

Incidence of Pancreatic Fistula after using N-butyl-2-Cyanoacrylate Glue for Pancreaticojejunostomy Anastomosis after Pancreatoduodenectomy in Rajavithi Hospital

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Background: Pancreatic fistula remains a common occurrence after pancreatoduodenectomy (PD). There is no consensus on which options should be used to reduce its incidence.

Objective: To assess the efficacy of N-butyl-2-cyanoacrylate glue (Histocryl) in reducing pancreatic fistula after PD.

Material and Method: This was a prospective study conducted between 2015 and 2017 at Rajavithi Hospital, of 67 consecutive patients who underwent PD with pancreaticojejunostomy. Patients were divided into two groups, with 25 patients in the N-butyl-2-cyanoacrylate glue group and 42 patients in the control group. Postoperative pancreatic fistula was assessed after the third postoperative day.

Results: Pancreatic fistula was diagnosed in eleven patients (16%): two (8%) in the N-butyl-2-cyanoacrylate glue group and 9 (21.4%) in the control group. There were no significant differences between the groups, and no patients in the present study died from pancreatic fistula-related complications.

Conclusion: The present study demonstrated that applying N-butyl-2-cyanoacrylate to pancreaticenteric anastomosis after PD may reduce the incidence of pancreatic fistula.

Keywords: N-butyl-2-cyanoacrylate glue, pancreatic fistula, pancreatoduodenectomy, whipple operation, pancreatic anastomosis

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Pancreatic operations are technically challenging surgical procedures. In the past, they were associated with high morbidity and mortality rates, and although these operations currently have mortality rates of below 5%, the incidence of morbidity is still common in high-volume centers⁽¹⁾. One of the most important and potentially life-threatening complications is the occurrence of an abdominal abscess or major hemorrhage which are common sequelae of pancreatic anastomotic leakage^(2,3).

Currently, there is no consensus on the best way of managing the pancreatic stump after PD. There are numerous variations in surgical techniques⁽⁴⁾, and another surgical strategy is to use the trans-anastomotic pancreatic ductal stent. No specific technique can

eliminate the possibility of development of a clinically relevant postoperative pancreatic fistula.

A wide variety of adhesive sealants have been used for many years in the surgical field. Methods of effectively sealing tissues in order to prevent postoperative fistula formation are still under debate as definitive evidence is lacking. Nowadays, not all studies use cyanoacrylate acrylate to protect pancreatic anastomosis.

The aim of the present study was to determine the efficacy of N-butyl-2-cyanoacrylate sealant in reducing pancreatic fistula after PD.

Material and Method

Patient selection

The study protocol was approved by Rajavithi ethics committee. From June 2015 to March 2017, 67 consecutive patients underwent PD with PJ anastomosis for a variety of disorders in this single institute, and their details were entered into a prospective database. All patients had elective

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operations after full workup and validation of the requisite preoperative conditions, and the operations were performed by experienced surgeons. Technical variations of PD such as pylorus-preserving techniques, types of pancreatic anastomosis, and ductal stenting with or without glue were performed according to the surgeons' preference. All patients had abdominal drainage after PD. The profile and pre-operative data show in Fig. 2. Eligibility criteria were all subjects who underwent PJ anastomosis after PD, and patients who underwent PG anastomosis, Roux-en-Y pancreatojejunostomy, Hepaticopancreaticoduodenectomy or laparoscopic pancreatoduodenectomy were excluded. Prophylactic antibiotics were routinely given 30 minutes preoperatively and continued until the third postoperative day unless infection was suspected. Neither octreotide nor somatostatin was used prophylactically.

Surgical technique

An SMA first approach⁽⁵⁾, with both medial and lateral approach with a standard lymph node dissection, was used. Upon completion of the PD, the proximal 2–3 cm of the pancreatic body remnant was mobilized in preparation for anastomosis. In this study, patients undergoing PJ anastomosis were divided into two groups, using 5 surgical anastomosis techniques as shown in Fig. 1. In the control group, all patients who underwent PJ anastomosis using the duct-to-mucosa technique, and apolyethelene tube (Fr. 5.0 to 8.0 according to the size of the pancreatic duct) were inserted to the pancreatic duct. Small bowel mucosa and the pancreatic duct were anastomosed with PDS 5/0, and the stent was fixed by PDS 5/0. In the second layer, four trans pancreatic U-sutures were placed straight through the pancreatic remnant about 1 cm distal from the cut end. Each of the sutures started at the ventral side of the gland, and the seromuscular layer of the jejunum was sutured on both sides to cover raw surface of pancreatic stump as shown in Fig. 2 (modified Blumgart technique⁽⁶⁾). Bilioenteric end-to-side anastomosis was performed 5 to 7 cm distal to the pancreatic anastomosis, or by a subsequent antecolic end-to-side gastrojejunostomy or pylorojejunostomy, depending on the type of resection (with or without preservation of the pylorus). If the pylorus was not preserved, a Braun anastomosis was constructed.

