
Thomas M. van Gulik
I. Quintus Molenaar
Koop Bosscha
Cornelis H.C. Dejong
Eric J. van der Jagt
Robert J. Porte; for the FRESCO Trial Group

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ABSTRACT

Objective: To evaluate efficacy of fibrin sealant in reducing resection surface-related complications in liver surgery.

Background: Bile leakage, bleeding and abscess formation are major resection surface-related complications after liver resection. It is unclear whether application of fibrin sealant to the resection surface is effective in reducing these complications.

Methods: In a multicenter, randomized trial in 310 non-cirrhotic patients undergoing liver resection, we compared prophylactic application of fibrin sealant to the resection surface (156 patients) with no application of fibrin sealant (154 patients). In addition to clinical assessments, patients underwent protocolized CT-scan one week postoperatively. Primary endpoint was a composite of postoperative resection surface-related complications (bile leakage, bleeding or abscess), as adjudicated by a clinical-events committee that was unaware of the study-groups assignments.

Results: Overall rate of resection surface-related complications was not different between the two groups: 24% (38/156 patients) in the fibrin sealant group and 24% (37/154 patients) in the control group. Bile leakage was detected in 14% of patients in the fibrin sealant group and in 14% of controls. CT-scans showed a fluid collection at the resection surface ≥100mL in 28% of patients in the fibrin sealant group and in 26% of controls (P value =0.800). The rate of reinterventions for resection surface-related complications (12% vs. 10%; P value =0.492) and severity of complications did also not differ between the two groups.

Conclusion: This randomized multicenter trial shows that prophylactic application of fibrin sealant at the resection surface after liver resections does not lead to a reduction in the incidence or severity of postoperative bile leakage or other resection surface-related complications. (Controlled trial number, ISRCTN85205641)
INTRODUCTION
Mortality and morbidity of liver surgery have decreased due to better patient selection, improvement in surgical techniques and perioperative management. Postoperative bleeding and bile leakage from the remnant liver resection surface, however, remain major complications. Bile leakage from the liver resection surface has been described in 1-14% of patients, leading to additional interventions, prolonged hospital stay, mortality, and higher costs.2-7

Fibrin sealants are commercial or homemade preparations of human fibrinogen and human or bovine thrombin that are mixed together on a wound surface to form a fibrin gel. Several studies have shown the safety and efficacy of these products in promoting local hemostasis during surgery.8-17 The worldwide market for these products is rapidly expanding and annual global sales are estimated around 1.5 billion US dollars.18 In many countries fibrin sealants are registered as adjuncts to achieve hemostasis at the liver resection surface in liver surgery. Apart from the hemostatic capacities, surgeons are also using these agents prophylactically with the assumption that this will reduce postoperative leakage of blood or bile from the resection surface.17,19,20 National surveys performed in the Netherlands and Japan have indicated that 80% of liver surgeons use fibrin sealants.19,21 However, half of them had doubts about their efficacy in reducing resection surface-related complications.19 Indeed, formal scientific evidence for this is lacking.

To test the hypothesis that the application of fibrin sealant to the raw surface of the liver remnant after resections decreases the incidence of resection surface-related complications, we conducted a multicenter, randomized trial comparing prophylactic application of fibrin sealant with no application of fibrin sealant.

METHODS
Patients
Patients were enrolled at 7 sites in the Netherlands. All patients provided written informed consent. Adult patients of 18 years and older who underwent resection of at least one liver segment or a non-anatomical resection were eligible for inclusion in the study. Exclusion criteria were: wedge resections, concomitant extrahepatic bile duct resection or bowel resection, cirrhosis, hemostatic disorders, polycystic liver disease, pregnancy, and history of hypersensitivity or allergic reaction to any plasma derived product.

Study design
This was a randomized, controlled study that was initiated by the investigators. Fibrin sealants were kindly provided by the distributor Johnson & Johnson, but this company was not involved in data collection and analysis. The study was coordinated and the data was analyzed by the coordinating study group of the University Medical Center Groningen. Medical ethical review committees at participating institutions approved the study protocol, and the study was performed in accordance with it.

