A Prospective Study of the Efficacy of Clinical Application of a New Carrier-Bound Fibrin Sealant After Liver Resection

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Objective: To examine the effectiveness of fibrin sealants as supportive treatment to improve hemostasis and decrease the incidence of bile leakage and intra-abdominal collections.

Design: Prospective, controlled, quasiexperimental study.

Setting: Tertiary referral center, University Hospital Reina Sofia.

Patients: A total of 115 patients (58 in the control group and 57 in the collagen sponge group) scheduled for conventional hepatectomies.

Interventions: Patients were distributed into groups for major and minor hepatectomies with or without application of a carrier-bound collagen sponge on the raw surface of the liver.

Main Outcome Measures: The main outcome measures were postoperative mortality, incidence and severity of postoperative surgical complications, and length of hospital stay. The secondary outcome measures were postoperative drainage output volume, transfusion requirements, and changes in biochemical parameters (hemoglobin, bilirubin, alanine aminotransferase, and platelet levels).

Results: The fibrin sealant after major liver resection was effective for decreasing drainage volume (mean [SD] volume, 1124.7 [842.8] mL in the control group and 691.2 [599.5] mL in the collagen sponge group; \( P = 0.007 \)) with a higher volume of output by drain each postoperative day in the control patients (\( P = 0.003 \)); postoperative blood transfusion requirements (18.9% vs 7.0%, respectively; \( P = 0.04 \)) moderate to severe postoperative complications (21% vs 8%, respectively; \( P = 0.03 \)); and mean (SD) hospital stay (12.6[6.7] vs 9.6[5.1] days, respectively; \( P = 0.03 \)).

Conclusion: The use of a new carrier-bound collagen sponge after major liver resection may be recommended because of its clinical and cost-savings effectiveness.

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Liver surgery has become safer in recent years. Many procedures have been devised by liver surgeons to reduce mortality after hepatectomy. As a result, surgical mortality is less than 1%; overall morbidity is around 20%, and blood transfusion is only required in 15% of cases.不幸地，出血和胆汁从切口流出是常见并发症，可能导致腹膜炎和死亡。技术进步未能阻止这些并发症的发生，并且有顶极的止血剂，如在切口处使用的聚维酮碘层表面可以被破坏。这些制剂可以用来促进止血和减少胆汁泄漏的腹膜炎和腹腔内收集。他们可以被分为聚氨基酸，聚碳酸酯和聚酸凝胶。然而，没有证据表明这些产品的有效性。

Tachosil (Nycomed-Pharma SA, Madrid, Spain) is a ready-to-use fixed combination of a collagen sponge coated with a fibrinogen and thrombin layer, combining the mechanical support of a collagen sponge with the hemostatic and adhesive properties of the coagulation factors I and IIa.

To assess the clinical value of this new agent, we designed a prospective study using this carrier-bound collagen sponge on the raw surface of the liver in patients who had hepatectomies. The study objectives included: 1) to establish whether this collagen sponge could decrease postoperative bleeding and blood transfusion;
(2) to assess the amount and quality of fluid drained following hepatectomy with or without collagen sponge; (3) to compare the incidence of postoperative complications; and (4) to assess the potential benefits of application of the new carrier-bound collagen sponge on postoperative length of hospital stay.

METHODS

The study was conducted in our tertiary referral center for hepatobiliary surgery and liver transplantation. The sample size was estimated assuming a hypothetical 1.5% higher overall complication rate in patients who have liver resection without topical hemostatics (control group) compared with patients who received the new collagen sponge (collagen sponge group) (80% power; type I error probability, 0.05; estimated loss, 5%). Theoretically, 53 patients were required in each group. From October 2006 to December 2007, 115 patients were recruited (58 in the control and 57 in the collagen sponge group) and assigned to hepatectomy with or without the sponge. Introduction of the new sealant was explained before surgery. Abdominal closure was performed by 2 independent surgeons (A.N., R.C., R.D.-N., and J.-M.S.-H.) without any communication with the previous surgeons. No specific criteria were defined for this step, attaching the structure of a quasiexperimental study. In this moment, the “closure team” decided whether to apply the Tachosil sponge, with no additional application of other surgical instruments or procedures. In the collagen sponge group, 1 or 2 collagen sponges were applied relative to the cut surface. Before application, blood and other fluids were wiped from this surface and the sponge(s) were premoistened in saline solution and immediately applied to the liver with gentle pressure for 3 minutes. In the control group, no collagen sponge or any other hemostatic sealant was used. Patients with cirrhosis, bilioenteric anastomosis, and more than 1 hepatectomy in the same surgery were recruited.

