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ORIGINAL ARTICLE

Sequential drain amylase to guide drain removal following pancreatectomy

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Abstract

Background: Although used as criterion for early drain removal, postoperative day (POD) 1 drain fluid amylase (DFA) $\leq$ 5000 U/L has low negative predictive value for clinically relevant postoperative pancreatic fistula (CR-POPF). It was hypothesized that POD3 DFA $\leq$ 350 could provide further information to guide early drain removal.

Methods: Data from a pancreas surgery consortium database for pancreatoduodenectomy and distal pancreatectomy patients were analyzed retrospectively. Those patients without drains or POD 1 and 3 DFA data were excluded. Patients with POD1 DFA $\leq$ 5000 were divided into groups based on POD3 DFA: Group A ($\leq$350) and Group B (>350). Operative characteristics and 60-day outcomes were compared using chi-square test.

Results: Among 687 patients in the database, all data were available for 380. Fifty-five (14.5%) had a POD1 DFA > 5000. Among 325 with POD1 DFA $\leq$ 5000, 254 (78.2%) were in Group A and 71 (21.8%) in Group B. Complications (35 (49.3%) vs 87 (34.4%); p = 0.021) and CR-POPF (13 (18.3%) vs 10 (3.9%); p < 0.001) were more frequent in Group B.

Conclusions: In patients with POD1 DFA $\leq$ 5000, POD3 DFA $\leq$ 350 may be a practical test to guide safe early drain removal. Further prospective testing may be useful.

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Introduction

Many surgeons use intraperitoneal drains after pancreatectomy to allow for early identification, and mitigation, of complications associated with clinically relevant postoperative pancreatic fistulae (CR-POPF). However, it has been suggested that leaving drains in patients at lower risk of developing CR-POPF can be detrimental.[1] Bassi and colleagues demonstrated that early drain removal improved outcomes in patients with a postoperative day 1 drain fluid amylase (POD1 DFA) $\leq$ 5000 U/L.[2] They randomized low risk patients into early (POD3) and late ($\geq$POD5) drain removal. Early drain removal was associated with lower rates of pancreatic fistula, abdominal complications, and a shorter length of stay (LOS).[1]

Patients with a POD1 DFA > 5000 U/L have a 70% incidence of CR-POPF.[3,4] However, POD1 DFA $\leq$ 5000 U/L does not reliably predict the absence of CR-POPF.[3] Previous reports have identified a POD1 DFA cutoff of <90 U/L as having the highest negative predictive value (98.2%) for pancreatic fistula.[5] This uncertainty has discouraged some surgeons from removing drains early in the postoperative course. A meta-analysis by Giglio *et al.* included 13 studies (n = 4416 patients) with the aim of defining the accuracy of drain amylase values in predicting postoperative pancreatic fistula (POPF).[3] The authors determined that the probability of developing a CR-POPF if POD1 drain amylase is < 100 U/L is 3%. However, only 34% of patients had a POD1 drain amylase <100 U/L. The authors suggested that a cut-off value of 350 U/L may be more clinically useful since

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50% of patients were found to have values in this range and the incidence of CR-POPF was only 4%.

In addition to POD1, a second analysis of DFA later in the postoperative course may add additional useful data to predict an evolving or subsequent CR-POPF. Partelli *et al.* demonstrated that POD5 DFA > 200 U/L had a sensitivity of 90% and a specificity of 83% in predicting POPF.[4] Okano and colleagues calculated drain amylase output as the product of DFA concentration and the volume of fluid. The ratio of POD3/POD1 drain amylase output was lower in those patients that did not develop a CR-POPF.[6]

It is important to note that drains were not removed on POD1 in the only randomized prospective trial of early drain removal.[1] Drains were removed on POD3-5 if additional criteria were met. If the appearance of the drain fluid suggested a pancreatic fistula, early post-pancreatectomy hemorrhage, or bile leak, the drain was left in place. In addition, abdominal ultrasound was performed on POD3 and, if this showed a fluid collection >5 cm, the drain was left in place. Presumably, the reason for this additional scrutiny was that, as patients resume oral intake in the first few days after surgery, a POPF may become evident. A simple, inexpensive, clinically predictive test to reassess the risk of subsequent CR-POPF on POD3 would be useful in directing drain removal, since visual appearance of the drain may not be a reliable way to assess risk and use of abdominal ultrasound for every patient is likely not economically or logistically feasible.

