

Original Paper

Does Fibrin Glue Prevent Biliary and Pancreatic Fistula after Surgical Resection?

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Running title: Fibrin glue in hepato-pancreatectomy

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ABSTRACT

Background/Aims: Efficacy of fibrin glue to prevent biliary or pancreas fistula at the resected edge of the liver or pancreas is controversial. We examined surgical results of fibrin glue use in 322 patients who underwent hepatectomy and 137 patients who underwent pancreatectomy to assess the efficacy of use of fibrin glue.

Methodology: Subjects were divided into two groups; the fibrin glue group in hepatectomy (n=228) and in pancreatectomy (n=113), and the non-fibrin glue group in hepatectomy (n=94) and in pancreatectomy (n=24). In case of hepatectomy, the fibrin glue was sprayed on the cut-surface or anastomotic site of hepatico-jejunostomy. In case of pancreatectomy, the fibrin glue was sprayed on the anastomotic site of pancreato-jejunostomy or closed pancreatic stump.

Results: In the hepatectomy group, uncontrolled ascites were more frequent in the fibrin glue group than in the non-fibrin glue group ($p < 0.05$). Non-use of fibrin glue was more frequent in recent years for the hepatectomy group. Prevalence of biliary fistula was not significantly different between groups. Hospital stay in the fibrin glue group was significantly longer than that in the non-fibrin glue group. In pancreatectomy, non-use of fibrin glue was more frequent in recent years. There was no significant difference of any complications including pancreatic fistula between groups. In each pancreaticoduodenectomy and distal pancreatectomy, prevalence of pancreatic fistula was not significantly different between the fibrin glue group and the non-fibrin glue group. Hospital stay in the fibrin glue group was not significantly different between groups.

Conclusions: Use of fibrin glue did not prevent biliary or pancreatic fistula in patients who underwent hepatectomy and pancreatectomy with or without enteric anastomosis.

Key Words: Hepatic resection; Pancreatic resection; Fibrin glue; Fistula; Prevention.

INTRODUCTION

Postoperative morbidity after hepatobiliary and pancreas surgery has markedly improved in recent years due to advances in surgical techniques and peri-operative management [1, 2].

However, bile leakage at the transected cut-plane or hepaticojejunostomy after hepatectomy, and pancreatic fistula at pancreatico-jejunostomy or pancreatic stump after pancreatectomy are still not rare [3, 4]. To prevent these complications of bile and pancreatic leakage, sealing with fibrin glue has been reported and is commonly used for various fistulas worldwide [5-11].

However, these leakages still occur, based on our observations, and a few recent reports showed no significant evidence that fibrin glue prevented biliary and pancreatic fistula [12-17].

We intended to have a policy of avoiding use of fibrin glue in the hepatobiliary pancreas surgery in the present series and we attempted to re-evaluate the efficacy of fibrin glue use in these surgery. In the present study, we examined the effects of fibrin glue to prevent biliary and pancreas fistulas after operation in 322 patients who underwent hepatectomy and 137 patients who underwent pancreatectomy. The aim of the present historical study was to assess the efficacy of use of fibrin glue.

METHODOLOGY

Patients

The subjects were 459 consecutive patients with hepato-biliary-pancreas diseases who underwent hepatectomy or pancreatectomy in the Division of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) from 1996 to 2009. The study protocol was approved by the Human Ethics Review Committee of NUGSBS and written informed consent for treatment was obtained from each patient. The present study was retrospectively analyzed but was not a randomized controlled study. Clinical data were consecutively retrieved from the NUGSBS database.

Use of fibrin glue

Subjects were divided into two groups based on use of fibrin glue in each operation; the fibrin glue group in hepatectomy (n=228) and in pancreatectomy (n=113), and the non-fibrin glue group in hepatectomy (n=94) and in pancreatectomy (n=24). Used fibrin glue sealants were 3ml of Beriplast ® P (CSL Behring, King of Prussia, PA) [18]. This fibrin glue was applied by the spray method by use of air pressure. In case of hepatectomy, the fibrin glue was uniformly applied on the cut-surface or anastomotic site of hepatico-jejunostomy after hepatectomy. In case of pancreatectomy, the fibrin glue was applied around the anastomotic site of pancreato-jejunostomy after pancreaticoduodenectomy and closed pancreatic stump after distal pancreatectomy. No adverse effects or transmitted viral infections were observed in these series.

Statistical analysis

Distribution of time to treatment from the beginning of study was compared between both groups by the Wilcoxon rank-sum test. Clinical data including the prevalence of biliary or pancreatic fistula were compared between groups. Continuous data were expressed as mean \pm

SD. Data of the two groups were compared using one-way analysis of variance or the Mann-Whitney's U-test. The Chi-square test was used to compare categorical data. Potentially predictive variables were identified using a significance level of $P < 0.05$ by univariate analysis. Statistical analyses were performed using STATISTICATM software (StatSoft, Tulsa, OK).

