Application of Fibrin Glue Sealant After Hepatectomy Does Not Seem Justified

Results of a Randomized Study in 300 Patients

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Objective: To evaluate the efficacy, amount of hemorrhage, biliary leakage, complications, and postoperative evolution after fibrin glue sealant application in patients undergoing liver resection.

Summary Background Data: Fibrin sealants have become popular as a means of improving perioperative hemostasis and reducing biliary leakage after liver surgery. However, trials regarding its use in liver surgery remain limited and of poor methodologic quality.

Patients and Methods: A total of 300 patients undergoing hepatic resection were randomly assigned to fibrin glue application or control groups. Characteristics and debit of drainage and postoperative complications were evaluated. The amount of blood loss, measurements of hematologic parameters liver test, and postoperative evolution (particularly involving biliary fistula and morbidity) was also recorded.

Results: Postoperatively, no differences were observed in the amount of transfusion (0.15 ± 0.66 vs. 0.17 ± 0.63 PRCU; $P = 0.7234$) or in the patients that required transfusion (18% vs. 12%; $P = 0.2$), respectively, for the fibrin glue or control group. There were no differences in overall drainage volumes (1180 ± 2528 vs. 960 ± 1253 mL) or in days of postoperative drainage (7.9 ± 5 vs. 7.1 ± 4.7). Incidence of biliary fistula was similar in the fibrin glue and control groups, (10% vs. 11%). There were no differences regarding postoperative morbidity between groups (23% vs. 23%; $P = 1$).

Conclusions: Application of fibrin sealant in the raw surface of the liver does not seem justified. Blood loss, transfusion, incidence of biliary fistula, and outcome are comparable to patients without fibrin glue. Therefore, discontinuation of routine use of fibrin sealant would result in significant cost saving.

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Blood or bile leak from the cut parenchymal surface after hepatic surgery is a frequent and often particularly troublesome complication. This complication is especially difficult to manage in patients with liver cancer or cirrhosis because of reduced platelet and blood coagulation activity.[1] A number of hemostatic methods have been evaluated as adjunctive procedures in hepatic resection.[2] Topical hemostatic agents have been used with varying degrees of success in this setting. These agents include oxidized cellulose,[3] absorbable gelatin sponge,[4] microfibrillar collagen,[2] and fibrin sealants produced with pooled plasma blood.[5,6] Fibrin sealants have become popular for improving perioperative hemostasis, reducing the need for allogenic red cell transfusion,[7–10] and in preventing bile leakage.[11] They generally contain 2 major components, fibrinogen (with or without factor XIII) and thrombin (plus calcium with or without antifibrinolytic drugs). They can be applied to the raw surface of the liver after hepatectomy using a dual syringe system in a liquid or an aerosol form.

Although fibrin sealant has been shown to be safe and well tolerated, comparative studies would assist in the clarification of the place of fibrin glue in hemostasis and avoidance of biliary fistulas after hepatic resection. Generally, previously published trials in the literature regarding its use in liver surgery are limited and of poor methodologic quality.[7] A large and rigorous methodologic trial of fibrin sealant application after elective hepatectomy is needed.

To address these issues, we designed a prospective, randomized, controlled trial, with or without the application of fibrin sealant, using an aerosol form in the raw surface of the liver in patients undergoing elective hepatectomies.

The primary objective was to determine whether fibrin sealant could decrease postoperative bleeding and allogenic blood transfusion. The secondary objective addressed the postoperative outcome (particularly postoperative drainage debit), the development of complications (particularly biliary fistula), the frequency of reoperations (owing to bleeding or biliary leakage), and the frequency of intra-abdominal abscesses needing percutaneous drainage. Finally, we wanted to determine the risk factors for the development of complications and mortality after hepatectomy.

PATIENTS AND METHODS

From February 2002 to November 2004, 308 patients underwent hepatic resection in our department. Eight patients were excluded from the study because they were included in another study.[12] A total of 300 patients were randomly assigned to undergo hepatectomy with or without application of 5 mL of Tissucol (Baxter-Inmuno, Vienna, Austria) in aerosol form on the raw surface of the liver. An absorbable collagen sponge (Johnson & Johnson) was also applied with manual pressure, after spraying the fibrin glue. In the control group, neither the fibrin sealant nor the collagen sponge was used. Patients who required contralateral hepatic resection, concomitant bowel resection, or bilioenteric anastomosis were also included in the study, since we wanted to determine which patients more greatly benefited from fibrin sealant application.

