ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 06, pp.51882-51888, June, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

ISOLATED LOOP PANCREATICOJEJUNOSTOMY VS. CONVENTIONAL PANCREATIC STUMP ANASTOMOSIS FOLLOWING PANCREATICODUODENECTOMY: ANOBSERVATIONAL STUDY

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ARTICLE INFO

Article History:
Received 23rd March, 2017
Received in revised form
10th April, 2017
Accepted 13th May, 2017
Published online 20th June, 2017

Key words:

Isolated loop pancreaticojejunostomy,
Pancreaticoduodenectomy,
Postoperative pancreatic fistula,
Delayed gastric emptying.

ABSTRACT

Background: Surgical resection is the only potentially curative therapy for pancreatic and periampullary cancer. The morbidity and mortality of pancreaticoduodenectomy (PD) is related to the outcome of anastomosis**.**

Methods: This was a retrospective analysis of prospectively collected datafrompatients undergoing PD for pancreatic or peri-ampullary cancers between 2010 and 2014.Whipple's pancreaticoduodenectomy was performed by three expert, senior surgeons. Pancreatico-enteric anastomoses were either in the form of a pancreaticogastrostomy/pancreaticojejunostomy (PG/PJ; Group A), or isolated loop pancreaticojejunostomy (IPJ; Group B). The primary outcomes were pancreatic fistula formation, delayed gastric emptying, intra-abdominal abscess formation, post-pancreatectomy hemorrhage, and mortality. Operative variables such as duration of surgery, blood loss, and transfusion requirements were also assessed, and minor morbidities including pneumonitis, urinary tract infections, and wound infections were analyzed.

Results: 140 patients underwent Whipple's pancreaticoduodenectomy, 100 patients underwent PG/PJ (Group A) and 40 patients underwent IPJ (Group B). DGE was significantly less frequent in Group B compared to Group A patients, occurring in 10% and 33%, respectively (p=0.003). Pancreatic leak occurred in 31% of Group A patients and 15% of IPJ patients (Group B), with clinically significant grade B and C leaks occurring significantly less frequently in patients undergoing IPJ (13% in Group A vs. 0% in Group B, p=0.002). Intra-abdominal collections occurred in 14% of Group A patients compared to 12.5% of Group B patients. The mean postoperative hospital stay was 12.6 days in Group A and 11.2 in Group B patients. Post pancreatectomy hemorrhage was significantly higher in Group A (n=7) than in Group B (n=0).

Conclusions: Isolated loop reconstruction has a significant influence on the frequency of delayed gastric emptying and the grade of leak. The overall leak rate was significantly different between groups, and clinically significant grade B and grade C leaks were significantly less frequent in patients receiving IPJ reconstructions. The IPJ technique also showed a trend toward lower mortality**.**

Citation: Prabhakaran Raju, John Grifson John Rose, Chandrasekar Thiruvarur Sivaraman, Amudhan Anbalagan, Bennet Duraisamy and Kannan Devy Gounder. 2017. "Isolated loop pancreaticojejunostomy vs. conventional pancreatic stump anastomosis following pancreaticoduodenectomy: anobservational study", *International Journal of Current Research*, 9, (06), 51882-51888

INTRODUCTION

Surgery is potentially curative for pancreatic and periampullary cancers. However, pancreatic stump anastomosis is the Achilles heel of pancreaticoduodenectomy (PD), with the high morbidity (up to 45%) and mortality (up to 7%)observed following PD often related to the outcome of anastomosis (Aroori, 2011). Efforts are still being made to improve anastomotic techniques to optimize PD outcomes, but, despite many randomized and prospective studies, a consensus opinion on the optimal or preferred technique hasyet to be reached. Drainage of the pancreatic remnant into the gastrointestinal tract is an importantstep in reconstruction, but there is a risk of anastomotic breakdown. Pancreatic leaks can be devastating, particularly when sepsis occurs, and theyare a major causeof post-PD mortality (Berberat, 1999), Of the various techniques used, simple duct occlusion results in higher rates of fistula formation andan increased risk of exocrine and endocrinepancreatic insufficiency (Goldsmith, 1971). Pancreatico-enteric anastomosis has captured the attention of many surgeons, resulting in a search for reliable techniquesthat minimize or avoid anastomoticleaks. However,

