

Use of Hemopatch Does Not Prevent Post-Operative Pancreatic Fistula Rates in Distal Pancreatectomies

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Abstract

Aims

Many techniques are employed to prevent Post-Operative Pancreatic Fistula (POPF) but these appear largely equivocal. We aimed to determine the effect of Hemopatch use on the incidence of POPF post distal pancreatic resection.

Methods

A retrospective review of a prospectively maintained multi-institutional pancreatic resection database of patients was conducted. Cohorts were divided into those who had a Hemopatch applied to the pancreatic stump and those who did not. Demographics, rates and grade of POPF, peak drain amylase after day 3, complications, and 30 day mortality were analysed. Statistical analysis was conducted using SPSS. Fischer's test, chi-squared and T-tests were employed with a p-value of <0.05 deemed significant.

Results

Demographics were similar between cohorts. The use of Hemopatch demonstrated a reduction in clinically significant POPF at 2 of 33 (6%) versus 7 of 38 (19%) in the standard group (p-value 0.122). Mean peak drain amylase was 7989IU/L and 1818IU/L in the standard and Hemopatch cohorts respectively (p-value 0.097). Drains remaining in situ for longer than five weeks occurred in five cases of standard DP and zero cases of the Hemopatch cohort (p-value 0.031).

Discussion

The routine use of Hemopatch is a safe adjunct in distal pancreatectomies, but does not reduce rates of POPF.

Introduction

Despite major advances in surgical techniques for distal pancreatectomy (DP), the post operative complication rate remains high.¹ Post-operative pancreatic fistula (POPF) is a source of substantial morbidity when it occurs. It can lead to infection, life-threatening sepsis, prolonged hospitalisation, delayed chemotherapy, and increased mortality rates.² A clinically significant POPF occurs in approximately 25% of patients undergoing a DP.^{3,4}

The International Study Group of Pancreatic Fistula (ISGPF) classify a clinically relevant POPF as a grade B or grade C POPF.^{5,6} A grade A POPF is not deemed to be a true fistula, and instead refers to a “biochemical leak”. A grade B POPF is a pancreatic leak with >3 times the upper limit of normal serum amylase on or after postoperative day 3 with one or more of the following; persistent drainage >3 weeks, resulting in a clinically relevant change in the management of POPF, requires percutaneous or endoscopic drainage, necessitates angiographic procedure for bleeding, or ongoing signs of infection without organ failure. Whenever a grade B POPF leads to organ failure or to clinical instability such that a re-operation is needed, the POPF is classified as grade C.

Various strategies have been employed in attempts to decrease the incidence of, and mitigate the complications arising from an occurrence of a POPF. These include variations in the closure method of the pancreatic stump (stapled closure, hand sewn closure, oversewing the pancreatic remnant), using prophylactic transpapillary pancreatic ductal stents, ligation of the pancreatic duct, administration of somatostatin analogues, reinforcement of the closure line with autologous / non-autologous absorbable and non-absorbable tissues to buttress the pancreatic stump (seromuscular patches, falciform patches, bio-absorbable meshes). However, as yet none have proved a successful remedy in the prevention of POPF.⁷

HemopatchTM is a haemostatic bovine derived patch consisting of a formulated collagen matrix and a protein-reactive monomer (N-hydroxylsuccinimide functionalized pentaerythritol polyethylene glycol ether tetrasuccinimidyl glutarate: NHS-PEG), which adheres to blood or physiological fluid. The hydrolysis process combines with platelet and collagen activation within the coagulation cascade to release coagulation factors and enable fibrin formation.⁶ These properties have led to the postulation that Hemopatch may prevent POPF in DP's by mechanically sealing the pancreatic stump.⁸

Preliminary studies have investigated the effects of application of fibrin sealants on rates of POPF in DP.⁹⁻¹³ These have been limited by failing to adhere to the ISGPS definition of a POPF, heterogeneity in the method of fibrin application, and differences in proprietary products utilised (e.g. glue versus patch, TachoSilTM versus HemopatchTM).⁸

Therefore, we aimed to assess the use of Hemopatch™ application in preventing clinically relevant POPF in distal pancreatectomies.

Methods

A retrospective cohort study was conducted at Cork University Hospital and the Mercy University Hospital, Cork; the combined hepatico-pancreaticobiliary (HPB) tertiary referral centre for the province of Munster in the Republic of Ireland. A prospectively maintained database of all patients undergoing a pancreatic resection is maintained. This was reviewed to identify all patients who met the inclusion criteria and who had surgery between 01/01/2018 and 01/01/2023. This constituted the sample for our retrospective cohort study. Ethical approval was received from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

All elective patients undergoing distal pancreatectomy (excision of the pancreatic body and tail lateral to the midline or superior mesenteric vessels) during the aforementioned time period were eligible for inclusion. No restrictions were placed on the indication for surgery; be it benign or malignant, or as part of a larger multi-visceral resection. Patients were excluded if they were less than 18 years of age when having a resection, if they did not consent, or if they had a known contraindication to Hemopatch or its constituents.