RESULTS

Table 1 shows a comparison of clinical data in patients who underwent hepatectomy between the fibrin glue group and non-fibrin glue group. In the present study, a period of non-use of fibrin glue was performed recently. Patient demographics and surgical records were not significantly different between groups. With respect to postoperative morbidity, uncontrolled ascites were more frequent in the fibrin glue group than in the non-fibrin glue group. Prevalence of biliary fistula and intraabdominal infections were not significantly different between groups. Hospital stay in the fibrin glue group was significantly longer than that in the non-fibrin glue group.

Table 2 shows a comparison of clinical data in patients who underwent pancreatectomy between the fibrin glue group and non-fibrin glue group. In the present study, a period of non-use of fibrin glue was performed recently. Blood loss and operating time were more frequent and longer in the non-fibrin glue group than in the fibrin glue group. Use of lost tube for pancreatic duct drainage was more frequent. With respect to postoperative morbidity, there were no significant differences of any complications including pancreatic fistula between groups. In the pancreaticoduodenectomy, prevalence of pancreatic fistula was not significantly different between the fibrin glue group and the non-fibrin glue group (15 of 87 patients [17%] and 5 of 20 [25%], $p=0.64$). In the distal pancreatectomy and central pancreatectomy, prevalence of pancreatic fistula was not significantly different between the fibrin glue group and the non-fibrin glue group (6 of 26 patients [23%] and 0 of 4 [0%], $p=0.6$). Hospital stay in the fibrin glue group was not significantly different between groups.

DISCUSSION

In the 1990's, the use of fibrin glue was noted because of its efficacy for hemostasis or preventing biliary and pancreas fistula in hepato-biliary and pancreas surgery [6, 9, 11] and use of this material was a standard method [5-17]. However, contradictive opinions have been recently reported [12, 14, 15]. Surgical techniques such as vessel sealers or vascular staplers have been developed at this stage [19-22]. Fistulas might also be reduced and hemostasis achieved [23, 24]. Therefore, we have questioned whether fibrin glue was still necessary as a routine method or not, and we attempted to examine surgical results in 2 groups in which fibrin glue was used or not used in the present study. As this trial is a historical study, we attempted to perform operations without fibrin glue recently because the advanced technique was applied in the recent series. In the present result, choice of no use of fibrin glue tended to be applied more frequently.

In patients who underwent hepatectomy, biliary leakage was carefully checked by the leakage test using saline injection in the bile duct at the end of operation. Furthermore, intra-biliary drainage tube via cystic duct or bilio-enteric anastomosis was routinely applied to avoid biliary fistula in the present series (not published yet). Under this situation, 18 of 322 patients (5.6%) showed biliary fistula in the present study. Prevalence of biliary fistula was similar in the non-fibrin glue group. Nevertheless the background liver or extension of hepatectomy was similar between groups, in the fibrin glue group, long-term ascites were more frequently observed and hospital stay was longer according to this complication in comparison with the non-fibrin glue group. Use of fibrin glue might influence the increased intraabdominal fluid collection. As a counter opinion, it has been previously reported that fibrin glue reduced intraabdominal or intrathoracic fluid because of sealing of lymphatic fluid from the cut surface [25, 26]. On the other hand, fibrin glue might not be usually sprayed to the dissected area. We

did not consider that fibrin glue prevented lymphatic fluids, and we speculate that the fibrin glue may conversely lead to an increase of intraabdominal fluid by physical responses.

In patients who underwent pancreatectomy, new surgical procedures have also been developed [20, 22, 27]. In the present series, larger operations tended to be performed more frequently in the non fibrin glue group compared to the fibrin glue group. Furthermore, applying a lost stent occurred more in the non fibrin glue group and applying an external drainage tube was frequently performed more in the fibrin group. Recent reports showed that technique of lost stent tube or no-stent did not lead to an increase of pancreatic fistula [28]. Nevertheless, pancreatic fistula was observed in 26 of 137 patients (19%) and no difference of prevalence of pancreatic fistula including Grade B, C fistula between groups was observed in the present study. Other recent reports also showed a similar prevalence of pancreatic fistula after pancreaticoduodenectomy and distal pancreatectomy even though most cases use of fibrin glue as well [6, 11, 14-17]. In the present series, all complications were similar between groups as well and hospital stay was eventually similar. No adverse effects associated with fibrin glue use were observed in patients undergoing hepatectomy.

In recent years, a new application of fibrin glue was proposed [29-31]. Combination of fibrin glue and covering sheet or powder was applied. Oida et al reported wrapping of pancreato-enteric anastomosis by this material [30]. Trials using this method would be promising to reduce biliary and pancreas fistulas, although definite evidence has not been clarified at this stage.

The present study examined the utility of fibrin glue in 459 patients undergoing hepatic resection and pancreatic resection between 1996 and 2009. The results showed that use of fibrin glue was not significantly associated with postoperative morbidity including fistula and shorter hospital stay. Fibrin glue did not prevent postoperative fistula after hepatic or pancreatic resections and the new glue agent or technique will be expected in the future.

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TABLE 1 Clinical and surgical data in patients who underwent hepatectomy between the fibrin glue group and non-fibrin glue group.

