J Nepal Health Res Counc 2022 Oct-Dec;20(57): 820 - 4

Day One Drain Amylase as a Predictor of Postoperative Pancreatic Fistula Following Pancreaticoduodenectomy

Sumita Pradhan,[1] Bishnu Kandel,[1] Ramesh Singh Bhandari,[1] Paleswan Joshi Lakhey [1]

[1]Department of Surgical Gastroenterology, Institute of Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal

ABSTRACT

Background: Postoperative pancreatic fistula remains the most challenging complication following pancreaticoduodenectomy. As per the definition by the International Study Group on Pancreatic Fistula, post operative pancreatic fistula is diagnosed on or after postoperative day 3. However, several studies have demonstrated that drain fluid amylase on postoperative day 1 may be a better predictor. This study was conducted to determine the diagnostic value of day one drain amylase in predicting the development of post-operative pancreatic fistula.

Methods: This was a prospective observational study of patients, who underwent pancreaticoduodenectomy between April 2016 and May 2017. Post operative pancreatic fistula was defined by the International Study Group on Pancreatic Fistula (2005) criteria. The diagnostic value of day one drain amylase was determined by doing a receiver operating curve analysis and compared with the postoperative day 3 value.

Results: A total of 49 patients were included. Post operative pancreatic fistula developed in 28 patients (Grade A - 40.8%; B - 12.2%; C - 4.1%). Receiver operating curve analysis confirmed the predictive relationship of day one drain amylase with an area under the curve of 0.79 and kappa 0.5. For clinically relevant postoperative pancreatic fistula, day 3 drain amylase was the better predictor (AUC for DFA3 was 0.73 while AUC for DFA1 was 0.51). A day one drain amylase cut-off value of 350 U/L demonstrated a sensitivity of 75% and specificity of 77.8% with an accuracy of 76.2%.

Conclusions: Day one drain amylase predicts postoperative pancreatic fistula in patients following pancreaticoduodenectomy but for clinically relevant postoperative pancreatic fistula, day three drain amylase is a better predictor.

Keywords: Amylase; drain fluid amylase; pancreaticoduodenectomy; Pancreatic fistula

INTRODUCTION

In-hospital mortality following pancreaticoduodenectomy (PD) has come down to < 2.8% in high-volume centers,[1] however, it is still associated with significant postoperative pancreatic fistula (POPF) with an incidence of 2 - 51%.[2] POPF can lead to hemorrhage, sepsis, delay in adjuvant therapy, and even death. Advantages of early diagnosis include timely intervention before the clinical deterioration.[3]

International Study Group on Pancreatic Fistula (ISGPF), 2005 has graded POPF into three groups Grade A, B, C.[2] Drain fluid amylase (DFA) is sent on the 3rd postoperative day (POD) and drain is removed at the surgeon's discretion.

A systematic review concluded that day 1 DFA, instead of DFA 3, might identify POPF early.[4] Another study concluded that high DFA is not a sensitive or specific predictor of POPF.[5] This study aims to determine the diagnostic value of day 1 DFA with the risk of developing POPF.

METHODS

This was a prospective observational study conducted from April 2016 to May 2017, over 14 months in Tribhuvan University Teaching Hospital. Ethical approval was taken from Institutional Review Board. All patients undergoing PD were included and patients who refused to give consent to participate were excluded.

Two intra-abdominal drains were placed routinely,

Correspondence: Dr Sumita Pradhan, Department of Surgical Gastroenterology, TUTH, Kathmandu, Nepal. Email: sumiepradhan@gmail.com, Phone: +9779841198822.

one at the Morrison's space near the HJ site, and the other near the PJ anastomosis. The DFA levels were recorded on 1st, 3rd, 5th, 7th POD. POPF was defined according to ISGPF, 2005 [2] and Grade B and C POPF were considered as clinically relevant pancreatic fistula (CR-POPF). Drain was removed if the DFA values were low and at the surgeon's discretion. Surgical morbidity was defined according to ISGPF and managed accordingly.[6-8] All patients were followed till 30th POD and the highest complication was reported according to Clavien Dindo.[9]

The data was analyzed in IBM SPSS Version 23 software (Statistical Package for the Social Sciences). The area under the ROC curve was calculated to find the diagnostic and predictive value of day 1 drain fluid amylase (DFA1) for predicting POPF and compared with day 3 drain fluid amylase (DFA3).