The use of Tachosil was not known to the clinical team in the postoperative period. Postoperative evaluation of patients was performed by the surgeons who did the main surgery, not by those who did the closure.

Informed written consent was obtained from every patient before surgery, and the study was approved by the liver research review board of our hospital.

LIVER RESECTION PROCEDURE

Liver anatomy terms used are based on Couinaud’s classification.7 Liver parenchymal transection was accomplished using an ultrasonic dissector. Intermittent inflow occlusion was applied when necessary. The cut surface of the liver was secured with TissueLink (TissueLink Medical Inc, Dover, New Hampshire), electrocautery, and clips. Vessels more than 2 mm in diameter were ligated or sutured with 4/5-0 stitches. At the end of hepatectomy, the raw surface of the liver was carefully assessed to rule out bleeding or bile leakage. After 5 minutes with a clean cut surface, 1 or more Tachosil sponges were applied in the collagen sponge group. In the control group, the cut surface was secured with electrocautery and, mainly, with TissueLink, with no additional management. All hepatectomies were performed by 2 surgeons (J.B. and P.L.-C.)

DRAIN MANAGEMENT

Closed mixed capillary suction drains were left with the tip facing the cut surface of the liver. Closed mixed capillary suction drains were used in all patients who had major liver resection (see definitions). No surgical drains were used in minor liver resections.

Fluid content from drains was divided into 3 categories: • Clear fluid discharge: a clean, almost transparent fluid with a red blood cell (RBC) concentration lower than 1000/mm3.
• Mildly hematic fluid discharge: a red, almost transparent fluid with an RBC concentration of 100 to 100 000/mm3.
• Hematic fluid discharge: a red, thick fluid with an RBC concentration higher than 100 000/mm3.
• Biliary fluid discharge: drainage with a conjugated bilirubin concentration of 20 mg/dL or higher (to convert to micromoles per liter, multiply by 17.104).

Drains with a clear fluid discharge were removed within 24 hours. Those with mildly hematic fluid discharge were removed when the total volume was less than 50 mL for 2 consecutive days. Drains with hematic fluid discharge were kept until the fluid became clear or mildly hematic or repeat surgery was required.8 Drains with a biliary fluid discharge were maintained until the fluid became clear and were managed conservatively except when bile output exceeded 500 mL in a single measurement or more than 200 mL for 3 consecutive days, in which case surgical or radiological intervention was required.

POSTOPERATIVE MONITORING

All patients were monitored in the intensive care unit after surgery. Postoperative ascites was treated with 50 g of albumin daily for 5 days and low doses of diuretics were given when abdominal discharge exceeded 500 mL/d. Broad-spectrum antibiotics were given for 3 days and discontinued thereafter. Hemoglobin levels lower than 8 g/dL (to convert to grams per liter, multiply by 10) or signs such as tachycardia (>120 beats per minute), persistent hypotension (<90/50 mm Hg), and weakness with significant decrease (even when more than 8 g/dL) in hemoglobin level, excluding other causes, were the transfusion criteria.

Routine liver biochemical parameters were recorded daily in the first postoperative week. Abdominal ultrasonography was performed in every patient before drain removal (major hepatectomy) and hospital discharge (major and minor hepatectomies).Computed tomographic scans were performed when patients had fever, abdominal pain, or biochemical signs of infection such as leukocytosis or neutrophilia.