This study was conducted in accordance with the Declaration of Helsinki; the research review board of our hospital approved the protocol, and informed written consent was obtained from each patient before surgery. Randomization was performed using sealed envelopes and was stratified to include similar numbers of cirrhotic patients in each study group.

Surgical Technique

The technique has been extensively described previously.[12,13] Briefly, a subcostal incision or J-shaped, upper median, and right oblique incisions were used in all cases. After meticulous ultrasonographic study,[14] the liver was mobilized in a standard way. The gallbladder was removed and a catheter introduced in the cystic duct.

In major hepatectomies, the control of the intrahepatic portal triad was achieved by hepatotomy near the corresponding portal pedicle.[13] Either the right or left portal pedicle was isolated and secured using a large curved clamp and encircled with a rubber tape. The TA-30 vascular stapler (United States Surgical Corporation, Norwalk, CT) was introduced to transect the pedicle. During transection, a firm countertraction of the rubber tape is necessary to prevent accidental damage of the contralateral pedicle. When the tumor was located close to the pedicle, the portal vein, the hepatic artery, and the biliary duct were dissected in the hilum by opening the peritoneal fascia. The corresponding portal vein was transected using vascular clamps and closed with a running suture with a nonabsorbable monofilament. The corresponding hepatic artery and the biliary duct were also ligated and cut before transection of the parenchyma.

Transection of the liver was performed under intermittent clamping by means of occluding blood inflow, either pedicular or selective, for 15 minutes, followed by a 5-minute release. Separate clamping of the accessory left hepatic artery was performed when present. The parenchyma transection was performed in all cases with an ultrasonic dissector (Cavitron Ultrasonic Surgical Aspirator System 200; Valleylab Inc., Boulder, CO). During liver transection, small vessels were occluded with the irrigated monopolar forceps, larger vessels or bile ducts on the resected side were clamped with metallic clips, and vessels on the preserved side were ligated with silk. Potential sites of biliary leakage were identified after resection by injection of methylene-blue-dyed saline solution through the cystic duct. Sites of leakage on the transection surface or at the biliary stump were repaired with fine sutures. Hemorrhagic sites after transection on the preserved side were managed with the "Argon beamer" or more recently with the TissueLink (Tissuelink Medical Inc., Dover, NH), in accordance with preferences of the surgeon. Closed suction abdominal drainage was placed routinely in the resected space.

Protocol Design

For the purposes of this study, the amount of intraoperative blood loss was measured from the volume of blood collected in the container of the aspirator and the ultrasonic dissector and from the weight of the soaked gauzes. Packed red blood cells (PRBCs) were transfused only when the hemoglobin value dropped below 10 g/L, and fresh frozen plasma only when the prothrombin time was higher than INR 1.8. After completion of the liver hepatectomy, the transection surface was calculated with the aid of a graph paper. Volume and quality of suction drainage were measured daily. If biliary fistula was suspected, measurements of bilirubin levels in plasma and in the drainage liquid were performed. The abdominal drainage tube was left until aseptic fluid discharge was lower than 50 mL/day; it was then removed when the biliary fistula was discarded. Culture of the drains at the time of removal was done only when infection was suspected.

On postoperative days 1, 2, 3, 5, and 7, measurements of liver enzymes alanine aminotransferase, aspartate aminotransferase, prothrombin time, bilirubin, alkaline phosphatase, γ-glutamyltransferase, hematocrit, hemoglobin, and albumin were recorded. All patients underwent ultrasonographic abdominal study and chest x-ray before leaving the hospital. Patient demographic data, complications, postoperative evolution, hospital stay, and results of the histopathologic study were prospectively introduced in a computer database. All patients were followed in outpatients clinic at 1, 3, and every 6 months thereafter with blood biochemistry tests and spiral CT scan of the abdomen.

Definitions

Major hepatectomy was defined as the resection of 3 or more liver segments.

The diagnosis of biliary fistula was based on the postoperative findings of one or more of the following: drainage of bile from the abdominal wound or drains with bilirubin content higher that the plasma levels; intra-abdominal collection of bile at the time of reoperation or percutaneous drainage; and cholangiographic evidence of biliary leakage.

Hepatic insufficiency was defined by a prothrombin time of less than 50% of normal and/or by serum bilirubin more than 50 μmol/L on postoperative day 5 or thereafter and/or encephalopathy.[15] Postoperative ascites was defined by an abdominal output greater than 500 mL/day of ascites that required medical treatment to be controlled.

