



## Cohort Study

# Clinical outcomes and costs of the use of fibrin sealant in pancreaticojejunal anastomosis after pancreaticoduodenectomy: a retrospective analysis study

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## ABSTRACT

**Objectives:** The benefits of using a fibrin sealant to reinforce the pancreaticojejunal anastomosis are still contentious, a fact that justifies the study of its effects on clinical outcomes and costs of pancreaticoduodenectomy.

**Methods:** Study of 62 consecutive patients submitted to pancreaticoduodenectomy, divided into two groups of 31 patients each: GWS = group with sealant and GWOS = group without sealant that were compared according to demographic, clinical, laboratory aspects, the incidence of postoperative pancreatic fistula (POPF), according to the definition of the International Study Group on Pancreatic Fistula, updated in 2016, and its postoperative complications categorized according to the Clavien classification, as well as hospital costs evaluated by the absorption costing method (with the exception of those related to medications).

**Results:** The groups were homogeneous and there were no significant differences in the postoperative clinical course or in the indicators of hospital care between them. Hard texture of pancreatic tissue was the only protective factor against the development of POPF (RR = 0.29 (95%CI:0.12–0.68); p = 0.005). Moreover, hospital costs were higher in GWS than in GWOS (p < 0.0001).

**Conclusions:** The use of fibrin sealant to reinforce pancreaticojejunal anastomosis did not improve the clinical and healthcare outcomes and, in addition, increased hospital costs.

## 1. Introduction

Pancreaticoduodenectomy is the treatment of choice for resectable tumors of the pancreato-duodenal confluence, but despite the decline in mortality rates to approximately 5% over the years, morbidity rates remain high ranging between 30% and 50% [1]. The most frequent complications from the procedure are attributed to pancreatic fistula which is associated with delayed gastric emptying, postoperative bleeding, and complications after arterial reconstruction [2].

Pancreatic fistula is the most feared post pancreatic surgery complication and its occurrence increases the length of hospital stay and treatment costs, requires additional investigations and procedures, and may result in further complications such as abdominal collections and sepsis [3]. The reported incidence of pancreatic fistula in patients submitted to pancreaticoduodenectomy differs among studies, varying

between 5% and 35% [4].

Several alternatives have been used in an attempt to decrease the incidence of pancreatic fistula including the administration of octreotide [5], alternative techniques of pancreatico-jejuno-stomy [6], stent placement in pancreatic duct [7], drain management [8], use of microscropy [9], and use of adhesives or fibrin sealants [10–13].

The fibrin sealant, produced in the laboratory in 1980 and sold in 1998, consists of an adhesive formed from the union of fibrinogen and thrombin, with the principle of mimicking the last step of the human coagulation cascade. Despite several commercial formulations, the principle of use is the same, with different indications for its use, such as control of local hemostasis, sealing and adhesion of stapling lines and anastomoses, in addition to strengthening wound healing [11].

Studies on the effects of using fibrin sealant in pancreatic surgery are scarce and controversial. There is only one systematic review on the

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topic [12] which reported a 35% incidence of pancreatic fistula and a trend of reduction in the incidence of postoperative bleeding and formation of postoperative intra-abdominal collections. Thus, the adoption of alternatives to reduce morbidity and mortality after pancreatic resection, namely in the contexts of clinical management [14–16], clinical care [17], and surgical technique [14,18], is pertinent. In this context, the scarcity of data on the effects of fibrin sealant used in pancreaticojejunal anastomosis, the controversial results of the available studies, the lack of assessment of the costs incurred, and the claims of the pharmaceutical industry emphasizing its advantages warrant a detailed study on the effects of using fibrin sealant to reinforce pancreaticojejunal anastomosis on clinico-surgical outcomes and hospital costs.

## 2. Materials and methods

### 2.1. Study design, location, and data collection

The present study was a retrospective analysis, with uncontrolled intervention, based on a collection of data from medical records of 62 patients submitted to pancreaticoduodenectomy (with or without pylorus preservation), treated consecutively by the same team of surgeons between 2007 and 2012, regardless of the disease that prompted the procedure, divided into two groups of 31 patients each: GWS = group with sealant and GWOS = group without sealant.

The patients underwent surgery at the Hospital das Clínicas of the Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP), a tertiary public teaching hospital.

The data retrieved from active, semi-active, and death records and from the clinical and administrative data system of the hospital were registered in a data sheet created for the purpose of the present study, along with the demographic, clinical and morphological characteristics, preoperative assessment, perioperative care, surgical technique, anatomopathological findings, postoperative complications, consumables, and costs. The work has been reported in line with the STROCSS criteria [19].