In the study group, transanastomosis pancreatic duct stent was performed using an internal or external stent. The same techniques for anastomosis and fixing of the stent were used as described in the

control group. Cyanoacrylate 0.5 ml was aspirated with an insulin syringe then applied to the PJ anastomosis before the last knots were tied and 1 to 2 drops were applied around the anastomosis. The PJ anastomosis was not sutured between pancreatic ducts and the small bowel mucosa. We performed suture of the second layer using the same technique after passing the transanastomosis pancreatic duct stent. Cyanoacrylate 0.5 ml was used before the last knot was tied.

Postoperative management

On the third postoperative day, serum amylase and fluid amylase from the drain were collected and analyzed. Diagnosis of postoperative pancreatic fistula was in accordance with the International Study Group of Pancreatic Surgery (ISGPS) criteria⁽⁷⁾. The nasogastric tube was removed and early enteral feeding was encouraged. The abdominal drains were removed on the seventh post-operative day when pancreatic fistula (PF) was not diagnosed.

Definition of pancreatic fistula (PF)

PF was defined as levels of amylase of fluid from drain after the third operation day of more than 3 times the serum level.

PF was graded according to the clinical impact on the patient's hospital course (grade A, B, or C). A proportion of PF patients will be asymptomatic (grade

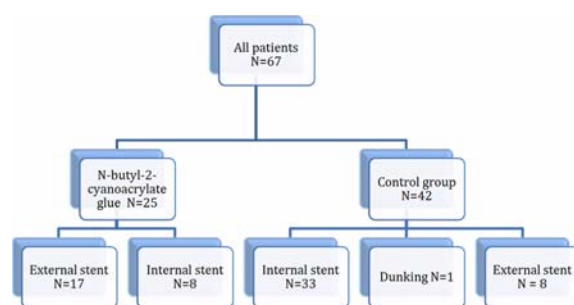


Fig. 1 Flow diagram showing the study population and distribution of patients after inclusion.

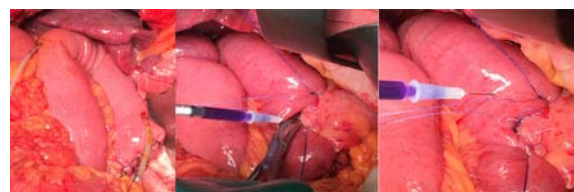


Fig. 2 Modified Blumgart pancreatojejunostomy anastomosis.

A) or poorly symptomatic (grade B), whereas others will develop abscesses, peritonitis, sepsis, hemorrhage or require interventional procedures, and these are classified as grade C.

Statistical analysis

Statistical analysis was performed using the software program SPSS for windows version 17.0. Patient characteristics and other numerical data were expressed as descriptive statistics such as mean, standard deviation, minimum-maximum. Fisher's exact test and Chi-square test were used to compare categorical variables between groups. Student t-test and Mann-Whitney U test was used to compare continuous variables. A p -value <0.05 was considered statistically significant.

Results

Patient population

The patients' demographic and pre-operative data are shown in Table 1. There were no significant differences with regard to gender or pre-operative factors between the 25 patients in the N-butyl-2-cyanoacrylate glue and the 42 patients in the control group. There were also no significant differences between the groups in terms of pre-operative biliary drainage or pancreatic duct diameter.

The histopathological findings are shown in Table 1. Six patients (24%) in the N-butyl-2-cyanoacrylate glue group had underlying disease compared with eight patients (19%) in the control group. In addition, there was significantly less positive margin in the study group than in the controls (0% vs. 7%;

Table 1. Baseline Characteristics

Characteristic	N-butyl-2-cyanoacrylate glue n =25	Control group n = 42	p -value
Gender			1.000
Male	11 (44.0)	19 (45.2)	
Female	14 (56.0)	23 (54.8)	
Age	62.16 \pm 11.19	57.05 \pm 12.96	0.094
Diagnosis			0.533
Ampulla	15 (60.0)	16 (38.1)	
Distal CCA	1 (4.0)	3 (7.1)	
Head of Pancreas	6 (24.0)	6 (14.3)	
Duodenum	0 (0.0)	3 (7.1)	
GIST	1 (4.0)	4 (9.6)	
Chronic pancreatitis	0 (0.0)	3 (7.1)	
IPMN	1 (4.0)	3 (7.1)	
Cystic pancreas tumor	0 (0.0)	2 (4.8)	
PNET	1 (4.0)	2 (4.8)	
Underlying disease			
Diabetic mellitus	4 (16.0)	6 (14.3)	1.000
Neurofibromatosis	0 (0.0)	1 (2.4)	0.373
Non-Hodgkin Lymphoma	1 (4.0)	0 (0.0)	0.373
Coronary artery disease	1 (4.0)	0 (0.0)	0.373
Deep vein thrombosis	0 (0.0)	1 (2.4)	1.000
Pre operation laboratory			
BUN (mg/dL)	12.28 \pm 5.41	12.10 \pm 5.2	0.890
Cr (mg/dL)	0.74 \pm 0.30	10.72 \pm 0.22	0.800
Alb (mg/dL)	3.80 \pm 0.60	3.75 \pm 0.87	0.775
TB (mg/dL)	0.99 (0.12 to 23.89)	0.80 (0.18 to 28.70)	0.912
Pre operation biliary stent	17(68.0)	26(61.9)	0.793
PD size			0.135
1-3 mm	13 (52.0)	29 (69.0)	
4-6 mm	9 (36.0)	6 (14.0)	
≥ 7 mm	3 (12.0)	7 (16.7)	