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successful management of the pancreatic anastomosis depends more on meticuloussurgical technique and experience rather than the anastomosis technique used (Trede, 2001). An ideal reconstruction would not only minimize the risk of pancreatic fistula formation but also ensure that, should a pancreatic fistula form, complications are reduced or prevented. The use of an isolated jejunal loop for pancreatico-enteric anastomosis theoretically achieves these desired endpoints. Previous studies of isolated jejunal loops for pancreatico-enteric anastomosis have been shown to reduce the risk of developingpancreatic fistulas, although the effect of this approachonpancreatic fistula-related morbidity is less clear (Khan, 2002l; Sutton, 2004; Funovics, 1978; Kingsnorth, 1994; Albertson,1994 and Papadimitriou, 1999). Advocates of this technique believe that diverting bile away from the pancreaticojejunostomy site reduces pancreatic enzyme activation and thus the risk of pancreatico-enteric anastomotic fistulas(Jover, 2006). Another argument for using a Roux loop in pancreaticojejunostomy relies on the belief that if a pancreatico-enteric anastomotic fistula forms it will be a 'pure' pancreatic fistula that causesfewer complications than'complex'pancreatic fistulas, in which pancreatic enzymes are activated by bile to producemore severe complications. Funovics et al. (Bassi, 2005), first described the isolated Roux loop pancreatico-jejunal end-to-side anastomosis in 48 patients with double Roux loops to separate the pancreatic and hepatic anastomoses. The aim of this study was to compare outcomes from isolated Roux loop pancreaticojejunostomyversus conventional pancreatic stump anastomosis (pancreaticojejunostomy and pancreaticogastrostomy) in terms of pancreatic fistula formation and postoperative morbidity and mortality.

PATIENTS AND METHODS

Study overview

This was a retrospective analysis of prospectively collected dataof patients undergoingPD for pancreatic or peri-ampullary cancers in the Institute of Surgical Gastroenterology, Madras Medical College,between 2010 and 2014. Medical records were reviewed to obtain preoperative, intraoperative, and postoperative variables.Clinical parameters were recorded in a proforma including age, gender, diagnoses, co-morbid illnesses, dietary history, smoking history, and alcohol consumption. Physical examination findings, in particular stigmata ofchronic liver diseaseand the presence of a palpable gallbladder, hepatomegaly, and free abdominal fluid, were noted. A rectal examination was performed in all patients to exclude rectal metastases. Routine biochemical and hematological investigations including a complete blood count, renal function tests, and liver function tests were performed. Coagulation profiles and serum tumor markerswerealso performed in all patients. All patients were investigated by abdominalultrasonography, upper GI endoscopy, and multi-detector contrast-enhanced computerized tomography with vascular reconstruction. The institutional ethics committee of Madras medical college reviewed and approved the study (Ref:43032010).

Whipple's pancreaticoduodenectomywas performed by three expert, senior surgeons. The pylorus was not preserved in any case. Pancreatico-enteric anastomoses were either in the formof a pancreaticogastrostomy, pancreaticojejunostomy, or isolated loop pancreaticojejunostomy, the latter conducted by two senior surgeons.Patients werecategorized into two groups:(i) conventional technique (pancreaticogastrostomy (PG)or pancreaticojejunostomy (PJ) (Group 1; see Figure 1) or (ii) isolated loop pancreaticojejunostomy (IPJ) (Group 2; see Figure 2).