Operative mortality was defined as death within 30 days of hepatic resection or within the same hospital admission for surgery. All patients had a minimum follow-up of 6 months.

Statistical Analysis

Continuous data were analyzed using the Student *t* test. The Fisher exact test and the Pearson χ^2 test were used to analyze categorical data. $P < 0.05$ was considered statistically significant.

Data were initially analyzed on the intention-to-treat principle. To assess whether other parameters, apart from the main variable of the study (fibrin glue application), may have influenced the development of complications, a univariate analysis of all baseline-studied parameters was performed.

All data analysis was performed on an IBM-compatible PC using SPSS 10.0 for windows (SPSS Inc., Chicago, IL).

Sample size was calculated using the PS (Power and Sample Size) program by Dupont and Plummer.[16] Previous studies[12,13,17] established that the mean rate of complications after hepatectomy in our institution was 40%. The sample size needed to detect a true difference of 30% in intra-abdominal postoperative complications with the use of fibrin glue, with a 0.8 power and type I error probability of 0.05 (given a standard deviation of 4), was 145 patients per group. Assuming the possibility that some patients would be missing from the protocol after randomization, we decided to include 300 patients.

The trial was powered to detect differences in the overall intra-abdominal complications rate since we thought that it was the most accurate and discriminant of the evaluated parameters.

RESULTS

A total of 150 patients were included in the fibrin glue sealant group and 150 in the control group. The groups were equally matched according to age, sex, diagnosis, and degree of steatosis of the nontumorous liver (Table 1). Patients with underlying liver disease were distributed homogeneously between groups.

There were no significant differences between the 2 groups regarding the type of liver resection performed or the number of associated surgical procedures (Table 2). The duration of the whole procedure was approximately 4.5 hours, and there were no differences between groups regarding the application of hilar clamping (Table 2). The overall ischemia time, and the transected area was similar in both groups. No differences were observed in the amount of hemorrhage. Only 38 patients required transfusion intraoperatively (12.5%) with no difference being recorded between groups (Table 2). The amount of PRBC, fresh frozen plasma, and platelet units transfused intraoperatively remained low, without significant statistical differences (Table 2).

Surgical Outcome

The mean hospital stay was 13 days, without differences between groups (Table 3). Forty-six patients were transfused postoperatively (mean ± SD 0.16 ± 0.64 PRBC units). The overall number of patients transfused throughout the study was 69 (mean ± SD, 0.31 ± 0.74 PRBC units), without differences between groups.

The abdominal drainage tube was left for a median of 1 week, and overall discharge volume was 1 L per patient. The daily amount of drainage volume declined progressively

TABLE 1. Patient Characteristics of the Fibrin Glue and Control Groups

	Fibrin Glue	Control	*P*
Number	150	150	
Sex (F:M)	91:59	104:46	0.12
Age (yr) (mean ± SD)	62 ± 11	60 ± 11	0.99
Body weight (kg) (mean ± SD)	72.8 ± 10.7	72.6 ± 12.3	0.91
Diagnosis (%)			0.91
Metastasis	103 (68)	100 (67)	
Hepatocellular carcinoma	19 (13)	23 (15)	
Hilar cholangiocarcinoma	7 (5)	8 (5)	
Hydatid cyst	5 (3)	4 (3)	
Other	16 (11)	15 (10)	
Jaundice (%)	10 (7)	5 (3)	0.18
Previous hepatopathy	34 (22)	22 (15)	0.34
Cirrhosis	10 (7)	11 (7)	0.82
Chronic hepatitis	14 (9)	11 (7)	0.53
Severe steatosis (>30%)	17 (12)	25 (16)	0.56
Steatosis (%)	10.2 ± 16.6	12.9 ± 19.9	0.2
Previous chemotherapy (%)	61 (41)	57 (38)	0.64

No significant differences were noted between groups.

