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Original Research Article

Drain fluid amylase in defining clinically relevant postoperative pancreatic fistula following pancreaticoduodenectomy: day 5 is better than day 3

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ABSTRACT

Background: Postoperative pancreatic fistula (POPF) remains the most serious complication of Pancreaticoduodenectomy. ISGPF defined POPF in 2005 based on drain fluid amylase on or after day 3 and graded the severity. But as Grade A fistulas are not clinically relevant, most of the clinicians do not consider them as POPF. Hence exact incidence of POPF is not known. Our aim is to see weather drain fluid amylase on or after day 5 can define clinically relevant POPF better than day 3.
Methods: Prospective study included all patients who underwent Pancreaticoduodenectomy during the period January 2013 to November 2016. Serum and Drain fluid amylase were analyzed on Day 3. Those who met criteria of POPF underwent repeat amylase on Day 5. These patients were divided into 2 groups. Group A includes patients whose Day 5 amylase normalized and Group B where elevated Amylase persisted. Outcomes were compared in 2 Groups in terms of clinically relevant POPF (CRF), DGE, Haemorrhage (PPH), hospital stay and 30 Days mortality. Results were analysed and p value <0.05 was considered significant.
Results: On 110 patients, 44 (40%) met ISGPF criteria of POPF. Of 44, 36 (82%) had normalized Amylase on Day 5 (Group A). Only 8 (18%) had persistent elevated amylase (Group B). None in Group A had CRF, whereas in Group B, 6(75%) had CRF and 2(25%) had only biochemical leak (p<0.0001). DGE was significantly higher in Group B (87.5% vs. 33.3%; p=0.013). PPH was seen in only 1 patient (Group A). Duration of hospital stay and 30day mortality were similar.
Conclusions: Drain fluid amylase levels on or after Day 5 defines clinically relevant POPF better than levels on or after day 3.

Keywords: Delayed gastric emptying, Pancreaticoduodenectomy, Pancreatic fistula

INTRODUCTION

Postoperative pancreatic fistula (POPF) remains the most serious complication of Pancreaticoduodenectomy. It is the major cause of morbidity and mortality.[1,2] Until 2005, there was no universally accepted objective definition in literature. International Study Group on Pancreatic Fistula (ISGPF) in 2005 defined POPF as drain output of any measurable volume on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity.[3] POPF was also graded based on severity into 3 grades (Table 1). Grade of severity may

only be decided after completing follow up including discharge from hospital or death. Grade A fistulas are not clinically relevant as it does not affect the outcome of patients. Whereas Grade B and C POPF are clinically relevant as they alter the course of disease. As Grade A fistulas are not clinically relevant, some clinicians do not consider them as POPF and included only Grade B and C as POPF. Studies which have included Grade A fistulas have twice the POPF rates when compared to studies which have excluded Grade A POPF.[4] Hence there is a discrepancy in literature regarding the exact incidence of POPF following Pancreaticoduodenectomy. When a clinician reports POPF rates in their study, we do not know whether it is overall POPF or only clinically relevant POPF i.e. Grade B and C.

Table 1: Grading of postoperative pancreatic fistula (POPF).

Clinical variable	Grade A	Grade B	Grade C
Clinical condition	Well	Often well	Ill appearing/Bad
Supportive treatment	No	Yes/No	Yes
Imaging results	Negative	Negative/Positive	Positive
Persistent drainage >3 weeks	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to fistula	No	No	Yes
Clinical signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	No

In a study by Molinari E et al.[5] the drain fluid amylase levels tend to decrease from day 1 to day 5 both in normal recovery or complicated course. But the values were higher in complicated group.

In a study by Safi F et al, serial estimation of serum and drain fluid amylases were done from Day 1 to Day 10.[6] They were elevated in 20% of patients. But all returned to normal by day 10 and none of these patients had clinically relevant fistula. From the literature it is evident that drain fluid amylase levels may be elevated even in normal recovery patients and it is significant only if elevation persists. Hence, we conducted a study to see if drain fluid amylase on or after day 5 would better define clinically relevant POPF and avoid Grade A POPF which are not clinically relevant.

METHODS

It is a prospective observational study conducted after approval by Institutional Research and Ethics committee. It included all patients who underwent Pancreaticoduodenectomy from January 2013 to November 2016. All patients underwent serum and drain fluid amylase estimation on postoperative day 3.

All patients who met criteria of POPF based on ISGPF definition were again subjected to serum and drain fluid amylase estimation on post-operative day 5. These patients were divided into 2 groups. Group A included patients whose Day 5 amylase normalized, and Group B included patients where elevated Amylase levels persisted or not normalized. Outcomes were compared in 2 Groups in terms of clinically relevant POPF (CRF), Delayed gastric emptying (DGE), Post Pancreatectomy Hemorrhage (PPH), wound infection, hospital stay and 30 Days mortality. All Grade B and C fistulas based on ISGPF criteria were considered as CRF. Grade A fistulas were considered as not clinically relevant fistulas.

DGE was assessed based on the 2007 International Study Group of Pancreatic Surgery (ISGPS) definition and grading.[7] PPH was assessed and graded based on International Study Group on Pancreatic Surgery (ISGPS) definition.[8]

Wound infection was defined as infection less than 30 days after surgery involving skin, subcutaneous tissue, deep soft tissues (fascia and muscle) plus one of following purulent discharge, diagnosis of infection by pus for culture and sensitivity and symptoms of local pain, erythema, oedema, and fever.[9]

Patients were discharged if they were able to tolerate oral diet, passing stools, afebrile and no wound complications requiring hospital stay. Data was recorded in a predesigned proforma and results were analysed. P value <0.05 was considered as significant.