Values are represented as n (%), mean \pm SD, Median (Min-Max)

P0.04). Intra-operative parameters are shown in Table 3. There were no differences in operative time, blood loss, pylorus preserving or portal vein resection in this study.

Complication

Post-operative complications and course are shown in Table 3. The overall mortality rate was 4.5%, one patient in the N-butyl-2-cyanoacrylate glue group and two in the control group. There was one pancreatic

fistula related death in the control group. The most common post-operative complication was post-operative pancreatic fistula (17.9%), and there were no significant differences in post-operative complications or length of hospital stay.

Discussion

Pancreatic leak after pancreaticojejunostomy is the most frequent and serious complication of PD. Its incidence varies between 2% and 50%^(8,9), and there

Table 2. Intraoperative parameters

Characteristic	N-butyl-2-cyanoacrylate glue	Control group	p-value
Pylorus preserve	0 (0.0)	7 (16.7)	0.040*
Portal vein resection	4 (16.0)	6 (14.3)	1.000
PJ anastomosis			<0.001*
Internal stent	8 (32.0)	33 (78.6)	
External stent	17 (68.0)	8 (19.0)	
Dunking	0 (0.0)	1 (2.4)	
Operative time			0.418
<6	10 (40.0)	18 (42.9)	
6 to 8	9 (36.0)	19 (45.2)	
>8	6 (24.0)	5 (11.9)	
Blood loss			0.745
0 to 500	7 (28.0)	14 (33.3)	
501 to 1,000	6 (24.0)	12 (28.6)	
1,001 to 1,500	5 (20.0)	4 (9.5)	
1,501 to 2,000	4 (16.0)	5 (11.9)	
≥2,000	3 (12.0)	7 (16.7)	

Values are represented as n (%). * = Significant at $p < 0.05$

Table 3. Postoperative out come

Characteristic	N-butyl-2-cyanoacrylate glue	Control group	p-value
Complication			
Chyle leakage	3 (12.0)	4 (9.5)	1.000
Intraabdominal collection	2 (8.0)	3 (7.1)	1.000
PPH*	0 (0.0)	1 (2.4)	1.000
Pancreatic fistula	2 (8.0)	9 (21.4)	0.512
Diarrhea	0 (0.0)	1 (2.4)	1.000
Acute kidney injury	1 (4.0)	1 (2.4)	1.000
Pulmonary complication	1 (4.0)	0 (0.0)	0.373
Delay gastric emptying time	1 (4.0)	4 (9.5)	0.643
Dead	1 (4.0)	2 (4.8)	1.000
Length of hospital stay	11 (7 to 60)	15 (5 to 45)	0.981
R1	0 (0.0)	7 (16.7)	0.040**
NodePositive	6 (24.0)	15 (35.7)	0.417

PPH = post pancreaticoduodenectomy hemorrhage

* = Significant at $p < 0.05$. Values are represented as n (%), mean \pm SD, median (min-max)

have been several studies of many different risk factors such as age, BMI, operative time, blood loss, pathology of pancreas, diameter of the main pancreatic duct (MPD) and texture of pancreatic parenchyma^(10,11). Since the 1990s, octreotide has been used to reduce the incidence of pancreatic fistula, but its efficacy remains controversial, and a meta-analysis performed in 2013 did not find any benefits resulting from its use⁽¹²⁾. Many organic (fibrin glue, photodynamic fibrin glue) or inorganic (cyanoacrylate derivatives, hydrogel) tissue adhesives have been evaluated in a number of surgical settings with various findings, such as their ability to achieve improved local hemostatic control, reinforce suture lines and stimulate wound healing; however, their effectiveness in pancreatic surgery remains unsatisfactory. Many studies during the last two decades have focused on the role of fibrin glue sealant as an adjunct in the healing of pancreatic anastomoses including its use as either a topical application or as an intraductal injection for temporary pancreatic ductal occlusion during PD or distal pancreatectomy; however, its use has revealed variable results and has failed to demonstrate tangible benefits⁽¹³⁻¹⁵⁾. In 1984 Tashiro et al⁽¹⁶⁾ reported an overall mortality rate of 10.6%, 1 patient (2.4%), using biological adhesive for PJ anastomosis. In the present study, 10 of 14 patients' deaths were due to complications after pancreatic leakage, the incidence of which was as follows: minor leakage 7.1%, 5.7%; major leakage 2.4%, 8.6%; and total leakage 9.5%, 14.3% in the adhesive and control groups, respectively. The mortality rate in the study group was significantly lower than in the control group ($p < 0.05$). This paper defined pancreatic leakage as a difference from ISGPF by volume of the drain, with a major leakage cut off point of more than 100 ml/day.