TABLE 2. Intraoperative Data of Patients in the Fibrin Glue and Control Groups

	Fibrin Glue (n = 150)	Control (n = 150)	*P*
Major hepatectomy (%)	87 (58)	94 (63)	0.34
Right hepatectomy	23 (15)	32 (21)	
Right extended hepatectomy	30 (20)	27 (18)	
Left hepatectomy	9 (6)	13 (9)	
Left extended hepatectomy	19 (13)	11 (7)	
Other	6 (4)	11 (8)	
Minor hepatectomy (%)	63 (42)	56 (47)	0.14
Bisegmentectomy	37 (24)	24 (16)	
Segmentectomy	17 (11)	14 (9)	
Limited resection	9 (6)	18 (12)	
Associated hepaticojejunostomy (%)	14 (9)	11 (7)	0.53
Duration of operation (min) (mean ± SD)	282 ± 76.3	263 ± 73.1	0.027
Patients with hilar clamping (%)	125 (83)	132 (88)	0.5
Ischemic time (mean ± SD) (min)	31.8 ± 23.8	32.7 ± 23.3	0.75
Transection surface area (cm^2) (mean ± SD)	75.3 ± 32	74.8 ± 36.3	0.92
Total blood loss (mL) (mean ± SD)	883.9 ± 614	820.3 ± 522	0.34
Patients with intraoperative transfusion (%)	20 (13)	18 (12)	0.57
Blood transfusion PRBC units (mean ± SD)	0.24 ± 0.73	0.26 ± 0.85	0.83
Patients with FFP transfusion (%)	2 (1)	1 (1)	0.56
Patients with platelet transfusion (%)	5 (3)	2 (1)	0.25

PRCB indicates packed red cell units; FFP, fresh frozen plasma. No significant differences were noted between groups.

TABLE 3. Postoperative Outcome of Patients in the Fibrin Glue and Control Groups

	Fibrin Glue (n = 150)	Control (n = 150)	*P*
Postoperative hospital stay (days) (mean ± SD)	13.3 ± 13	12.6 ± 9	0.57
Patients with postoperative transfusion (%)	27 (18)	19 (12)	0.2
Postoperative transfusion PRBCU (mean ± SD)	0.15 ± 0.66	0.17 ± 063	0.72
Overall transfusion (PRBCU) [no. (%) of patients]	40 (27)	29 (19)	0.14
Overall transfusion (mean ± SD)	0.3 ± 0.74	0.31 ± 0.53	0.26
Days of postoperative drainage (mean ± SD)	7.9 ± 5	7.13 ± 47	0.94
Overall drainage volume (mL) (mean ± SD)	1180 ± 2528	960 ± 1253	0.34
Characteristics of fluid from drainage (%)			
Serous	133 (89)	130 (87)	0.64
Hematic	6 (4)	7 (5)	
Bile	11 (7)	13 (8)	

PRCB indicates packed red cell units. No significant differences were noted between groups.

TABLE 4. Overall Postoperative Morbidity and Hospital Mortality

	Fibrin Glue (n = 150)	Control (n = 150)	*P*
Complications related with hepatectomy (%)	35 (23)	35 (23)	1
Biliary fistula (%)	15 (10)	17 (11)	0.8
Intra-abdominal abscess (%)	9 (6)	8 (5)	
Intra-abdominal bleeding (%)	2 (1)	1 (1)	
Others (%)	9 (6)	9 (6)	
Percutaneous drainage of collection (%)	20 (13)	17 (11)	0.59
Abscess	12 (8)	7 (4)	0.58
Bilioma	4 (3)	3 (2)	
Hematoma	1 (1)	0	
Fluid collection	2 (1)	1 (1)	
Surgical reoperation (%)	9 (6)	5 (3)	0.27
Intra-abdominal bleeding	2 (1)	1 (1)	0.23
Biliary fistula	1 (1)	0	
Abscess	0	3 (2)	
Gastrointestinal leakage	4 (3)	0	
Other	2 (1)	1 (1)	
Hospital mortality	6 (4)	2 (1)	0.15

No significant differences were noted between groups.

in similar fashion for both groups (Fig. 1). There were no significant differences between groups in terms of length, amount, or characteristics of fluid drainage (Table 3). Eleven patients developed rebleeding, while only 3 were reoperated (Table 4).

A total of 127 (85%) and 128 (85%) patients underwent routine abdominal ultrasonographic study, with normal findings in 86 (68%) and 92 (72%) cases, respectively, in the fibrin glue and control groups. Echography demonstrated free ascitic fluid in 27 (11%) patients, fluid collection in the resected cavity in 31 (12%) cases, hematoma in 15 (6%) patients, and bilioma in 4 cases (2%). The ultrasonographic findings were distributed uniformly among groups.