The study was approved by the ethics committee (CEP HCFMRP-USP, 723,520, July 21, 2014).

### 2.2. Reconstruction of the gastrointestinal tract

Pancreaticoduodenectomy was performed through a wide bilateral subcostal incision with resection of the pancreatic head, duodenum, gastric antrum (in cases without pylorus preservation), common extrahepatic bile duct, and gallbladder.

Tract reconstruction was performed in a single intestinal loop with three anastomoses. Pancreaticojejunal anastomosis was performed in two layers: pancreatic capsule/jejunal serosa with interrupted, nonabsorbable polyester 2-0 suture, and pancreatic duct/jejunal mucosa using interrupted, polypropylene 5-0 suture. A transanastomotic internal plastic stent was placed with the exception of one case in each group for which telescoping of the pancreatic stump in the jejunal loop was performed because the main pancreatic duct was not identified. In these cases, the free pancreatic stump was invaginated into the jejunal lumen and fixed with nonabsorbable polyester 2-0 suture in two layers between the pancreatic capsule and the jejunal wall. The end-to-side bilio-jejunal anastomosis was performed in the same jejunal loop, approximately 10 cm from the pancreatic anastomosis in a single layer with continuous absorbable 4-0 suture. After approximation of ligaments and peritoneum which shape the duodenojejunal flexure, duodenojejunal or transmesocolic end-to-side gastrojejunal anastomosis was performed approximately 15–20 cm distal to the bilio-jejunal anastomosis, in a single layer, with continuous nonabsorbable monofilament 3-0 or 4-0 suture, and was sutured in the inframesocolic space with interrupted stitches between the peritoneum and the stomach using the same type of thread.

### 2.3. Fibrin sealant

Fibrin sealant in pancreatic anastomosis was used by convenience and availability in the first four years (19 patients in GWOS, 61% of total; 7 patients in GWS, 22% of total) and subsequently randomly (like yes/no) until the two groups were formed. The size of the groups was adjusted according to the availability of the material (sealant fibrin) in our hospital.

It was always applied at the end of the procedure, after the removal of fluids around the anastomosis, and the volume varied between 1.5 mL and 7 mL (mean 3.55 mL). The following brands were used depending on availability: BERIPLAST (3 mL kit) (CSL Behring, Marburg - Germany) in 85% of the cases and TISSUCOL (0.5 mL kit) (Baxter AG, Viena, Austria) in 15% of the cases. All the elements in the package were assembled and the sealant was applied homogeneously to the entire pancreatic anastomosis on its anterior and posterior sides. A tubular silicone drain was placed in the supramesocolic space, anterior to the bilio-jejunal and pancreaticojejunal anastomoses, with its end behind the posterior wall of the stomach and exteriorized on the right side.

### 2.4. Pancreatic fistula and surgical complications

Pancreatic fistula was classified according to the universally accepted definition and revised in 2016 by the International Study Group on Pancreatic Fistula, in BL (Biochemical leak), B and C, and any drainage of cavity secretion used as a definition of pancreatic fistula beyond the 3rd day of postoperative, with the liquid amylase 3 times the higher serum normal value, associated with any relevant clinical condition related to the fistula itself [20].

The postoperative complications were categorized based on the Clavien-Dindo classification [21,22].

### 2.5. Cost analysis

The micro-costing method was used to assess the costs of the procedures performed in the operating room, in the ward of the Digestive Surgery Division or in the intensive care unit. The cost accounting department of the HCFMRP-USP determined the costs of hospitalization, laboratory tests, and imaging exams during hospitalization using the absorption costing method with simple apportionment of all fixed expenses (e.g., staff, materials, technologies, water, electricity, telephone). Expenses with medications were accounted for separately. The costs of medications included all medications used during the hospitalization period and surgery costs included only the materials used during the procedure with fixed costs being excluded.

### 2.6. Statistical analysis

The groups were compared using the non-parametric Mann-Whitney test for quantitative analysis and Fisher's exact test for comparative analysis, with a significance level of 5%. For multivariate analysis of predictors of risk for POPF, Poisson regression models with robust variance were fitted to the data, with POPF as the independent variable. The relative risks of each covariable were evaluated, with a confidence interval of 95%, and significance set at  $p < 0.05$ .

## 3. Results

The groups were homogeneous for the demographic, clinical, and perioperative care variables, among others, as shown in Table 1. The global incidence of POPF in both groups was 24% ( $n = 15/62$ ).

The histopathological findings were similar between the groups (Table 2).