RESULTS

Out of the 52 patients eligible for the study, three patients were excluded from the study. Two patients were found unresectable and underwent triple bypass. The third case, suspected cystic neoplasm of pancreas, was found to be hydatid cyst communicating with the pancreatic duct, for which a partial cystectomy with Roux en Y cysto-jejunostomy was done. Pancreaticoduodenectomy was performed in 49 patients, 26 men (53.1%), 23 women (46.9%) with a mean age of 53.8 ± 12.5 years. Jaundice was present in 35 patients (71.4%) and was the commonest presentation. Preoperative biliary drainage was performed in 6 patients (12.2%). The most common indication for PD was ampullary carcinoma (53.1%) followed by distal cholangiocarcinoma (12.2%), Carcinoma head of pancreas (14.2%), duodenal carcinoma 10.2%), neuroendocrine tumor 2.04%. Benign pathologies constituted 8.4% cases.

The mean operative duration was 6.81±1.0 hours. The average drain removal of the right (HJ) side was 4.4±0.8 days and for the left (PJ) side was 8.16±2.9 days. The mean length of hospital stay was 11.16 ± 4.8 days. Twenty-eight (57.1%) patients developed postoperative complications among which post pancreatectomy hemorrhage (PPH) was seen in 12.3%, bile leak in 2%, surgical site infections (SSI) in 8.1%, delayed gastric emptying (DGE) in 20.4%, and POPF in 57.14% cases. Among the POPF cases, Grade A was seen in 40.8%, Grade B in 12.2% and Grade C in 4.1% cases. There were four mortality (8.16%) out of which one was due to bile leak, sepsis, and ARDS, another due to POPF with sepsis with hospital-acquired pneumonia, and two cases were delayed intraluminal grade C PPH.

Pancreatic fistula was observed in 28 patients (57.1%), of which 20 patients (40.8%) had Grade A fistula, six patients had Grade B fistula (12.2%) and two patients had Grade C fistula (4.1%). The rate of CR-POPF in this study was 16.3%. Out of 28 cases that developed POPF, DFA1 was high only in 23 cases (Table 1). Seven cases were false positive, and five cases were false negative (Table 2). On applying the Kappa test, it showed fair agreement between ISGPF and DFA1 (kappa 0.5, p-value 0.001). For prediction of POPF, DFA1 showed an area under the ROC curve (c-statistic) of 0.799 (95 % CI 0.677-0.922) which shows that the test was fair in predicting POPF (Figure 1). The cutoff at 350U/L had the highest accuracy of 76.2 (Table 3). The DFA1 AUC was 0.509 (95 % CI 0.323-.696, p 0.935) in comparison to DFA3, whose AUC was 0.729 (95%CI 0.573-.885, p 0.42) showing that for predicting CR-POPF (Grade B and C), DFA3 was better than DFA1 (Figure 2).

Table 1. POPF cases predicted by DFA1.

ISGPF	Number	POPF Predicted by DFA1
POPF	28	23
Grade A	20	17
CRPF	8	6
B	6	5
C	2	1

Table 2. Comparison of POPF between DFA 1 and ISGPF Criteria.

		POPF according to ISGPF		Total
	POPF	YES	NO	
POPF according to DFA1	YES	23	7	30
	NO	5	14	19
Total		28	21	49

POPF: postoperative pancreatic fistula

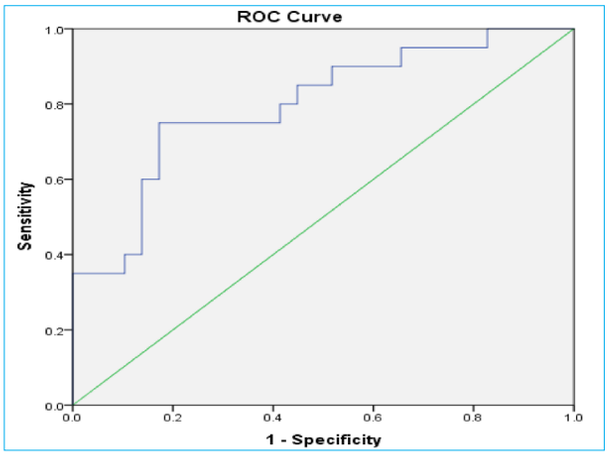

Figure 1. ROC curve of DFA1 in predicting POPF.