All patients were managed in a consensus manner after discussion at the HPB and Upper GI multi-disciplinary team meeting. Neoplastic indications for surgery were guided by the European Society of Medical Oncology for pancreatic cancer¹⁴ and the International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas.^{15,16}

Surgery was undertaken in a laparoscopic or open approach dependant on the patient and surgeon preference by two surgeons (AOS, COS). If significant disparity existed in operative approach between intervention and control cohorts, these subsets would be analysed using propensity score matching and multivariate analysis. Where the indication to proceed with distal pancreatectomy was secondary to a pancreatic lesion, routine mobilisation of the pancreas, with formal transection at the level of the superior mesenteric artery was carried out using a stapler device. If the distal pancreatectomy was carried out as part of a multi-visceral operation, division of the pancreas occurred in the same manner, but may have been more lateral to the midline dependant on necessity for adequate clear margins. Intra-operative ultrasound was used to ensure adequate removal of the desired lesion if not macroscopically palpable.

A Hemopatch was applied to the pancreatic stump in all cases from 01/01/2020. No sutures were used to fixate the patch in place. The Hemopatch sponge was placed overlapping the closure line by at least 2.5cm in all directions, with a secondary sponge applied if required to ensure adequate coverage. A non-suction Robinsons drain was left in situ along the pancreatic bed with the tip lying at the remnant of the pancreatic stump, but not touching it or the patch, in all cases.

Complications were treated at the discretion of the surgeon in accordance with evidence based guidelines and international best practise.

The primary outcome was to determine the effect of Hemopatch use on the development of a clinically significant (Grade B or C) POPF using the ISGPF definition in comparison to standard closure with a stapler.⁵ Secondary outcomes included ascertaining peak drain amylase level, 30 day peri-operative morbidity and mortality rates, length of stay, and comparing rates of POPF with benchmarked international standards of care.

All patients are reviewed in the outpatient's clinic six weeks after discharge to ensure adequate follow up, and completion of data collection for the prospectively maintained database.

A sample size of 64 patients was calculated to be required to demonstrate a 60% relative reduction in Grade B/C POPF from expected baselines, with a type I error of 0.2 and power of 0.75.

Serum amylase is calculated after centrifugation and the measurements quoted in international units per litre (IU/L). Statistical analysis was conducted using SPSS (SPSS software, Chicago, IL). Continuous variables were summarized using mean and standard deviation (SD). Categorical variables were reported using frequency and percentages, and analysed using Fischer's exact test. Chi-squared and T-Test analysis was used in continuous data of normal distribution. P-values with a result of less than 0.05 were deemed statistically significant.

Results

Patient Demographics

Seventy one consecutive patients underwent a distal pancreatectomy during the study period. All were included in the study. Thirty eight patients had a DP and closure of the transected pancreatic stump with a stapler device alone (standard). Thirty three patients had a Hemopatch applied to the pancreatic tail remnant as an adjunct to the stapler closure (intervention group) (*Table One*).

The mean age was comparable between the two groups at 61.1 years of age. There was a male to female ratio of 1 : 2.17 in the standard group, and 1 : 1.75 in the Hemopatch cohort. Indications for DP included intraductal papillary mucinous neoplasms / mucinous cystic neoplasms (n=21), neuroendocrine tumours (n=20), and pancreatic adenocarcinoma (n=17) (*Table One*).

Peri-operative Details

The majority of patients underwent an open DP in both the standard (n=37, 97.3%) and intervention cohorts (n=31, 94%). There was one (2.6%) and two (6%) laparoscopic DP operations performed in the standard and intervention groups respectively. No cases of robotic assisted DP or laparoscopic converted to open DP were performed in included patients.

Thirty four (89%) patients in the standard group, and twenty two patients (67%) in the intervention group underwent a DP with or without splenectomy. There were four (11%) instances where the DP occurred as part of a larger multi-visceral resection in the standard group, and eleven multi-visceral cases (33%) in the intervention group (p-value 0.019).

All patients were discharged home. The total length of stay for the Hemopatch cohort was 12.2 days, and 11.4 days for the standard cohort.

Drains were removed when pancreatic fluid content output had ceased, be it within the index hospital admission, or on reattending the outpatients or dressing clinic once discharged.

Post-Operative Pancreatic Fistula and Outcomes

The rate of a clinically significant POPF in the standard group was seven of thirty eight patients (18%), while in the Hemopatch group it occurred in two of thirty three patients (6%) (p-value 0.122, *Table Two*). The mean peak drain amylase was 7989iu/l in the standard cohort and 1818iu/l in the cohort who had a Hemopatch applied.

No mortality or readmissions occurred in either group. Fourteen patients (37%) who underwent a standard DP developed a post-operative complication. Nine patients (27%) who underwent a DP with application of a Hemopatch developed a post-operative complication (*Table Two*). A grade III or greater Clavien-Dindo complication occurred in 21% (n = 8) and 6% (n = 2) of the standard and Hemopatch groups respectively.