D'Andrea⁽¹⁷⁾ and Keith D. Lillemoe et al⁽¹⁴⁾ demonstrated an increased incidence of pancreatic fistula in their non-sealant group (13.9% and 11.1%, 30% vs. 26%, respectively); however, fibrin glue sealant did not reduce the incidence of pancreatic fistula or total complications after PD in either study. Recently, systemic reviews by Cheng et al⁽¹⁸⁾ included 9 trials involving 1,095 participants. There was no evidence of differences in overall postoperative pancreatic fistula (fibrin sealant 29.6%; control 31.0%; RR 0.93, 95% CI 0.71 to 1.21; $p = 0.58$). Nevertheless, systemic reviews have many confounding factors (*e.g.* different sealing locations, different types of fibrin sealants, different types of operations) and may also have an effect on the incidence of postoperative pancreatic fistula (POPF). Subgroup analysis found that of the 251

participants who had fibrin sealants applied to pancreatic anastomosis reinforcement, the overall POPF rate was 23.1%.

Most studies have tended to use biological tissue adhesives. One of the main reasons why fibrin sealant did not decrease the rate of POPF was because pancreatic juice antiprotease can cause dissolution of fibrin glue from biological material⁽¹⁹⁾ while the addition of aprotinin may inhibit the degradation effect⁽²⁰⁾.

Cyanoacrylate (CA) is a synthetic tissue adhesive. In 1968, N-butyl-2-cyanoacrylate was approved by the FDA and was widely used during the Vietnam War. The direct use of CA on abdominal organs has been addressed by a number of trials in animals, including a study of the repair of traumatic liver injuries, traumatic duodenum and pancreas anastomosis⁽²¹⁾. The healing results, especially of solid organs, demonstrated effectiveness. In humans, CA has been used in many surgical fields. In 2011, a series of biliary and enteric fistulas were successfully resolved through transcatheter embolization⁽²²⁾. In pancreatic surgery, CA adhesives can be useful in the occlusion of the pancreatic duct to prevent PF or treatment after resection. The results of these studies confirmed that the use of the adhesive in the main pancreatic duct seems to be an effective and safe occlusion method⁽²³⁾.

In our study, 25 patients undergoing PD with external or internal pancreatic duct stent were operated on using N-butyl-2-cyanoacrylate glue to fill up pancreatojejunostomy anastomosis. Our study demonstrated decreased incidence of pancreatic fistula compared with that of a control group (8% and 21.4%). Although the results were not statistically significant, the majority of the fistulas in N-butyl-2-cyanoacrylate glue group were caused by biochemical leakage (grade A). Our data showed no major difference in duration of postoperative hospital stay or time to recovery between patients with grade A fistula and those without fistula. We used pancreatic stents to divert pancreatic juice from the anastomosis in order to avoid early fibrinolytic effect, and we observed a decrease in PF with both external and internal stents. Although our study did not clearly demonstrate decreased incidence of POPF in patients at high risk, especially when the pancreas has a soft consistency, small pancreatic duct or anastomosis between the pancreatic duct and the mucosa of the jejunum, operating is difficult technically and alternatively methods may be more suitable.

A disadvantage of N-butyl-2-cyanoacrylate glue is its relatively high cost, and the outcomes of its use with clinically significant postoperative pancreatic

fistula in this study did not demonstrate a statistically significant difference between the two groups. More trials are needed to confirm this hypothesis.

In conclusion, the present study demonstrated that applying N-butyl-2-cyanoacrylate to pancreaticenteric anastomosis after PD may reduce the incidence of pancreatic fistula, total complications, and length of hospital stay; regardless, the results are at least comparable with those achieved using conventional methods.

What is already known on this topic?

The incidence of POF is still high, varying between 2% and 50%, and potentially life-threatening complications occur most frequently after pancreatic anastomotic leakage. As yet, there is no consensus on the best method to reduce this event.

What this study adds?

Applying cyanoacrylate (CA) is a feasible and safe procedure that helps secure pancreatic anastomosis.

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Potential conflicts of interest

None.

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