Hepatectomy complications were classified as reported by Dindo et al9 (Table 1).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Includes any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed drugs include antimetics, antipyretics, analgesics, diuretics, electrolytes, and physical therapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>II</td>
<td>Requiring pharmacological treatment with drugs other than allowed for grade I complications, blood transfusions, and total parenteral nutrition</td>
</tr>
<tr>
<td>III</td>
<td>Requiring surgical, endoscopic, or radiological intervention</td>
</tr>
<tr>
<td>IV</td>
<td>Life-threatening complication requiring immediate care and/or intensive care unit management</td>
</tr>
<tr>
<td>V</td>
<td>Death of a patient</td>
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DEFINITIONS

• Anatomic resection: any hepatectomy that involves complete resection of a liver segment, a liver sector, or a lobe, with its individual portal triad and hepatic vein drainage confined by tumor-bearing portal tributaries.10 Nonanatomic resection was equivalent to wedge resection.

• Major hepatectomy: resection of 3 or more Couinaud segments.

• Minor hepatectomy: resection of fewer than 3 Couinaud segments (sectorectomy, segmentectomy, subsegmentectomy, and wedge resection).

• Bile leakage: continuous drainage of 50 mL or more with a bilirubin concentration of 20 mg/dL or more from the surgical drain or from drainage of an abdominal collection in 3 or more consecutive days.11,12

• Postoperative liver failure13: in the absence of any treatable complication, the lack of significant improvement on postoperative day 5 with a bilirubin level of more than 2.9 mg/dL and prothrombin index of less than 50% of normal or an international normalized ratio higher than 1.7.

• Operative mortality: death within 30 days of hepatectomy.

• Operative morbidity: any complication within 30 days of liver resection.

STATISTICAL ANALYSIS

Quantitative variables were analyzed using the t test. Pearson χ² testing (Fisher exact test when appropriate) was used to analyze categorical data and percentages. Overall time-dependent comparison of quantitative data was analyzed using the general linear model. Multivariate analysis was performed to identify independent covariates predicting for postoperative complications. A value of P < .05 was considered significant for all analyses. The Statistical Package for the Social Sciences (SPSS, release 11.0 for Windows; SPSS Inc Chicago, Illinois) was used for all analyses.

RESULTS

A total of 115 patients were recruited (58, control group; 57, collagen sponge group). Figure 1 shows a flowchart of the groups. In the control group, 30 and 28 patients had minor and major liver resection, respectively. In the collagen sponge group, 32 and 25 patients had minor and major liver resection, respectively. Both groups were well matched for baseline variables (Table 2). There were no differences between the groups in the type of liver resection (Table 3). Similarly, no differences were found in intraoperative requirements of blood (packet red blood cells), fresh frozen plasma, and platelet transfusions, operating time, need for clamping, clamping duration between the control and collagen sponge groups, or between major hepatectomy and minor hepatectomy subgroups (Table 4).

CHANGES IN FLUID DISCHARGE FROM SURGICAL DRAINS OVER TIME

In patients who had major hepatectomy, a closed suction abdominal drain was placed. The mean (SD) total fluid discharge volume was 1124.7 (842.8) mL in the control group and 691.2 (499.5) mL in the collagen sponge group (P = .007). Changes over time in abdominal drainage volume are shown in Figure 2. An overall time-dependent comparison using the general linear model revealed a higher volume of output by drain in the control patients (P = .043). Surgical drainage was maintained for a mean (SD) of 6.1 (2.2) days in the control and 3.8 (1.7) days in the collagen sponge group (P = .04). Fluid discharge quality was also different between the groups, with more patients draining a clear fluid discharge in the collagen sponge.
in the control and collagen sponge groups (P = .07), respectively. Table 5 shows the distribution of complications by severity and type of resection. The distribution of complications was similar in patients with minor hepatectomies irrespective of treatment. However, patients in the collagen sponge group who had major hepatectomy experienced more mild complications (grade I) (28% vs 21%; P = .05). Conversely, control patients who had major hepatectomy had more moderate to severe complications (grade III, requiring surgical, endoscopic, or radiological intervention) than their counterparts in the collagen sponge group (21% vs 8%; P = .03). Grade III complications in 6 control patients who had major hepatectomy included intra-abdominal bleeding requiring surgical exploration (n = 3), intra-abdominal collections requiring radiological drainage (n = 1), and bile leakage requiring an endoscopic procedure (n = 2); grade III complications in 3 patients in the collagen sponge group who had major hepatectomy included intra-abdominal collections requiring radiological drainage (n = 2) and bile leakage requiring radiological intervention (n = 1). Two patients in both groups who had major hepatectomy developed postoperative liver failure (grade IV) that required management in the intensive care unit.