Management of POPF and complications

One patient required a repeat operation for a loculated collection which was not draining in the Hemopatch group. No patient required a re-operation in the standard group (p-value

0.286, *Table Three*). Radiological drainage was required in two (5%) of standard care patients, and in one (3%) of the patients who used a Hemopatch. Drains required to remain in situ for longer than five weeks secondary to ongoing output occurred for five patients in the standard group, and for no patients in the Hemopatch group (p-value 0.031).

	Standard	Standard + Hemopatch	P-Value
Total	38	33	-
Age			
Mean	61	61	0.995
Standard Deviation (SD)	+/- 16 years	+/- 13.4 years	
Male : Female	12 : 26	12 : 21	0.676
Indication for Resection			
Mucinous cystic neoplasm/IPMN	11 (30%)	10 (30.3%)	0.554
Pancreatic adenocarcinoma	10 (27%)	7 (21.2%)	
NET	11 (30%)	9 (27.3%)	
Metastatic melanoma	1 (2.6%)	0 (0%)	
Metastatic RCC	1 (2.6%)	1 (3%)	
Trauma/Sarcoma/GIST/Other	4 (8.1%)	6 (18.2%)	
Extent of Resection			
Pancreas +/- Splenectomy	34 (89%)	22 (67%)	0.019*
Multi-visceral	4 (11%)	11 (33%)	
Approach			
Open	37 (97.3%)	31 (94%)	0.481
Laparoscopic	1 (2.6%)	2 (6%)	
Length of Stay			
Mean	11.4 days	12.2 days	0.528
Standard Deviation	+/- 4.7 days	+/- 6.5days	

Table 1: Demographics of Patients

	Standard	Standard + Hemopatch	P-Value
POPF			
None	7 (19%)	18 (55%)	0.122
Grade A	24 (63%)	13 (39%)	
Grade B/C	7 (19%)	2 (6%)	
Clavien Dindo Complication			

I/II	6 (15%)	7 (21%)	0.322
III or above	8 (18%)	2 (6%)	
30 Day Mortality	0 (0%)	0 (0%)	-
30 Day Readmission	0 (0%)	0 (0%)	-
Peak Drain Amylase (IU/L)			
Mean	7989	1818	0.097
Standard Deviation	+/- 17951	+/- 3127	

Table 2: Post-operative pancreatic fistula and outcomes

	Standard	Standard + Hemopatch	P-Value
Re-operation	0	1	0.286
Interventional Radiology Drain Insertion	2	1	0.647
Drain in Situ for Greater than Five Weeks	5	0	0.031*
Endoscopic Intervention	0	0	-
Escalation of Care to ICU/HDU	0	0	-

Table 3: Management of POPF and Complications. * = statistically significant p-value.

Discussion

A myriad of surgical techniques and adjuncts have been employed in an attempt to prevent the development of POPFs after a distal pancreatectomy. These interventions have proven equivocal, with limited success to date.¹⁷⁻¹⁹ It remains to be determined if the use of fibrin glues, including Hemopatch, can have a positive impact on the severity or frequency of a POPF developing post DP.

We have shown that clinically significant POPF rates are not reduced by the routine use of a Hemopatch adjunct in DP. Owing to the differences in methodological design, operative procedure, and type of fibrin glue applied, an indirect comparison is enabled with the wider literature corroborating these results.^{8,17}

The increased length of stay observed in the Hemopatch cohort may be accounted for by the differences in extent of resection, with eleven (33%) of the Hemopatch cohort undergoing a multi-visceral resection of multiple organs, in comparison to only four (11%) of the standard group.

Persistent pancreatic fluid discharge necessitating extended drain placement was noted in the non-Hemopatch cohort. While this did not extend inpatient length of stay, an analysis of

patient reported outcomes measures of quality of life may be a future indication for the use of Hemopatch in DP beyond binary quantitative morbidity metrics.

The safety and feasibility of Hemopatch use is demonstrated by the lack of a significant difference in morbidity or mortality between the groups. Our secondary aim was to audit our outcomes against international standards. International incidences of POPF after DP vary, but our rate of 12.67% is favourable when compared the generally quoted incidence of 25%.¹⁷

Limitations exist for this study. The relatively small sample size may contribute to inherent biases in patient selection and shield the appearance of rarer complications a larger study would identify. Though the database is prospectively maintained, its review in a retrospective manner further limits analysis, for example, uniform prospective recording did not occur for contributing co-morbidities (diabetes mellitus, smoking status) or intra-operative findings (pancreatic texture etc) to the development of a POPF, and thus this could not be explored in the multivariate analysis. To ameliorate against these risks data collation and analysis was conducted separately and independently by authors MD, MD, UN, ROC, and MA.

The use of Hemopatch is a safe adjunct in DPs. However, it does not reduce the rates of clinically significant POPF in comparison to stapler closure alone.

Declaration of Conflicts of Interest:

None declared.

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