Our objective was to study the efficacy of fibrin sealant in reducing resection surface-related
complications, including bile leakage, bleeding, or abscess formation at the resection surface, in patients undergoing liver resection. The hypothesis was that prophylactic application of fibrin sealant to the dry resection surface of the liver after a resection reduces the rate of resection surface-related complications.

**Study treatment and randomization**

The fibrin sealant used in this study was Quixil® (Johnson & Johnson Medical, New Brunswick, NJ). In the U.S. this fibrin sealant is approved and marketed under the name Crosseal®. It consists of a package containing two separate vials of 5 ml and a double-syringe spray-device. Vial I contains a concentrate of human fibrinogen (40-60 mg/mL) and tranexamic acid, a synthetic antifibrinolytic agent (85-105 mg/mL). Vial II consists of a high concentration of human thrombin (800-1200 IU/mL). After obtaining hemostasis and biliostasis at the liver resection surface by conventional techniques such as suture or clip application, or coagulation, patients were randomized. In the treatment group, 10 mL fibrin sealant was sprayed on the resection surface and on the bare surface of the diaphragm. In the control group nothing was applied. All local investigators were instructed by the company prior to trial commencement in the use of fibrin sealant.

A statistician who was not otherwise involved in the conduct of the study prepared the randomization list, using computer random number generation. Treatment allocation employed a sequentially numbered, opaque and sealed envelope system. Patients were stratified by center and by benign versus malignant diagnosis. Patients, who appeared to be irresectable, in whom only a wedge resection was performed, or in whom we could not achieve hemostasis without the use of a fibrin sealant, were not randomized.

Surgeons could not be kept unaware of treatment allocation, but patients, local investigators responsible for data gathering, data analysts, and radiologists did remain unaware of the study group assignment.

**Data collection**

Standard preoperative demographic and intraoperative characteristics were recorded. Postoperative data collection, including drain fluid analysis, was focused on detection of resection surface-related complications and general complications of liver surgery. At one week after surgery, a protocolized contrast enhanced CT-scan of the upper abdomen and chest was performed to objectively detect and quantify fluid collections in proximity of the resection surface of the liver or pleural effusion. CT images were collected in the coordinating center and were judged by two radiologists who were blinded for the study group assignment. Patients were followed at least until 30 days after discharge.

**Primary and secondary endpoints**

Primary endpoint was the occurrence of a resection surface-related complication, including bile leakage, bleeding or abscess, as detected by clinical symptoms, reinterventions, or protocol CT
scan (fluid collections ≥100 mL). These endpoints were analyzed individually as well as a composite endpoint. Bile leakage was defined as drainage of bile or bile containing fluid (bilirubin concentration ≥100 µmol/L) from the abdominal wound or drain, or intra-abdominal collection of bile confirmed at the time of reoperation or by percutaneous drainage, or cholangiographic evidence of bile leakage. Bleeding was defined as leakage of blood from an abdominal drain with hemodynamic instability, or the need for blood transfusion within 24hrs postoperatively, or evidence of a hematoma in proximity to the resection surface of the liver. Abscess was defined as a localized fluid collection near the resection surface, requiring radiological or surgical drainage based on clinical, radiological, or microbiological evidence of infection.

Secondary endpoints were: amount of drain fluid production (mL/day), hemoglobin (mmol/L) and bilirubin concentration (µmol/L) in drain fluid during the first three days postoperatively; postoperative morbidity and mortality. Complications were graded according to the Clavien-Dindo classification.22,23

**Statistical analysis**

For calculation of the required study-population size, resection surface-related complications such as bile leakage, bleeding, and/or abscess formation, and fluid collections (≥100 mL) in proximity to the resection surface detected on CT-scan, were considered the most important target variables. Based on experience and previous publications, overall proportion of these complications was estimated to be 15-20% when no fibrin sealant was used. A difference of about 50% was considered clinically significant. Based on this, we calculated that 220 patients were needed in each group to achieve 80% power at the 5% significance level. Because the exact incidence of CT-scan detected fluid collections was not known, we planned an interim analysis after 180 patients to determine the incidence of the composite primary endpoint in the control group only. This interim analysis, performed by an independent statistician, revealed a composite primary endpoint rate in the control group of 30.4%. This resulted in a recalculated study size of 131 patients in each group. To compensate for potential dropout it was decided to continue the study with enrollment of 150 patients in each group.