Isolated Roux loop pancreatico-jejunal anastomosis – operative technique

A 50cm isolated jejunal loop was fashioned and passed through the mesocolon in the retrocolic plane for pancreatico-jejunal anastomosis (see Figure 3). The anastomosis was performed using the duct-to-mucosa technique or the dunking technique using 3.0/4.0 Prolene interrupted sutures for the anastomosis based on the duct size (Figure 2). Pancreatic duct stenting was not performed in any patient. After completing the end-to-side hepaticojejunostomy and gastrojejunostomy to the distal jejunal limb, a side-to-side anastomosiswas performed between both limbs. A feeding jejunostomy was performed for enteral feeding in all patients. Two drains were placed,one near the pancreatic anastomosis and the other in the right sub-hepatic space. Post-operative octreotide was not administered to any patient. Drain fluid amylase levelswere routinely measured on post-operative daysthree and five, and a pancreatic fistula was defined as any measurable drain fluid with amylase levels three times the serum amylaseas perInternational Study Group of Pancreatic Fistula (ISGPF) guidelines (Bassi, 2005). Delayed gastric emptying was defined as a need for nasogastric decompression, reinsertion of the nasogastric tube after post-operative day three, or an inability to tolerate a solid diet by post-operative day seven as perInternational Study Group of Pancreatic Surgery(ISGPS) guidelines (Bassi, 2005). Any drain or nasogastric tube bleeding was considered post pancreaticoduodenectomy hemorrhage.

Pancreatic stump management

All patients with pancreatic leak were managed non-operatively. Grade A leaks were managed conservatively and grade B leaks were managed with supportive care in the postoperative ward with prolonged use of the drainage tube. Grade C leaks were managed aggressively in ICU with one or more image-guided percutaneous drainage tubes sited and nutritional support given. There were no reoperations for suspected leaks.

Study outcomes

The primary outcomes were pancreatic fistula formation,delayed gastric emptying,intra-abdominal abscess formation,post-pancreatectomy hemorrhage,and mortality. Operative variables such as duration of surgery,blood loss,and transfusion requirementswere also assessed, and minor morbidities including pneumonitis, urinary tract infections, and wound infections were also analyzed.

Statistical analysis

Continuous variables were described by their means and standard deviationsand proportions were computed for categorical variables. The chi-squared test was used to test the difference between two group proportions and the independent t-test was used to compare two group means. A p-value <0.05 was considered statistically significant.

Figure 1.

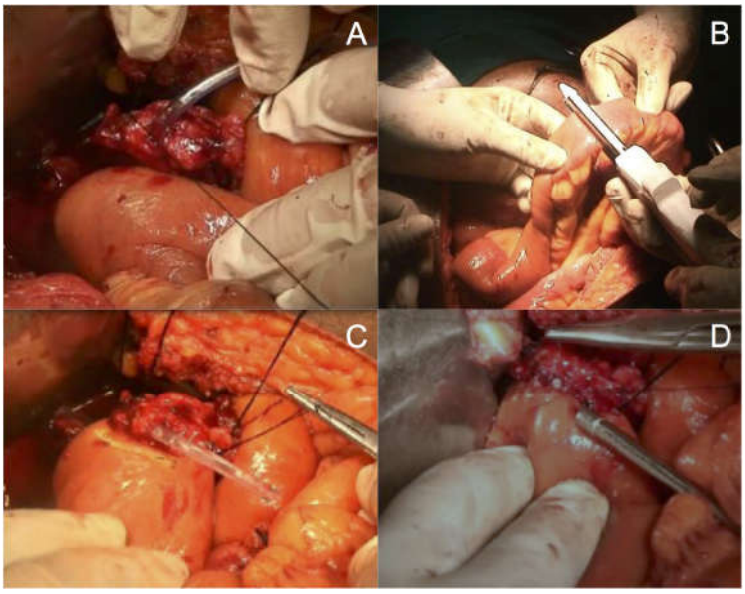

Figure 2.

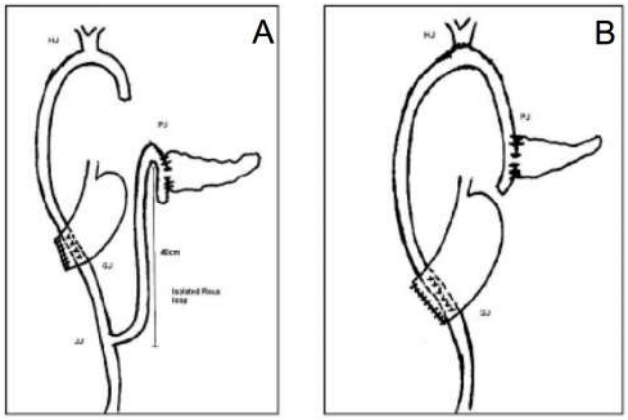

Figure 3.