The postoperative evolution of hematocrit (Fig. 2), hemoglobin, prothrombin time (Fig. 3), plasma alanine aminotransferase levels (Fig. 4), and plasma aspartate aminotransferase levels was similar between both groups. The postoperative evolution of plasma albumin levels, plasma alkaline phosphatase levels, γ-glutamyltranspherase levels and plasma total bilirubin levels was also similar between groups (data not shown). On day 14, prothrombin time was longer in the study group ($P = 0.02$), probably due to the higher proportion of patients with hepatic insufficiency.

Mortality and Morbidity

The overall mortality rate was 2.7% (8 of 300 patients). There were no intraoperative deaths. There were 2 deaths due

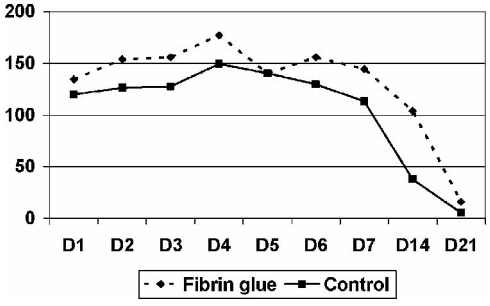

FIGURE 1. Daily evolution of abdominal drainage volume (mL).

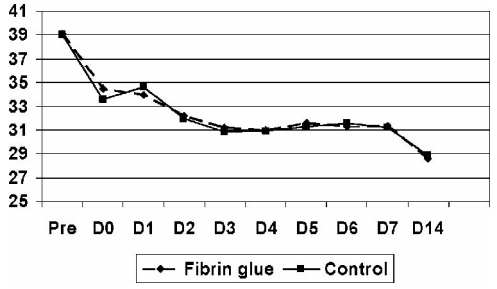

FIGURE 2. Postoperative evolution of hematocrit %.

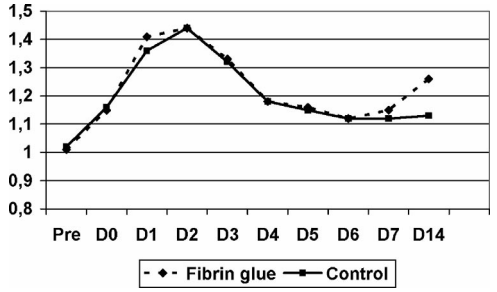

FIGURE 3. Postoperative of prothrombin time (INR): day 14, $P = 0.02$.

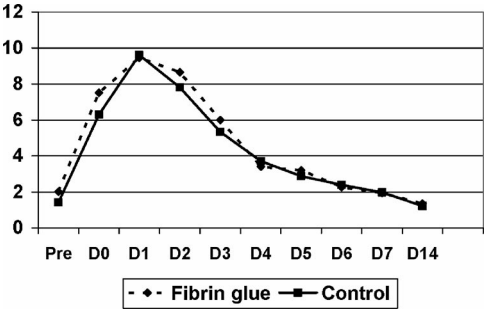

FIGURE 4. Postoperative evolution of plasma alanine aminotransferase levels (ALT) (normal values <0.60 μKat/L).

to intestinal anastomotic leakage, 2 due to respiratory insufficiency, 1 liver failure, catheter sepsis, intestinal ischemia, and MOF due to hemoperitoneum. Postoperative complications are shown in Table 4. In all, 70 patients (23%) developed intra-abdominal complications related to hepatectomy. The morbidity rates did not differ between the fibrin glue and control groups. Bile leakage was observed in 32 patients (11%): 15 (10%) in the fibrin glue group and 17 (11%) in the control group. Thirty-seven patients underwent ultrasonography-guided percutaneous drainage of collections. The most frequent cause of drainage was purulent abscess (n = 21). In the experimental group, 20 patients needed a percutaneous drainage of collections, 12 abscesses, 4 biliomas, 1 hematoma, and 2 fluid collections. There were no differences with the control group ($P = 0.58$).

The reoperation rate was 5% (14 of 300 patients), without differences among the groups (Table 4). Other medical complications were transitory or temporary hepatic insufficiency totaling 18 patients (6%) who recovered spontaneously (except in 1 case) and ascites in 21 patients with cirrhosis. There were no differences in postoperative morbidity between groups (Table 4).