	Fibrin glue group (n=228)	Non-fibrin glue group (n=94)	<i>P</i> Value*
Time to treatment (days) [†]			
Median (days)	3320	5240	<0.001
The 25 th sample percentile (days)	2760	4945	
The 75 th sample percentile (days)	4186	5496	
Age, mean, years	65.3 ±11.7	65.5±11.3	0.92
Sex, Male	148 [65]	71 [75]	0.08
Female	80 [35]	23 [25]	
Background liver disease			
Normal	122 [53]	48 [51]	
Alcoholic hepatitis	2 [1]	1 [1]	
Non-alcoholic fatty liver	0	3 [3]	
Chronic viral hepatitis	49 [22]	25 [27]	0.61
Cirrhosis	38 [17]	12 [13]	
Jaundice	17 [7]	5 [5]	
Background liver disease			
Hepatocellular carcinoma	90 [40]	35 [37]	
Intrahepatic cholangiocarcinoma	21 [9]	7 [8]	
Metastatic liver carcinoma	77 [34]	33 [35]	0.94
Bile duct carcinoma	20 [8]	9 [10]	
Gallbladder carcinoma	11 [5]	4 [4]	
Others	9 [4]	6 [6]	
Child-Pugh classification			
A	220 [96]	94 [100]	0.11
B	8 [4]	0	
Surgical records			
Blood loss (ml)	1196 ±1130	1101 ±943	0.12
Operating time (minutes)	408 ±176	428 ±203	0.18
Extent of hepatectomy			
Hemihepatectomy			
Sectionectomy or segmentectomy	87 [38]	35[37]	0.98
Partial resection	61[27]	25[27]	

Complications	80[35]	34[36]	
No			
Yes	169 [74]	82 [87]	0.02
Biliary fistula	59 [26]	12 [13]	
No			
Yes	200 [88]	88 [94]	0.17
Uncontrolled ascites	28 [12]	6 [6]	
No			
Yes	183 [80]	88 [94]	0.005
Hepatic failure	145 [20]	6 [6]	
No			
Yes	219 [96]	91 [97]	1.0
Intraabdominal abscess	9 [4]	3 [3]	
No			
Yes	205 [90]	88 [94]	0.40
Length of hospital stay (days)	23 [10]	6 [6]	
	32 ±21	22±14	<0.001

Numbers in parentheses represent range of values and those in square brackets represent percentages. †: Time to the treatment since January 1, 1996. Distribution of time to treatment from the beginning of study was compared between both groups by the Wilcoxon rank-sum test.

*By the Student t-test and chi-square test.

TABLE 2 Patient clinical and surgical data in patients who underwent pancreatectomy between the fibrin glue group and non-fibrin glue group.

	Fibrin glue group (n=113)	Non-fibrin glue group (n=24)	<i>P</i> Value*
Time to treatment (days) [†]			
Median (days)	3398	5103	<0.001
The 25 th sample percentile (days)	2437	4810	
The 75 th sample percentile (days)	4057	5422	
Age, mean, years	64.3 ±12.8	67.5±10.8	0.22
Sex, Male	71 [63]	18 [75]	0.37
Female	42 [37]	6 [25]	
Background pancreas			
Soft	72 [64]	16 [67]	0.97
Hard due to associated pancreatitis	41 [36]	8 [33]	
Main disease			
Ampullar carcinoma	15 [13]	2 [8]	0.23
Bile duct carcinoma	27 [24]	4 [17]	
Duodenal tumor	3 [3]	1 [4]	
Chronic pancreatitis	8 [7]	0	
Gallbladder carcinoma	2 [2]	1 [4]	
IPMN	12 [11]	7 [29]	
Pancreatic carcinoma	36 [31]	7 [29]	
Others	10 [9]	2 [8]	
PFD test	62 ±16	54 ±18	0.17
Surgical records			
Blood loss (ml)	1319 ±869	1612 ±916	0.07
Operating time (minutes)	519 ±168	695±253	<0.001
Type of pancreatectomy			
Pancreaticoduodenectomy	87 [77]	20[83]	0.72
Distal pancreatectomy	22[20]	3[13]	
Central pancreatectomy	4[3]	1[4]	
Pancreato-enteric anastomosis			
Stomach	18 [22]	7 [33]	0.34
Jejunum			

Tube drainage at anastomosis	73 [78]	14 [67]	
No			
Lost tube	1 [1]	0	0.018
External drainage	20 [22]	11 [52]	
Pancreatic fistula	70 [77]	10 [48]	
No			
Yes	92 [81]	19 [79]	1.0
Intraabdominal infection	21 [19]	5 [21]	
No			
Yes	87 [77]	17 [71]	0.71
Massive ascites	26 [23]	7 [29]	
No			
Yes	102 [90]	23 [96]	0.69
Length of hospital stay (days)	11 [10]	1 [4]	
	38 ±27	32±19	0.23

Numbers in parentheses represent range of values and those in square brackets represent percentages. †: Time to the treatment since January 1, 1996. Distribution of time to treatment from the beginning of study was compared between both groups by the Wilcoxon rank-sum test.

*By the Student t-test and chi-square test.