It was hypothesized that a supplemental analysis of DFA on POD3 could add to the value of POD1 DFA in providing a clinically useful and more reliable method to predict which patients will not develop a CR-POPF. The cut-off of 350 U/L was selected based on the meta-analysis by Giglio *et al.*[3] Data from a prospectively maintained consortium database were reviewed retrospectively to determine the association of DFA on POD1 and POD3 with postoperative outcomes.

Methods

Analyzed data were reviewed retrospectively from a prospectively maintained Pancreas Surgery Registry including three high-volume academic pancreas centers. After obtaining informed consent, data were entered prospectively into the database by trained data analysts under the supervision of the surgeons. All data were backed up by source documents and the accuracy of data entered to the electronic database was periodically reviewed and verified by the coordinating center (Baylor College of Medicine).[7] Permission for this study was obtained from an Institutional Review Board (H-38662).

Although patients who underwent pancreatoduodenectomy (PD) or distal pancreatectomy (DP) were included, outcomes for these two different operations were analyzed separately. Patients without intraperitoneal drains and without POD1 and 3 DFA data were excluded from the study. Patients with POD1 DFA $\leq$ 5000 U/L were divided into two groups based on their POD3 DFA concentration: Group A ($\leq$350 U/L) and Group B (>350 U/L). The measurement of DFA on POD1 and POD3 is part of the institutional protocol. In patients with multiple drains the highest DFA concentration from any drain was used. Drain removal was recorded as the date on which the last drain was removed.

Baseline demographics and comorbidities such as body mass index (BMI), hypertension, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, diabetes, chronic pancreatitis, renal insufficiency, and smoking history were obtained from the database. Perioperative characteristics included pancreatic texture, pancreatic duct size, anastomotic technique, pathologic diagnosis, estimated blood loss (EBL), transfusion requirement, American Society of Anesthesiologists (ASA) score, and length of procedure. Complications within 60 days of surgery were recorded and graded using the Accordion Severity Grading for Surgical Complications,[8] and the International Study Group of Pancreatic Fistula (ISGPF) and the International Study Group of Pancreatic Surgery (ISGPS) definitions[9,10] for pancreatic fistula and delayed gastric emptying (DGE). A detailed definition of complications has been previously reported.[8] Patients were followed for mortality for 90 days after surgery. The primary outcome of interest was CR-POPF. Chi-square or Fisher's exact tests, when appropriate, were used to analyze categorical variables. Student's *t*-test or Mann–Whitney tests were used to evaluate continuous variables. Simple logistic regression analysis was employed to evaluate the ability of POD1 DFA and POD1 in combination with POD3 DFA to predict the absence of CR-POPF. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS v24 (IBM Corp. Armonk NY, USA).

Results

Among 687 patients who underwent PD or DP, 380 had intraperitoneal drains placed at the time of surgery and had both POD1 and POD3 DFA data available. Fifty-five patients identified with a POD1 DFA > 5000 U/L were analyzed separately. Among the remaining 325 patients with POD1 DFA $\leq$ 5000 U/L, 254 patients (78.2%) had a POD3 DFA $\leq$ 350 U/L (Group A) and 71 patients (21.8%) had a POD3 DFA > 350 U/L (Group B) (Fig. 1). 241 (74.2%) patients underwent PD and 84 (25.8%) underwent DP. The overall rate of CR-POPF among patients with POD1 DFA $\leq$ 5000 U/L was 7.1%.

Among the 55 patients with POD1 DFA >5000 U/L, 43 (78.2%) underwent PD and 12 (21.8%) underwent DP. Overall, the median POD1 DFA was 9729 U/L (7330–13, 108 U/L) and median POD3 DFA was 1009 U/L (594–3076 U/L). The overall rate of fistula of any grade was 85.4% while the rate of CR-POPF was 34.5%. The date of drain removal was available for 45 (81.8%) patients in this group. All patients had their intraperitoneal drains removed after POD5 (median POD16, IQR POD8-

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