Figure 4.

RESULTS

Demographic and pre-operative data

Of the 140 patients undergoing Whipple's pancreaticoduodenectomy,100 patients underwent PG/PJ (Group A) and 40 patients underwent IPJ(Group B).There were no statistically significant differences between the two groups in terms of baseline demographic or clinical data, including laboratory test results (Tables 1 and 2). Tumorswere periampullary in104 patients (74.3%; see example in Figure 4), pancreatic in 15 patients (10.7%),distal common bile duct in six patients (4.3%), and duodenal in five patients (3.6%).

Table 1. Demographic and clinical data

	Group A, n = 100	Group B, n=40	p-value
Age (years)	54.8 ± 7.5	52.9 ± 6.16	0.121
Sex			
Male	62 (62%)	25 (62.5%)	0.956
Female	38 (38%)	15 (37.5%)	0.956
Abdominal pain	45 (45%)	15 (37.5%)	0.416
Weight loss	21 (21%)	7 (17.5%)	0.637
Icterus	87 (87%)	35 (87.5%)	0.936
Pallor	27 (27%)	10 (25%)	0.808
Cholangitis	13 (13%)	6 (15%)	0.757
Diabetes	32 (32%)	12 (30%)	0.817
Palpable gallbladder	70 (70%)	26 (65%)	0.567
Hepatomegaly	40 (40%)	13 (32.5%)	0.405
ERCP-stenting	38 (38%)	14 (35%)	0.739

Table 2. Preoperative laboratory test values

	Group A n = 100	Group B n =40	p-value
Bilirubin (mg/dl)	13.8 ± 7.6	12.2 ± 6.8	NS
Hemoglobin (gm%)	9.8 ± 1.86	9.2 ± 2.23	NS
Albumin (mg/dl)	3.1 ± 0.71	2.8 ± 0.62	NS
Creatinine (mg/dl)	0.9 ± 0.51	1.12 ± 0.46	NS
INR	1.2 ± 0.33	1.3 ± 0.25	NS

Table 3. Intraoperative variables

	Group A n = 100	Group B n =40	p-value
Duration of surgery (min)	270 ± 25	320 ± 45	0.000
Blood loss (ml)	625 ± 75	610 ± 100	0.573
Transfusion (units)	2.55 ± 0.56	3.45 ± 0.75	0.775

Table 4. Morbidity and mortality related to the different anastomotic techniques

Procedure	PG+ PJ n=100		Isolated PJ Group n = 40		P-value
	N	%	n	%	
Hemorrhage	7	7	0	0	0.028
Pancreatic leak	31	31	6	15	0.044
Grade A leak	18	18	6	15	0.667
Grade B-C leak	13	13	0	0	0.002
Delayed gastric emptying (DGE)	33	33	4	10	0.003
Intra-abdominal collection	14	14	5	12.5	0.814
Wound infection	10	10	2	5	0.378
Pulmonary complications	8	8	3	7.5	0.921
Mortality	5	5	1	2.5	0.487

The isolated loop technique tended to take longer to perform than the conventional technique, although this was not statistically significant. Blood loss and transfusion requirementswere comparable between groups (Table 3).

Postoperative morbidity

Delayed gastric emptying (DGE)was the most frequent complication, occurring in 29.9% of patients. Pancreatic leak occurred in 24.3%, hemorrhage in 5%, andintra-abdominal collections in 13.6% of patients. Minor complications occurred in 31% of patients overall. DGE was significantly less frequent in Group B compared to Group A patients, occurring in 10% and 33%, respectively(p=0.003) (Table 4). Pancreatic leaksoccurred in 31% of Group A patients and 15% of IPJ patients (Group B), withclinically significant grade B and C leaks occurring significantly less frequently in patients undergoing IPJ (13% in Group A vs. 0% in Group B, p=0.002).Intra-abdominal collections occurred in 14% of Group A patients compared to 12.5% of Group B patients, while nasogastric tubes were removed after a mean duration of 7.5 days in Group A patients and 4.0 days in Group B patients.