RESULTS

Over all 110 patients were included during the study period. Of these patients, 44 (40%) met ISGPF criteria of POPF. Of 44 patients with POPF, 36 (82%) had normalized drain fluid Amylase values on Day 5 and they were included in Group A. Only 8 (18%) patients had

elevated Amylase levels persisted or not normalized and were included in Group B.

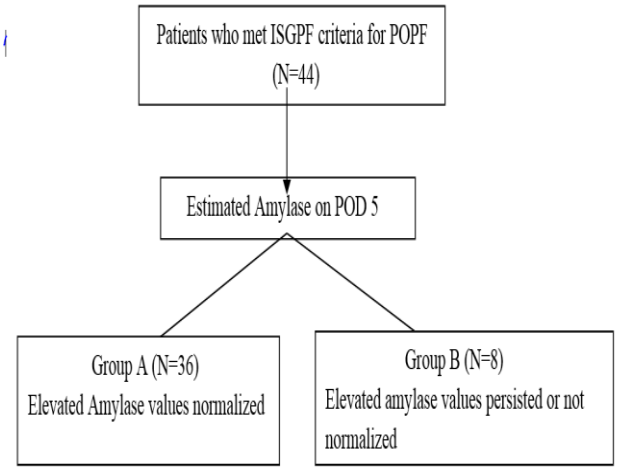

Figure 1: Consort diagram.

Results are summarized in Table 2. In Group A (patients with normalized drain amylase on day 5), none of the patients had CRF, where as in Group B (patients with elevated amylase drain amylase on day 5), 6 (75%) patients had CRF (p<0.0001). Of 6 patients with CRF, 4 (66%) had Grade B fistula and 2(34%) had Grade C fistula. DGE was seen in 12 (33.3%) patients in Group A and 7 (87.5%) patients in Group B.

Table 2: Results.

	Group A (N=36)	Group B (N=8)	P value
Pancreatic fistula			
Grade A	36 (100%)	2 (25%)	
Grade B	0 (0.00%)	4 (50%)	<0.0001
Grade C	0 (0.00%)	2 (25%)	
Delayed gastric emptying	12 (33.3%)	7 (87.5%)	0.0136
Hospital stay (Mean±SD)	12.78±3.83	13.75±4.03	0.523
Mortality	2 (5.5%)	2 (25.0%)	0.145

DGE was significantly more common in Group B patients (33.3% vs. 87.5%; p=0.0136). Only one patient in the study group had PPH which was managed conservatively. Postoperative hospital stay was similar in 2 groups (12.7 days vs. 13.7 days; p=0.52). There were 4 (3.63%) deaths are the study group. 2 deaths were reported in each group (p=0.145).

DISCUSSION

Incidence of postoperative pancreatic fistula following pancreaticoduodenectomy ranges from 20-30% and is associated with a mortality of 20-40%.[1,2,10] Various anastomotic techniques were tried to decrease the incidence of POPF. But none of techniques have proven to be superior to other techniques.[11,12,13] Until 2005, the exact incidence of POPF was not known due to lack of objective definition defining POPF.

In 2005, an international working group of pancreatic surgeons (The International Study Group of Pancreatic Fistula [ISGPF]) reached a universally accepted objective definition of POPF. POPF was defined as drain output of any measurable volume on or after postoperative day 3 with amylase content greater than 3 times the serum amylase activity.[3] Several studies have validated the definition and grading of POPF. But few studies have noted that the clinical outcomes of patients with Grade A fistulas were similar to patients with no fistulas.[14,15]

More recent studies focussing on the impact of POPF, have questioned the clinical relevance of Grade A fistulas and they considered only Grade B and C fistulas as clinically relevant.[16] Some studies have even excluded Grade A fistulas in their reporting of POPF. Therefore, there is a discrepancy in the literature regarding the exact incidence of POPF. It was seen that studies which included Grade A fistulas have twice the POPF rates when compared to studies which included only clinically relevant Grade B and C fistulas.[4] Also some surgeons do not place intraperitoneal drains following pancreaticoduodenectomy and hence diagnosis of Grade A fistulas in these patients is not possible. Hence, we need to have a definition which would actually focus only on clinically relevant POPF and avoid discrepancy in reporting the POPF rates.

Few studies have shown that drain fluid amylase levels tend to decrease over days in patients without clinically significant fistula.[5,6] Hence we have conducted a study to see the impact if drain fluid amylase levels are considered on or after day 5. In our study, the overall POPF rate was 40% based on considering Day 3 amylase levels. But when Day 5 amylase level was considered, only 7.2% had POPF. 82% of patients, who were considered to have POPF on the postoperative day 3, had no fistula based on postoperative day 5 amylase levels.

None of these patients had any clinically significant altered postoperative course. Out of 7.2% patients with POPF on postoperative day 5, 75% had clinically relevant fistula (Grade B and C) altering the postoperative course. Hence by considering the drain fluid amylase levels on postoperative day 5 in defining POPF, we could reduce the clinically relevant POPF rates by 82%, without any adverse effects on clinical outcomes. This can also minimize the confusion on term like Biochemical leak which was recently coined by ISGPF in 2016.[17]

CONCLUSION

Drain fluid amylase levels on Day 5 defines clinically relevant POPF better than the levels on day 3. It can avoid discrepancy in reporting POPF rates and also

minimize confusion regarding the term "Biochemical leak".

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Ethical approval: The study was approved by the Institutional Ethics Committee

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