There was a predominance of POPF graded as type B and C according to the ISGPS 2016 classification, instead of BL, but no significant difference was observed between the groups. Overall mortality was 4.8%

**Table 1**

Comparison of the demographic, clinical, laboratory, morphological, and peri-operative care variables, expressed as absolute values, means or medians, between the group without fibrin sealant (GWOS) and the group with fibrin sealant (GWS).

	GWOS (n = 31)	GWS (n = 31)	p
Age (years)	60.9	58	0.4775
Male Sex	18 (58.1%)	14 (45.1%)	0.4462
Total bilirubin (mg/dL), mean	17.48	12.43	0.1453
Direct bilirubin (mg/dL), mean	11.47	8.86	0.2586
Alkaline phosphatase (U/L), mean	1154.13	1275.8	0.7033
Gamma-glutamyltransferase (U/L), mean	537.9	456.83	0.5864
Albumin (g/dL), mean	3.83	3.53	0.094
Preoperative biliary drainage (N), mean	9 (29%)	5 (16.1%)	0.3627
Mean time (days) between biliary drainage and surgery	41.5	19	0.4312
Duration of surgery (min), mean	479.84	494.84	0.4998
POPF (n)	9 (29%)	6 (19%)	0.5541
Mean length of hospital stay (days)	16.39	19,3	0.3336
Mean time (days) for collection of drain amylase	5.4	5.67	0.7493
Drain amylase (U/L), median	1184	8200	0.1419
Mean time (days) to fistula diagnosis	5.6	7	0.7912
Mean drain output (mL)	545.4	417	0.1469
Duration of fistula/drain dwell time (days), mean	19.4	22.56	0.3432
Postoperative antibiotic therapy (days), mean	21 (67.7%)	15 (48.4%)	0.1978
Positive bile culture (n, total)	10/23 (43.5%)	14/26 (53.8%)	0.5709

POPF, post-operative pancreatic fistula (ISGPS 2016).

**Table 2**

Histopathological findings in the groups without (GWOS) and with (GWS) fibrin sealant.

	GWOS (n = 31)	GWS (n = 31)
Pancreatic adenocarcinoma	12 (38.7%)	12 (38.7%)
Adenocarcinoma of the papilla	9 (29%)	12 (38.7%)
Bile duct adenocarcinoma	3 (9.6%)	1 (3.3%)
Duodenal adenocarcinoma	2 (6.5%)	1 (3.3%)
Endocrine neoplasia	2 (6.5%)	2 (6.4%)
Other	3 (9.7%)	3 (9.6%)

**Table 3**

Grading of fistulas in the groups without (GWOS) and with (GWS) fibrin sealant.

	GWOS (n = 31)	GWS (n = 31)	p
Classification of complications of pancreatic surgery (Clavien score)	I	15 (48%)	17 (55%)
	II	12 (38%)	11 (35%)
	IIIa	2 (7%)	1 (3.3%)
	IIIb	0	1 (3.3%)
	IVa	0	0
	IVb	0	0
Grading of POPF	V	2 (7%)	1 (3.3%)
	BL	1 (10%)	3 (33.3%)
	B	3 (30%)	3 (33.3%)
C	6 (60%)	3 (33.3%)	

POPF, post-operative pancreatic fistula.

(Table 3).

Multivariate analysis showed that hard consistency of pancreatic tissue was an independent predictor of protection against the occurrence of POPF (RR = 0.29 (95% CI 0.12–0.68); p = 0.005) (Table 4).

There was no significant difference in the costs of hospitalization, medications, laboratory tests, and imaging exams in the postoperative

**Table 4**

Risk predictors for postoperative pancreatic fistula in the groups without (GWOS) and with (GWS) fibrin sealant.

	Adjusted RR	Confidence interval 95%		p value
		Lower limit	Upper limit	
Use of fibrin sealant	1.05	0.42	2.60	0.921
Age (>65 years)	1.01	0.38	2.67	0.980
Albumin (<3.5 mg/dl)	1.39	0.56	3.44	0.474
Preoperative biliary decompression	0.86	0.32	2.26	0.754
Texture of the pancreas (hard)	0.29	0.12	0.68	<b>0.005</b>
Pancreatic duct diameter (<3 mm)	2.06	0.86	4.95	0.104
Duration of surgery (>480 min)	1.39	0.63	3.09	0.413
Antibiotic (prophylaxis)	2.12	0.82	5.47	0.121
Bile culture (Positive)	0.84	0.47	1.50	0.550

period until discharge. The cost of the surgical procedure in GWS was higher than that in GWOS (Table 5).

#### 4. Discussion

Topical application of fibrin with the aim of improving local hemostasis and healing has been practiced for over a century [23]. Although there is a vast literature on the use of fibrin sealant in various areas of surgery, including orthopedic [24], cardiac [25], and hepatic [26] surgery, its use in pancreatic surgery remains controversial and literature on the topic is scarce [13].