All analyses were based on intention-to-treat methods. Missing data were treated as missing according to a list wise deletion approach. Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as number and percentage. Comparisons of categorical variables between the two study groups were performed with the use of Fisher’s exact test or chi-square tests. For comparison of continuous variables we used the Mann-Whitney U test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of PASW Statistics Software, version 18.0 (SPSS, Chicago, IL).
RESULTS

Patients and surgical characteristics

Overall, 310 patients were randomized in 7 centers in the Netherlands between June 2006 and June 2010. (Figure 1) No patients were lost to follow-up. The median follow-up was 39 days, ranging from 33 to 149 days. In total, 156 patients were assigned to the sealant group and 154 patients to the control group. The groups were balanced with regard to baseline characteristics, indications for liver resection, and surgical characteristics. (Table 1) The majority of patients underwent liver resection because of colorectal metastases (74% in both groups) and 52% of the resections were major liver resections, defined as resection of 3 or more segments. The size of the resection surface did not differ between groups. Overall, a drain was placed at the resection surface in 68% of the patients and a postoperative CT scan was performed in 95% of the patients (no significant differences between the groups).

Figure 1. Enrollment and Randomization
Table 1. Baseline and Surgical Characteristics of the Patients, According to the Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fibrin Sealant (n=156)</th>
<th>Control (n=154)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age - yr</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>62 (53-68)</td>
<td>61 (51-69)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Male sex - no. (%)</strong></td>
<td>83 (53)</td>
<td>76 (49)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Tumor type - no. (%)</strong></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Colorectal metastases</td>
<td>116 (74)</td>
<td>114 (74)</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>8 (5)</td>
<td>8 (5)</td>
<td></td>
</tr>
<tr>
<td>Other malignant tumor</td>
<td>7 (5)</td>
<td>10 (7)</td>
<td></td>
</tr>
<tr>
<td>Benign tumor</td>
<td>25 (16)</td>
<td>22 (14)</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy &lt; 3 months before surgery - no. (%)</strong></td>
<td>30 (20)</td>
<td>17 (12)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Previous abdominal surgery - no. (%)</strong></td>
<td>121 (78)</td>
<td>120 (78)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Previous liver surgery - no. (%)</strong></td>
<td>19 (12)</td>
<td>15 (10)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Preoperative laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin - mmol/l</td>
<td>8.5 (7.8-9.0)</td>
<td>8.5 (7.9-9.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Serum bilirubin - μmol/l</td>
<td>10 (7-14)</td>
<td>9 (7-14)</td>
<td>0.42</td>
</tr>
<tr>
<td>Serum creatinin - μmol/l</td>
<td>74 (64-86)</td>
<td>76 (66-86)</td>
<td>0.46</td>
</tr>
<tr>
<td>Platelet count - 10E9/l</td>
<td>243 (199-295)</td>
<td>244 (201-307)</td>
<td>0.95</td>
</tr>
<tr>
<td>Serum alanine aminotransferase - U/l</td>
<td>27 (17-37)</td>
<td>24 (18-32)</td>
<td>0.52</td>
</tr>
<tr>
<td>Prothrombin time - sec</td>
<td>10.7 (10.4-11.2)</td>
<td>10.7 (10.4-11.6)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Surgical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of liver resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major resection - no. (%)†</td>
<td>84 (54)</td>
<td>76 (49)</td>
<td>0.50</td>
</tr>
<tr>
<td>Inflow occlusion - no. (%)‡</td>
<td>38 (24)</td>
<td>37 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>Resection combined with RFA- no. (%)§</td>
<td>14 (9)</td>
<td>17 (11)</td>
<td>0.58</td>
</tr>
<tr>
<td>Parenchymal transection technique - no. (%)§</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasonic</td>
<td>57 (37)</td>
<td>55 (36)</td>
<td></td>
</tr>
<tr>
<td>Electric coagulation based</td>
<td>43 (28)</td>
<td>31 (20)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>55 (35)</td>
<td>66 (43)</td>
<td></td>
</tr>
<tr>
<td>Clamp crush</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Size resection surface - cm²¶</td>
<td>75 (43-101)</td>
<td>72 (38-100)</td>
<td>0.73</td>
</tr>
<tr>
<td>Drain placed at resection surface - no. (%)</td>
<td>106 (68)</td>
<td>106 (69)</td>
<td>0.90</td>
</tr>
<tr>
<td>CVP during transection - mmHg</td>
<td>4 (2-6)</td>
<td>4 (3-6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Estimated intra-operative blood loss - ml</td>
<td>675 (300-1140)</td>
<td>550 (300-1000)</td>
<td>0.30</td>
</tr>
<tr>
<td>Intraoperative RBC transfusion - no. units (%)</td>
<td>24 (15)</td>
<td>14 (9)</td>
<td>0.12</td>
</tr>
<tr>
<td>CT scan 1 week after resection - no. (%)#</td>
<td>149 (96)</td>
<td>145 (94)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