Table 3. DFA1 cutoffs at different level.

DFA1 cut off (U/L)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy
5,000	14.3	100	100	36.7	51.0
2,500	21.4	100	100	48.8	55.1
1,000	50	90.5	87.5	57.6	67.3
350	75	77.8	81.8	70	76.2
229.5	82.1	66.7	76.7	73.7	75.5
90	100	23.8	63.6	100	67.3

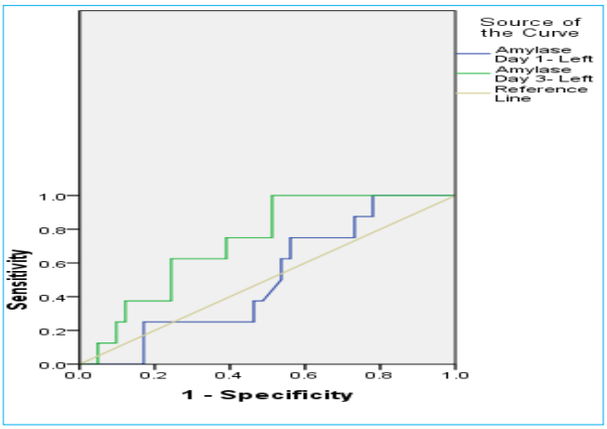

Figure 2. Comparison of ROC of DFA1 and DFA 3 in predicting CR-POPF.

DISCUSSION

Pancreaticoduodenectomy is a high-risk, technically demanding operation associated with substantial perioperative morbidity and mortality. Incidence of POPF ranges from 2 - 51% depending on applied criteria.[2] After the standard definition of POPF by the ISGPF, it is still around 5-30%.[10] Our overall POPF was 57.14% and that of CR-POPF was 16.32%. However, ISGPF [11] have recently come up with an updated version of the postoperative pancreatic fistula where they have completely removed Grade A fistula and termed it as a biochemical leak stating that it has no clinical significance. This study was conducted before 2016 upgrade and thus for this study 2005 grading was followed.

From the earliest days of pancreatic surgery to the most recent clinical series, POPF has been recognized as the main determinant of morbidity. Successful management of POPF often depends on its early prediction. Up to now, different methods have been used to evaluate the POPF preoperatively, like pancreatic fistula predictive score systems, and analyzing various risk factors related to POPF.[12] Yet, the early prediction of POPF remains controversial. The definition of POPF according to the ISGPF in 2005 [2] and even according to 2016 update,[11] offered the standard diagnosis of POPF according to the drain fluid amylase (DFA) content but we need to wait till POD three to diagnose POPF.

The usefulness of DFA as a predictive tool for the development of POPF was first investigated by Hashimoto in 2002.[13] This study of 67 cases of PD suggested that DFA1 > 4000 U/l is predictive of POPF development. Studies have emphasized the importance of early postoperative drain amylase values, by evaluating the accuracy of this simple test in predicting POPF.[14] In our study, the sensitivity of DFA1 was 75% and specificity of 77.8% at cut-off of 350 U/L with a diagnostic accuracy of 76.2. A strong correlation existed between pancreatic fistula and DFA1 ($p < 0.001$), confirmed by the area under the ROC curve of 0.799. On applying Kappa test, it showed fair agreement between ISGPF and DFA1 (kappa 0.5, p-value 0.001) indicating that DFA1 was a reliable predictor of POPF. In the meta-analysis by Ji Yang et al,[13] pooled sensitivity, specificity, diagnostic odds ratio, and the AUC of DFA1 in estimating the POPF were 81%, 87%, 16.83, and 0.897 respectively indicating that DFA1 has moderately high diagnostic accuracy for diagnosing POPF. The rate of cutoff level has also been highly variable ranging from as low as 90 U/L to as high as 5000 U/L. The cut-off level for our institute was low and this could have been because of the use of octreotide for all our patients as Octreotide reduces pancreatic exocrine secretion and may have decreased the leak rate but Molinari et al [14] had a cut-off level of 5000U/L and even they had used octreotide routinely for all their cases. The best cut-off value of DFA1 remains unclear due to the different cut-off values in different studies.