There is only one systematic review with a meta-analysis [12] that included 897 patients submitted to pancreatic surgery (pancreaticoduodenectomy and body-tail or left pancreatectomy), with seven randomized controlled studies in which it was concluded that the fibrin sealant did not affect the incidence of POPF or its complications, but requires further investigations.

A recent randomized multicenter study assessed the effects of fibrin sealant on 142 patients submitted to pancreaticoduodenectomy, with each group containing 71 patients. The analyzed variables, including incidence and severity of POPF showed no significant difference [27].

Although the groups assessed in the present study weren't randomly formed, all patients were treated under similar care conditions and using similar clinical-surgical protocols. The demographic, epidemiological, clinical, and morphological characteristics and the preoperative laboratory findings were also homogenous among the groups. Some aspects related to the characteristics of the study location such as duration of surgery, length of hospital stay and abdominal drain dwell time were also not significantly different between the study groups.

The histopathological findings were similar between the groups. Frequency results were in line with the literature, with a predominance of pancreatic head adenocarcinoma [28]. The incidence of POPF, which was 24%, did not differ between groups, and was very similar to the findings reported in the literature [29]. This indicated that the use of fibrin sealant did not prevent the occurrence of POPF.

In addition, fibrin sealant did not alter the severity of pancreatic

**Table 5**

Cost (in dollars) of treatment in the groups without (GWOS) and with (GWS) fibrin sealant.

	GWOS (n = 31)	GWS* (n = 31)	p
Cost of surgery	388.96	876.66	<0.0001
Cost of hospitalization	2236.61	2521.35	0.7212
Cost of medications	266.66	355.62	0.3535
Cost of exams	249.96	363.19	0.1472
Total cost	3142.21	4116.83	<b>0.0124</b>

\* The mean cost (in dollars) of the fibrin sealant was 423.29.

fistula because there was no difference between the groups with regard to the pancreatic fistula grade (BL, B, C) as per the International Study Group on Pancreatic Fistula classification, updated in 2016. There was a predominance of clinically relevant (types B and C) over BL in GWOS (although not significantly different) unlike what is reported in the literature, i.e., fistulas without clinical repercussions, which do not interfere with the postoperative clinical course (BL, old type A), predominate over types B and C fistulas [30].

The incidence and type of postoperative complications, according to the Clavien classification, were similar between the groups. There was a low incidence of more severe complications, which is in line with the literature [30], and the mortality rate was very close to that observed in the main specialized healthcare centers (between 3% and 7%) [28], with no significant difference between the groups.

The analysis of the individual potential predictors of risk for POPF [31,32] showed that there was no difference with respect to the study variables, including the use of fibrin sealant. The hard consistency of pancreatic tissue was shown to be the only protective factor against the occurrence of POPF.

The use of fibrin sealant did not affect the costs of hospitalization, medications, laboratory tests, and imaging exams performed during the postoperative period. However, expenses for materials used during the surgical procedure were greater in the GWS (\$ 388.96; \$ 876.66;  $p < 0.0001$ ), reaching almost 50% of the total cost of the materials used in the procedure in some cases. As a result, the total costs (including hospitalization, medications, exams and surgery) were higher in the GWS.

In conclusion, the results obtained from the present study show that the application of fibrin sealant to reinforce pancreaticojejunal anastomosis in patients submitted to pancreaticoduodenectomy did not reduce surgical morbidity or its severity but increased the costs of treatment.

#### Provenance and peer review

Not commissioned, externally peer-reviewed.

#### Ethical approval

The study was approved by the Medical Ethics Committee of this hospital (HCRP process no 723.520, July 21, 2014).

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#### Author contribution

Alberto Facury Gaspar - study design, data collections, writing, José Sebastião dos Santos - writing, study design, revisor, Rafael Kemp - contributor, João Almiro Ferreira Filho - contributor, Daniel Martone - contributor, Gustavo de Assis Mota - contributor, Jorge Resende Lopes Junior - contributor, Ajith Kumar Sankarankutty - contributor.

#### Research registration

Name of the registry: Clinical outcomes and costs of the use of Fibrin Glue in Pancreatic Surgery.

Unique Identifying number or registration ID: RBR-10t84b5s  
Hyperlink to your specific registration (must be publicly accessible and will be checked):

Brazilian Clinical Trials Registry (ReBec).  
<https://ensaiosclinicos.gov.br/rg/RBR-10t84b5s>.

#### Guarantor

Alberto Facury Gaspar.  
José Sebastião dos Santos.

#### Declaration of competing interest

No conflicts of interest.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102531>.

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