* To convert values for hemoglobin to g/dl, multiply by 1.650. To convert values for bilirubin to mg/dl, divide by 88.4. RFA denotes radiofrequency ablation of tumor nodules in the remnant liver, IQR interquartile range, and RBC red blood cells.
† Major liver resection was defined as resection of at least 3 liver segments
‡ Inflow occlusion (Pringle maneuver) during liver parenchyma transection
§ Ultrasonic based parenchymal transection means use of CUSA; electric coagulation based means use of argon or diathermia transection, radiofrequency transection devices (Habib sealer or tissue link) or sealing devices (Ligasure); Combined means a combination ultrasonic and electric coagulation.
¶ The size of the resection surface was approximated with the surface area equation of an ellipse: A=πab (a and b were measured after resection, and represent the two perpendicular diameters of the resection surface, both divided by 2)
# Contrast enhanced CT scan of the abdomen and chest was made according to study protocol at one week after surgery: volumetry of fluid collections at the resection surface or pleural effusions were calculated by a radiologist who was unaware of the study group assignment.
Primary endpoint

Resection surface-related complications, defined as a composite endpoint of bile leakage, bleeding or abscess, were observed in 24% of patients in both study groups. (Table 2) Bile leakage was diagnosed in 14% of the patients in both groups. Incidence of postoperative bleeding was 10% in the sealant group, versus 7% in the control group, and the incidence of abscess formation at the resection surface was 6% in the sealant group versus 8% in the control group. None of these differences was statistically significant.

The overall incidence of bile leakage requiring a reintervention was 7%, with no significant difference between the groups. The overall rate of reinterventions for resection surface-related complications was also not different between the two groups (12% in sealant group, compared to 10% in controls).