After hospital discharge, 3 control patients who had major hepatectomy were readmitted for intra-abdominal collections requiring radiological drainage (abcess, n = 2; biloma, n = 1) compared with none from the collagen sponge group (P = .09). Two control patients who had minor hepatectomy needed radiological drainage after discharge compared with none from the collagen sponge group (P = .14). The number of readmissions was higher in the control group than in the collagen sponge group (8.6% vs 1.7%; P = .03).

A multivariate analysis was performed to identify independent covariates that predict postoperative complications. Major hepatectomy (P = .005; odds ratio [OR], 3.2), use of collagen sponge (P = .02; OR, 2.1), underlying liver disease (cirrhosis) (P = .04; OR, 1.4), and postoperative transfusion of packed red blood cells (P = .05; OR, 1.1 per pack) were all found to be independent predictors of postoperative complications.
The main finding of the present study is that application of a new carrier-bound collagen sponge to the raw liver surface is useful for decreasing both postoperative drainage volume and blood transfusion requirements and hospital stay. Use of the collagen sponge is also associated with a significant decrease in moderate to severe postoperative complications requiring surgical and radiological intervention in patients who have major hepatectomy, while it is less effective in those who have minor resections.

Despite widespread use of topical hemostatic agents in liver surgery, it is surprising how liver surgeons accept without criticism the use of new devices and biological products with an apparent advantage but without evidence-based utility. In the past 5 years, more than 150 articles on the efficacy of topical sealants in liver surgery have been published in the indexed literature.14 However, except for a few prospective trials, most are level III evidence reports.

A preliminary trial by Frilling et al15 comparing the same carrier-bound collagen sponge to argon beamer showed

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**Figure 3.** Postoperative changes in the main biochemical parameters in the control and collagen sponge groups. Values are means for each postoperative day. ALT indicates alanine aminotransferase; INR, international normalized ratio.
a significant superiority of the sponge in terms of time to intraoperative hemostasis and lower hemoglobin concentration in drainage fluid after the second postoperative day. Intraoperative time to hemostasis, defined as the time from sealant application to the liver surface to the time when there was no further evidence of bleeding after direct observation for 1 minute, is an endpoint widely used. However, the clinical significance of a shorter time to hemostasis in terms of safety and prevention of postoperative complications is difficult to assess. Focus on parameters such as drainage volume, postoperative blood transfusion, and surgery-related adverse events may be more clinically relevant, and these were the main endpoints used in our study.

A controversial point of this study is the routine use of closed mixed capillary suction drains in patients who had major hepatectomy. Some authors have shown that prophylactic drains are of little value in patients with posthepatectomy both with and without liver disease. In agreement with such views, these drains have not been used in our institution since 2005. However, for the purposes of this clinical study, the daily volume drained was considered to be a direct measure of the effectiveness of the collagen sponge tested. Drains may be harmful after hepatic resection in chronic liver disease (grade A recommendation). In our series, wound infections (class I complications) were more common in patients who received the collagen sponge after major hepatectomy, while intra-abdominal collections (class III complications) were more common in control patients. Major hepatectomy was an independent predictor of postoperative complications in both groups.

The characterization of the fluid is self-made with the purpose of quantifying a subjective parameter such as the quality of the drained fluid. Identifying drainage as serious, serohemagic, or hematic could be somehow arbitrary. The quality (quantified in the previous terms) of the drainage was not a primary endpoint of our study but was a useful tool to use as a guide to drainage removal and as an objective parameter of a subjective medical opinion. The kind of drain used (a mixed capillary suction drain) avoids the methodological problem of a theoretical drain obstruction by the collagen sealant sponge, which would have surely happened if a suction-only drain had been placed.