Factors Related to Complications (Post Hoc Analysis)

The data were further analyzed to determine whether in patients with underlying liver disease, cirrhosis or jaundice, fibrin glue sealant was more effective. The analysis demonstrated a higher rate of complications in jaundiced patients, although the rate of complications in patients with chronic hepatopathy, as well as in the patient subgroup with cirrhosis, was similar to the other patients (Table 5). There were no differences in the subgroups when comparing the study group (fibrin glue) and the control group (data not shown).

The cost of fibrin glue is approximately of $300 (U.S.) per patients. In our hospital, we perform 120 liver resections yearly. Discontinuation of routine use of fibrin sealant would result in significant cost saving, of $36,000 (U.S.) per year in our center.

Because fibrin glue seemed to have no influence on postoperative complications, we next reanalyzed the data to elucidate which factors could be associated with postoperative complications. Univariate analysis confirmed that the application of fibrin sealant had no influence on morbidity.

TABLE 5. Univariate Analysis of Predictive Factor for Postoperative Complications

	Complicated (n = 70)	Uncomplicated (n = 230)	*P*
Left lateral bisegmentectomy	3 (4%)	18 (8%)	0.22
Left hepatectomy	8 (11%)	14 (6%)	
Right hepatectomy	9 (13%)	46 (20%)	
Extended right hepatectomy	19 (27%)	38 (16%)	
Extended left hepatectomy	9 (13%)	21 (9%)	
Bisegmentectomy	7 (10%)	33 (14%)	
Segmentectomy	8 (11%)	23 (10%)	
Limited resection	4 (6%)	23 (10%)	
Others	3 (4%)	14 (6%)	
Hepaticojejunostomy	16 (23%)	9 (4%)	<0.001
Chemotherapy	25 (36%)	93 (40%)	0.48
Jaundice	9 (13%)	6 (3%)	0.001
Cirrhosis	5 (7%)	16 (7%)	0.84
HCV ab+	5 (7%)	24 (10%)	0.41
Enolim	8 (11%)	24 (10%)	0.81
Steatosis >30%	9 (13%)	33 (14%)	0.93
Diagnosis			
Metastasis	35 (50%)	166 (72%)	<0.001
Hepatocarcinoma	9 (13%)	33 (14%)	
Klatskin's tumor	10 (14%)	5 (2%)	
Hydatid cyst	2 (3%)	7 (3%)	
Others	14 (20%)	19 (8%)	
Transection area (cm^2)	81.4 ± 34.7	72.3 ± 34	0.12
Duration of surgery (min)	285.2 ± 76.5	269.3 ± 74.6	0.13
Ischemic time (min)	37.2 ± 22.8	30.74 ± 23.4	0.04
Intraoperative transfusion of PRBC	0.39 ± 0.9	0.21 ± 0.7	0.11
Patients transfused intraoperatively	15 (21%)	23 (10%)	0.037
Blood loss (mL) (mean ± SD)	958.6 ± 693	777.7 ± 466	0.009
Postoperative stay (days)	19.6 ± 17	10.1 ± 7.1	<0.001

PRBC indicates packed red blood cell units; HCV ab+, hepatitis "C" virus antibody positive.

Moreover, no differences were found between patients with complications, and those without them, in preoperative data, such as age, sex, preoperative chemotherapy, type of hepatic resection performed, transection surface area, operative time, or the different causes of previous hepatopathy. However, in the univariate analysis, preoperative jaundice, diagnosis, associated hepaticojejunostomy, ischemia time, and obviously the amount of hemorrhage and blood transfusion were significantly associated with the development of complications. As expected, in-hospital stay was significantly longer in patients with complications (19.6 ± 17 vs. 10.1 ± 7.1 days ($P < 0.001$).

DISCUSSION

In this study, we sought to determine whether the application of fibrin glue on the raw surface of the liver would be effective in lowering postoperative bleeding and blood transfusion. The secondary objective included postoperative outcome, the development of complications, biliary fistula,

drainage of intra-abdominal biliomas or abscesses, and reoperation due to bleeding or biliary leakage. The clinical results were not different between the 2 groups. Postoperative blood loss and secretion were also similar. That only 2 patients in the fibrin glue group and 2 patient in the control group needed reoperation due to rebleeding was a satisfactory evidence. The cause of hemorrhage was from arterial vessels of the hilum, a phrenic vein, or the vena cava, which suggests that topical agents cannot completely replace surgical technique.[18] Mortality and morbidity rates were not different between those patients with and those without fibrin glue application, which suggests that fibrin sealant does not necessarily ensure an uneventful postoperative course.[18]

More than 2300 publications are available in the various fields of surgery regarding the use of hemostats, glues, and sealants. A very limited number of studies have focused on hepatobiliary and liver surgery.[19] The Heidelberg group identified the study features most appropriate for the assessment and evaluation of fibrin sealants with respect to hemostasis and biliostasis in hepatobiliary surgery. Our study meets the majority of these standards.[19] Nevertheless, we did not find definitive proof that postoperative rebleeding after liver resection is reduced by prophylactic surface-sealing. The number of complications associated with rebleeding, postoperative transfusion, abscesses, reoperation, and postoperative drainages was similarly unchanged.