Table 2. Characteristics of Postoperative Resection Surface Related Complications, According to the Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fibrin Sealant (n=156)</th>
<th>Control (n=154)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint bile leakage, abscess or bleeding at resection surface - no. (%)</td>
<td>38 (24)</td>
<td>37 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bile leakage*</td>
<td>22 (14)</td>
<td>21 (14)</td>
<td>1.00</td>
</tr>
<tr>
<td>Grade 1 §</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abscess†</td>
<td>10 (6)</td>
<td>12 (8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bleeding‡</td>
<td>18 (11)</td>
<td>11 (7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Grade 2</td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Any reintervention for resection surface related complications - no. (%)</td>
<td>19 (12)</td>
<td>15 (10)</td>
<td>0.59</td>
</tr>
<tr>
<td>Surgical reintervention</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Radiological reintervention</td>
<td>13 (8)</td>
<td>13 (8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Endoscopic reintervention</td>
<td>9 (6)</td>
<td>4 (3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Protocol postoperative CT scan - no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid collection at resection surface &gt;100 ml</td>
<td>41 (28)</td>
<td>38 (26)</td>
<td>0.90</td>
</tr>
<tr>
<td>Composite endpoint bile leakage, abscess, bleeding or reintervention or fluid collection at resection surface &gt;100 ml on CT scan - no. (%)</td>
<td>66 (44)</td>
<td>58 (40)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* Bile leakage was defined as drainage of bile from the abdominal wound or drain (bilirubin concentration >100 µmol/l or > 1.13 mg/dl), or intra-abdominal collection of bile (biloma) confirmed at the time of reoperation or percutaneous drainage, or cholangiographic evidence of biliary leakage.
† Abscess was defined as a localized fluid collection near the resection surface, requiring radiological or surgical drainage based on clinical, radiological, or microbiological evidence of infection
‡ Bleeding was defined as leakage of blood via the drain with hemodynamic instability or the need for blood transfusion within 24 hours postoperatively, or evidence of a hematoma in proximity to the resection surface of the liver.
§ Grading complications according to Clavien-Dindo classification.22,23
Secondary endpoints and safety
Median bilirubin concentration in drain fluid at day 1 was slightly lower in the sealant group, compared to the control group. (Table 3) Although this difference was statistically significant, clinical significance was minimal as there was no difference in the overall incidence of postoperative bile leakage. Total amount of drain production during the first three postoperative days and the duration of drainage did also not differ between the two groups.

There were no differences in microbiology-confirmed intra-abdominal infections in the fibrin sealant group and control group (11.5% vs. 10.4%, \( P \) value = 0.76). There were no side effects reported of the application of fibrin sealant, such as air-embolism or allergic reactions.

The incidence and severity of general postoperative complications, graded according to the Clavien-Dindo classification, was not different in both groups. (Table 4) Mortality was slightly higher in the sealant group, but this was not statistically significant. In none of the patients who died, the cause of death could be related to the use of fibrin sealant.

<table>
<thead>
<tr>
<th>Table 3. Drain Fluid Analysis, According to the Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Mean drain volume at day 1 to 3 - ml/day median (IQR)</td>
</tr>
<tr>
<td>Hemoglobin at day 1 - mmol/l* median (IQR)</td>
</tr>
<tr>
<td>Bilirubin at day 1 - µmol/l median (IQR)</td>
</tr>
<tr>
<td>Duration drainage - days median (IQR)</td>
</tr>
</tbody>
</table>

* To convert values for hemoglobin to g/dl, multiply by 1.650. To convert values for bilirubin to mg/dl, divide by 88.4. IQR denotes interquartile range.
DISCUSSION

Contrary to the initial expectations, we found that prophylactic application of fibrin sealant at the dry resection surface of the remnant liver does not lead to a reduction in the incidence or severity of resection surface-related complications after liver resection. We found no significant differences in the incidence of postoperative bile leakage, bleeding, or abscess formation in patients treated with or without fibrin sealant. In addition, there were no significant differences in overall postoperative morbidity or mortality. In general, the rate of resection surface-related complications, as well as overall morbidity and mortality were comparable to what has been reported in recent literature.\textsuperscript{4,5,6,12}

In liver surgery, fibrin sealants have been registered as adjuncts to stimulate hemostasis.\textsuperscript{10,13,15-17} Some studies have suggested that fibrin sealant may also reduce the incidence of postoperative bile leakage,\textsuperscript{11,14} although this could not be confirmed by others.\textsuperscript{12,13} All previous studies, however, were