A well-designed trial by Figueras et al recently demonstrated the lack of efficacy of a fibrin-glue sealant in aerosol form combined with an absorbable collagen sponge applied to the cut liver surface. The results of the study contrast with ours. The assumption of a 30% difference in the intra-abdominal complication rate for sample size calculation resulted in recruitment of 300 patients for the study by Figueras et al. Our sample size estimation was based on the assumption of a 15% difference in the overall complication rate (both intra-abdominal and other complications) and resulted in recruitment of 115 patients. Different procedures were used in these two studies to achieve hemostasis. The sponge used in the present study is a fixed application of fibrin glue followed by a collagen sponge, each from a different manufacturer used by Lam et al on 616 patients who had liver resection.

In conclusion, use of this new carrier-bound collagen sponge was its effect of decreasing postoperative hospital stays. Such decrease resulted from reduction in drainage volume, postoperative blood transfusion requirements, and lower rates of moderate to severe complications. Based on this, the use of the new collagen sponge after liver resection would result in significant cost savings, although this is only supported by indirect evidence. A quality cost-saving analysis may be performed.

Table 5. Distribution of Postoperative Complications by Severity and Type of Resection

<table>
<thead>
<tr>
<th>Grade of Severity</th>
<th>Control</th>
<th>Collagen Sponge</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hepatectomy (n=53)</td>
<td>(n=28)</td>
<td>(n=25)</td>
<td>.05</td>
</tr>
<tr>
<td>I</td>
<td>6 (21)</td>
<td>7 (28)</td>
<td>.99</td>
</tr>
<tr>
<td>II</td>
<td>9 (32.1)</td>
<td>5 (20)</td>
<td>.09</td>
</tr>
<tr>
<td>III</td>
<td>6 (21)</td>
<td>2 (8)</td>
<td>.03</td>
</tr>
<tr>
<td>IV</td>
<td>2 (7)</td>
<td>2 (8)</td>
<td>.84</td>
</tr>
<tr>
<td>V</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Minor hepatectomy (n=62)</td>
<td>(n=30)</td>
<td>(n=32)</td>
<td>.77</td>
</tr>
<tr>
<td>I</td>
<td>4 (13.3)</td>
<td>3 (9.3)</td>
<td>.47</td>
</tr>
<tr>
<td>II</td>
<td>5 (16.6)</td>
<td>3 (9.4)</td>
<td>.26</td>
</tr>
<tr>
<td>III</td>
<td>2 (6.6)</td>
<td>1 (3.1)</td>
<td>.13</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>V</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

aValues in boldface indicate statistical significance.

Figueras et al. A comparison of the two approaches for arresting liver surface bleeding would be interesting. Bile leakage incidence was approximately 3.6% to 12%. The biliostatic efficiency of these products is, again, controversial. Hayashibe et al analyzed 88 patients after liver resection without biliary reconstruction. They concluded that the combination of fibrin glue and bioabsorbable polyglycolic acid would be effective for preventing bile leakage after liver resection. On the other hand, in a study by Lam et al on 616 patients who had liver resection, fibrin glue did not help reduce the biliary leakage rate. In our study, 6 patients in the control group and 4 patients in the collagen sponge group developed postoperative bile leakage, without statistical significance. Research on the precise benefits of application of hemostatic agents to the resection surface to prevent biliary fistula is clearly needed.

The present study used a classification of the severity of surgical complications proposed by Dindo et al. This classification was not specifically designed for liver surgery but represents a simple, objective, and reproducible approach to comprehensive surgical outcome assessment.

In conclusion, use of this new carrier-bound collagen sponge after major liver resection may be recommended because of its effectiveness in decreasing drainage volume, postoperative blood transfusion requirements, moderate to severe postoperative complications, and hospital stay.

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