The mean postoperative hospital stay was 12.6 days in Group A and 11.2 in Group B patients. Mortality was 5% in Group A patients and 2.5%in Group B patients, which was not statistically significant. Post pancreatectomy hemorrhage was significantly higher in group A (n=7) than in group B patients (n=0; p=0.028).Other complications of wound infections and pulmonary complications were not statistically different between the two groups (p= 0.378 &0.921).

Mortality

Five Group A patients and oneIPJ Group B patient died (5% vs. 2.5%). Of the five deaths in Group A,four died due to Grade C pancreatic leak and one due to post-pancreatectomy hemorrhage. All patients who developed pancreatic leaksunderwent percutaneous drainage of collectionsbut rapidly deteriorated due to progressive organ dysfunction. Emergency exploratory laparotomy was performed in one patient, who developed a massive early extra-luminal bleed and collapsed fromhemorrhagic shock on post-operative day five. At laparotomy, the patient was found to be bleeding from the gastroduodenal artery stump, which was successfully controlled but precipitated organ failure in the immediate post-operative period.

application and,in another prospective randomized trial, Bassi et al. (2005), showed that both anastomosistypes do not significantly influence the subsequent risk of overall complications or pancreatic fistula formation. However, some pancreaticogastrostomy studies report a significantly decreased risk of associated complications, biliary fistulas, postoperative collections, and delayed gastric emptying. A Chinese meta-analysis of four randomized controlled trials suggested that pancreaticogastrostomy is superior to pancreaticojejunostomy after pancreaticoduodenectomy (Machado, 1976).

Funovics et al (Funovics, 1987), reported 48 patients receiving double Roux loops to separate the pancreatic and hepatic anastomoses and found that pancreatic fistulas occurred in 18.6% of cases; mortality only occurred in 2%.

Table 5. Summary of studies comparing conventional and isolated loop reconstruction techniques

Author	Year	Study type & groups	n	DGE N (%)	POPF n(%)	Mortality N (%)
Fragulidis et al.2009 [21]		Retrospective		15.9%	4.3 %	1.4%
		LIPJ vs. SIPJ	69 vs. 63	17.4%	14.2%	1.6%
Perwiaz et al.2009 [22]		Retrospective	53 vs. 55	9.4%	9.4%	3.7%
		IRPJ vs. CPJ		7.2%	10.9%	3.6%
Ballas et al.2010 [23]		Retrospective		15.2%	4.3%	2.2%
		IRPJ vs. CPJ	46 vs. 42	9.5%	7.1%	2.3%
Ke et al.2013 [24]		RCT	107 vs. 109	23%	15.7%	0
		IRPJ vs. CPJ		25%	17.6%	0
Nakeeb et al.2014 [20]		RCT		8.9%	20%	6.7%
		PG vs. IRPJ	45 vs. 45	20%	22%	8.7%
Current Study		Retrospective	39 vs. 61 vs. 40	33%	35%	5%
		PG vs. PJ vs. IRPJ		10%	15%	2.5%