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Variable & Fibrin Sealant (n=156) & Control (n=154) & P Value \\
\hline
Overall postoperative complications according to Clavien-Dindo – highest grade per patient - no. (%)\textsuperscript{*} & & & 0.14 \\
No complications & 74 (47) & 65 (42) & \\
Grade 1 & 8 (5) & 16 (10) & \\
Grade 2 & 40 (26) & 49 (32) & \\
Grade 3 & 22 (14) & 17 (11) & \\
Grade 4 & 6 (4) & 6 (4) & \\
Grade 5 & 6 (4) & 1 (1) & \\
Specific general complications - no. (%) & & & \\
Postoperative transfusion & 26 (17) & 22 (14) & 0.64 \\
Pleural effusion (>250ml on CT volumetry) & 30 (20) & 22 (14) & 0.17 \\
Pneumonia & 12 (8) & 8 (5) & 0.49 \\
Urinary tract infection & 10 (6) & 12 (8) & 0.67 \\
Wound infection & 13 (8) & 10 (7) & 0.67 \\
Ascites infection & 3 (2) & 5 (3) & 0.50 \\
Liver insufficiency & 9 (6) & 4 (3) & 0.26 \\
Renal insufficiency & 4 (3) & 5 (3) & 0.75 \\
Pulmonary embolism & 0 (0) & 5 (3) & 0.03 \\
Deep venous thrombosis & 0 (0) & 1 (1) & 0.50 \\
Portal vein thrombosis & 1 (1) & 1 (1) & 1.00 \\
Cerebrovascular accident & 1 (1) & 1 (1) & 1.00 \\
Myocardial infarction & 0 (0) & 1 (1) & 0.50 \\
Mortality - no. (%) & & & \\
In-hospital mortality & 5 (3.2) & 1 (0.6) & 0.21 \\
30-day mortality & 6 (3.8) & 1 (0.6) & 0.12 \\
Intra-operative mortality & 0 & 0 & \\
\hline
\end{tabular}

\textsuperscript{*} Grading complications according to Clavien-Dindo classification.\textsuperscript{22,23}
\end{table}
Fibrin sealant for prevention of resection surface-related complications after liver resection

primarily designed to study the intraoperative hemostatic efficacy and the effect on postoperative bile leakage was never studied as primary endpoint. In addition, most previous studies were of poor methodological quality or underpowered. In one well-designed, single center study, including 300 patients, postoperative complications were the main outcome parameter. Primary objective in this study was to determine whether fibrin sealant could decrease postoperative bleeding and blood transfusion. The secondary objective addressed other complications, such as bile leakage and intra-abdominal abscesses. Although another type of fibrin sealant was used in this study, it also did not show any reduction in resection surface-related complications.

Because it was not our aim to study the efficacy of fibrin sealant in obtaining intraoperative hemostasis, we only randomized patients after complete hemo- and biliostasis was obtained by traditional surgical methods such as suturing and coagulation. This allowed us to specifically study the efficacy of the prophylactic use of fibrin sealant in reducing postoperative complications. Only 17 patients (5.2%) would not be included because hemostasis could not be obtained without a fibrin sealant. This indicates that local hemostatic agents are needed in only a minority of patients and our data do not contradict their efficacy in obtaining hemostasis. Today, however, many surgeons are using fibrin sealants prophylactically, assuming that they may reduce postoperative complications. The results of our study indicate that the prophylactic use of fibrin sealants is not justified and only leads to increased costs.

One may argue the expected 50% reduction in complications required in this sample size calculation. While a smaller difference of 30% might not be detected by this sample size, we deliberately chose a higher percentage for two reasons. A reduction of 50% (from 15% to 7.5%) complications was considered clinically relevant, as opposed to, for example, a 30% reduction (from 15% to 10%) that would be less relevant considering the high costs of fibrin sealants and the higher number of patients needed to treat to obtain a benefit (from 13 to 20). Another argument was the high number of patients required to detect a smaller difference. Randomization of around 3 times more patients would have been impractical. While we did not show any difference at all between groups we do not think that the results would have been any different when a larger sample size was selected.