Intraperitoneal drainage after elective surgery is still routinely used in many hospitals worldwide. Our study was designed in 2001; in December 2004, a meta-analysis was published about the evidence-based value of drainage in surgery.[20] This study demonstrates a slight advantage for nondrained patients with respect to infected intraabdominal collections (OR, 2.83; CI, 0.82–9.71). Drainage status had no influence on the outcome of bile collections or pulmonary complications. The systematic use of closed suction drainage in our study could explain the relative high proportion of patients with intra-abdominal abscesses in our patients.

Few controlled trials have been conducted to determine the effectiveness of hemostatic agents in controlling bleeding at the raw surface of the liver.[4,21,22] Chapman et al,[21] in a randomized trial using a novel collagen-based composite combined with autologous plasma, found that the composite was effective in controlling and stopping diffuse hepatic bleeding. However, there were no differences between the treatment and control groups either in transfusion requirements; in the postoperative evolution of hematocrit, hemoglobin, or fibrinogen levels; or in the surgical outcomes and adverse events following treatment. The results of this trial[21] agree with those of a recent multicenter clinical trial analyzing hemostasis time obtained with Tachosil, an equine collagen fleece patch carrying the fibrin glue components human fibrinogen and human thrombin.[22] In this study, Tachosil was effective in reducing hemostasis time following liver resections, as compared with argon beam.[22] However, the number of patients is this trial was too small to reveal any difference in postoperative complications associated with liver surgery.[22]

Compared with other studies, our study is a single-center trial, and the number of patients is large enough to find a 30% difference in complication rate. The findings of this randomized controlled trial demonstrate that there are no advantages in spraying fibrin glue and application of a collagen sponge over a standard method of hemostasis. Indeed, our results were uniform, and no differences were found between groups favoring one over the other.

The sealing of small, undetected bile ducts lesions would be of great benefit to hepatic surgery. However, detection of biliostatic efficiency has only been a collateral investigation parameter in past studies. Currently, there is no evidence available to support that a reduction of bile leakage can be achieved with the help of fibrin sealant.[19] In our study, the amount of fluid drainage, the characteristics of the fluid, and the findings of routine ultrasonographic examination were similar in both groups. The rate of biliary fistula presentation, defined using strict criteria, was the same in the study 17 patients (11%), and the control group 15 (10%) ($P = 0.8$). We can conclude that our protocol has demonstrated that there is no such protection from bile leakage after liver surgery.

The causes associated with postoperative complications are not new.[1,17,23] Overall, mortality was 2.7%. The prevalence of postoperative intra-abdominal complications was 23%, which was mainly influenced by diagnosis $P < 0.001$, and the presence of jaundice $P = 0.001$. Blood loss ($P = 0.009$), intraoperative transfusion ($P = 0.037$), longer ischemia time ($P = 0.04$), and associated hepaticojejunostomy ($P < 0.001$) also significantly increased morbidity. The prevalence of biliary fistula was 11%, the need for percutaneous collection drainage 12%, due to abscesses (6%), and bilioma (2%). The reoperation rate was 5%, which can mainly related to intra-abdominal abscesses, intestinal leakage, and rebleeding.

Our study did not demonstrate any advantage when using fibrin sealant with absorbable collagen sponge in the cut surface of the liver. However, we did not find any detrimental effect of fibrin glue usage after liver resection on postoperative evolution. Consequently, the main impact of our findings would be the cost savings of the surgical procedure. Indeed, fibrin glue is expensive. Discontinuation of routine use of fibrin sealant after hepatectomy would result in significant cost saving per year in our center.

CONCLUSION

The present trial demonstrated that application of fibrin sealant on the raw surface of the liver does not seem justified. Blood loss, transfusion, incidence of biliary fistula, and overall outcome were comparable to patients without fibrin glue. Therefore, its systematic use cannot be recommended.

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