DISCUSSION

Provided that the basic surgical rules for a safe anastomosis are followed, including careful handling of the pancreatic tissues, a tension-free approximation, ensuring a good blood supply, and no distal obstruction, any pancreatico-enteric anastomotic techniquecan produce good outcomes. The pancreatico-jejunal anastomosis is commonly employed, as is anastomosis of the pancreatic stump to the stomach. Proponents of pancreaticogastrostomy cite various reasons for their choice of operation (Zenilman, 2000), first, it is easier to perform due to the close proximity of the stomach to the pancreas; second, the rich gastric blood supply makes the anastomosis less prone to ischemia;and third, because the exocrine enzymes encounter the acidic gastric environment, the leak rate is theoretically lower as the enzymes are not activated, although the validity of this latter hypothesishas been questioned. In a prospective randomized trial comparing pancreaticojejunostomy with pancreaticogastrostomy, the leak rates were not significantly different (11% and 12%, respectively) (Yeo, 1995 and Yeo, 1995). Yeo et al.concluded that pancreatic fistulasare a common complication of pancreaticoduodenectomy,the incidence of which is most strongly associated with surgical volume and the underlying pathology.The published data do not support the hypothesis that pancreaticogastrostomy is safer than pancreaticojejunostomy or is associated with a lower incidence of pancreatic fistula formation.

In their meta-analysis, Wente et al. (Wente, 2007), showed that all non-randomized observational clinical studies reported superiority of pancreaticogastrostomy over pancreaticojejunostomy but all randomized controlled studies reportedequivalence of the two techniques. Ramesh et al. (1990), suggested that pancreaticogastrostomy deserves wider

Sutton et al. (2004), reported a series of 61 patients who experienced no postoperative pancreatico-enteric leaks and a mortality rate of 5%.However, a recent randomized controlled trial of 90 patients randomly assigned to isolated Roux loop pancreaticojejunostomy or pancreaticogastrostomy after pancreaticoduodenectomyshowed thatIPJ anastomosis was not associated with a lower rate of post-operative pancreatic fistula formation but was associated with a decrease in the incidence of postoperative steatorrhea.Furthermore, the technique allowed for earlier oral feeding and the maintenance of oral feeding even in the presence of a post-operative pancreatic fistulas (Fragulidis, 2009). In contrast to published prospective studies, here we analyzed the outcomes of IPJ anastomosis and compared it to conventional PG and PJ methods. Although we found no overall difference in the frequency of morbidities between the two techniques, the severity of complications wasless with the IPJ technique, with 13% of conventional technique patients developing clinically significant Grade B and C leaks but none of the IPJ patients.Although mortality was comparatively lower in the IPJ group, this difference was not statisticallysignificant. Although our study has the limitations of being a relatively small comparative study, we identified a statistically significant difference in delayed gastric emptying and high-grade leaks between techniques, both of which are known tocontribute to morbidity and mortality. The IPJ can be constructed rapidly,but our analysis revealed statistically significant difference in the time taken to complete these procedures. Our reported mortality of patients undergoing IPJ is lower than that reported by Nakeeb et al. (Table 5).

Conclusion

Here we show that isolated loop reconstruction has a significant influence on the frequency of delayed gastric

emptying and the grade of leak. The overall leak rate was significantly different between groups, andclinically significant grade B and grade C leaks was significantly less in the patients receiving the IPJ reconstruction. The IPJ technique also showed a trend toward lower mortality, although this difference was not statistically significant, and the use of the dunking and duct-to-mucosa methods had no effect on outcome. IPJ has a role in pancreaticoduodenectomy, and every pancreatic surgeon must be familiar with this technique.

List of abbreviations

DGE: delayed gastric emptying; ICU: intensive care unit; IPJ: isolated loop pancreaticojejunostomy; ISGPF: International Study Group of Pancreatic Fistula; ISGPS: International Study Group of Pancreatic Surgery; PD: pancreaticoduodenectomy; PG: pancreaticogastrostomy; PJ: pancreaticojejunostomy.

Declarations

Competing interests: None

Funding: [Self]

Authors' contributions

Prabhakaran Raju designed and conducted the study. Chandrasekar T S collected the data and conducted analysis anddrafted the article. John Grifson JohnRose edited the article, defined the intellectual content, and performed statistical analysis. Amuthan Anbalagan and Bennet Duraisamy helped in manuscript preparation and performed review. Professor Kannan Duraisamy is the guarantor and approved the study.

Acknowledgements: Nil

Ethics approval: Ethical committee approval obtained
EC Reg No. ECR/270/lnst/TN/2008

Consent to publish: Not applicable

Availability of Data and Materials: Data sheet attached as supporting files

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