On the other hand, Shinichi [15] and Moskovic [13] have suggested that DFA is not a suitable predictor for the development of POPF. In our study, we found that the ability of DFA1 to predict CR-POPF was however low as the AUC was 0.509 in comparison to DFA3, who's AUC was 0.729. A study by Noji et al [16] also found that AUC for DFA1 and DFA3 was 0.614 and 0.726, respectively showing that drain amylase value on DFA3 was more useful than amylase value on DFA1.

Early predictability of POPF by DFA1 has two implications. First, the drain might be removed early in patients with a normal DFA1 value. Second, the patients with elevated amylase might require close observation and monitoring for the early detection of complications.

In our study, the average time to drain removal was 8.16±2.9 (5-18 days). Bassi et al [17] observed that prolonged drain insertion correlated with a significantly higher risk of abdominal complications and delayed

hospital discharge, concluding that drain removal around postoperative day 3 is thus beneficial for patient recovery and early discharge. This study demonstrates that DFA1 predicts the occurrence of POPF and may play a role in early drain removal and an enhanced recovery pathway (ERP) after surgery.

The main limitations of this study are that this is a single-center study and in the context of the newly published update of POPF from the ISGPF, the results need to be interpreted accordingly. In spite of the various evidence of DFA1 predicting POPF, the old definition was not changed. Keeping in view of newer definition, this study shows that DFA 1 does not predict CR-POPF and that DFA3 is a better predictor and thus further studies are warranted.

CONCLUSIONS

Day one drain amylase is useful in predicting postoperative pancreatic fistula in patients following pancreaticoduodenectomy but for clinically relevant postoperative pancreatic fistula, day three drain amylase is a better predictor. Further multicenter prospective studies are required to validate this finding.

CONFLICT OF INTEREST

The authors declare no conflict of interest

REFERENCE

1. Kimura W, Miyata H, Gotoh M, Hirai I, Kenjo A, Kitagawa Y, et al. A Pancreaticoduodenectomy Risk Model Derived from 8575 Cases from a National Single-Race Population (Japanese) Using a Web-Based Data Entry System: The 30-Day and In-hospital Mortality Rates for Pancreaticoduodenectomy. Ann Surg. 2014 Apr; 259(4):773–80.[Article]
2. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005 Jul; 138(1):8–13.[Article]
3. Ansorge C, Nordin JZ, Lundell L, Strömmer L, Rangelova E, Blomberg J, et al. Diagnostic value of abdominal drainage in individual risk assessment of pancreatic fistula following pancreaticoduodenectomy. Br J Surg. 2014 Jan 1; 101(2):100–8. [Full text link]
4. Yang J, Huang Q, Wang C. Postoperative drain amylase predicts pancreatic fistula in pancreatic surgery: A systematic review and meta-analysis. Int J Surg Lond Engl. 2015 Oct; 22:38–45. [Full text link]
5. Vd D, Dm K, Vn O, Mg G-D, Sv M, Ar P-M, et al. Drain amylase value as an early predictor of pancreatic fistula after cephalic duodenopancreatectomy. World J Gastroenterology.2014Jul14; 20(26). [PubMed]
6. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007 Jul; 142(1):20–5. [Aricle]
7. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007 Nov;142(5):761–8. [Full text link]
8. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: A definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011 May 1;149(5):680–8. [Full text link]
9. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. Ann Surg. 2004 Aug;240(2):205–13. [Full text link]
10. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2006 Nov;10(9):1199–210. [PubMed]
11. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161(3):584–91.[Article]
12. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013 Jan;216(1):1–14.[Article]
13. Hashimoto N, Ohyanagi . Pancreatic juice output and amylase level in the drainage fluid after pancreatoduodenectomy in relation to leakage. Hepatogastroenterology .2002 Mar-Apr;49(44):553–555.[Article]
14. Molinari E, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, Falconi M, Pederzoli P. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. Ann Surg. 2007 Aug;246(2):281-7 [Full text link]
15. Shinchi H, Takao S, Maemura K. A new technique for pancreaticogastrostomy for the soft pancreas: the transfixing suture method. J Hepatobiliary Pancreat

Surg. 2006;13: 212–7. [Article]

16. Davidson TB, Yaghoobi M, Davidson BR, Gurusamy KS. Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection. Cochrane Database Syst Rev. 2017;4(4) 7. [Full text link]

17. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg. 2010 Aug;252(2):207–14. [Article]