An important aspect of this study was the objective assessment of fluid collections at the resection surface using a CT-scan. While one may argue that fluid collections detected by CT-scan are not always clinically relevant, this did provide us the most objective tool to assess the main endpoint. Importantly, the results of this study did not change when only symptomatic outcome parameters, including reinterventions or medication for resection surface-related complications, were compared. Despite the lack of any clinically relevant difference in complications, we did find a statistically significant lower bilirubin concentration in drain fluid at postoperative day 1 in the fibrin sealant group, compared to controls. This suggests that there may be a minor effect of fibrin sealant that is short lasting and does not result in an overall clinically relevant reduction of resection surface-related complications.

We intentionally did not standardize the surgical technique for parenchymal transection. Today,
various surgical techniques are used in liver surgery and even within one patient surgeons may switch between techniques. The current study, therefore, reflects everyday surgical practice, allowing extrapolation and generalization of the results. The multicenter setting of this study adds to the generalisability of the results.

The results of this study are unambiguous, but they are opposite from what we initially expected. Application of a layer of fibrin gel to the liver resection surface seemed a logical method to reduce resection surface-related complications and the question remains why fibrin sealants are not effective in reducing bile leakage from the liver surface? An answer to this question may be derived from a recent in vitro study in which the effect of bile on stability of fibrin clots was examined.24 Human bile was shown to contain a significant amount of tissue-type plasminogen activator, which contributes to the premature lysis of fibrin clots. Addition of a high dose of plasminogen activator inhibitor-1 did not attenuate the fibrinolytic activity, raising the possibility that tissue-type plasminogen activator in bile is resistant to plasminogen activator inhibitor-1 inhibition. This was not different for fibrin sealants with or without an antifibrinolytic agent.24

The results of this study have clinical and financial implications. Fibrin sealants are increasingly used in surgical practice and global sales are rising annually.18 Surveys in the Netherlands and Japan have shown that fibrin sealants are used in the vast majority of patients undergoing liver resection.19,21 In the U.S. more than 14,000 liver resections for colorectal liver metastases are performed annually.25-27 Based on the average costs per application of fibrin sealant of 400 US dollars and the assumption that, similar to Japan and the Netherlands, fibrin sealants are used in 80% of the cases, the estimated annual costs for fibrin sealants in liver surgery in the U.S are 4.5 million dollars. Abrogation of the routine use of fibrin sealants in liver surgery, therefore, would lead to a significant reduction of procedure-related costs.

A limitation of this study is that we examined the efficacy of only one fibrin sealant. Based on the minor differences in composition of the commercially available fibrin sealants, however, it is not likely that outcome would have been different with another fibrin sealant. Nevertheless, we did not compare the efficacy of this fibrin sealant with the newer, so called carrier-bound fibrin sealants, consisting of a solid matrix (e.g. collagen fleece) with an active component consisting of thrombin and fibrinogen.9,13,28 Other well-powered studies will be needed to determine whether these carrier-bound fibrin sealants are more effective.

In conclusion, our multicenter trial shows that the prophylactic application of fibrin sealant at the resection surface of the remnant liver after liver resection does not lead to a reduction in the incidence or severity of postoperative bile leakage or other resection surface related complications.
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APPENDIX

In addition to the authors, the following investigators participated in this study (all institutions are in the Netherlands): University Medical Center Groningen, Groningen – P.M.J.G. Peeters, K.P. de Jong, E. Sieders, M.J.H. Slooff, P. Kele; Medisch Spectrum Twente, Enschede – J.J.G.M. Gerritsen, J. Mulder, A. Stam; Erasmus Medical Center, Daniel den Hoed Hospital, Rotterdam – N. Ayez, A. van der Pool; Maastricht University Medical Center, Maastricht – M.H.A. Bemelmans, S.W.A.G. Dello; Academic Medical Center, Amsterdam – O.R.C. Busch; N. van de Esschert, M. Bieze; University Medical Center Utrecht, Utrecht – R. van Hillegersberg.

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