Randomized Controlled Trial

ANNALS OF SURGERY OPEN

OPEN

Clinical Impact of Stump Closure Reinforced With Hemopatch on the Prevention of Clinically Relevant Pancreatic Fistula After Distal Pancreatectomy: A Multicenter Randomized Trial

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Introduction: Postoperative pancreatic fistula (POPF) is the most dreaded complication after distal pancreatectomy (DP). This multicenter randomized trial evaluated the efficacy, safety, and tolerance of Hemopatch in preventing clinically relevant (grades B/C according to the ISGPS classification) POPF after DP.

Material and methods: After stump closure, patients were randomized to affix Hemopatch to the stump or not. Statistical significance was set at 0.025. Clinical significance was defined as the number of patients needed to treat (NNT) to avoid 1 B/C POPF.

Results: Of 631 eligible patients, 360 were randomized and 315 analyzed per protocol (155 in the standard closure group; 160 in the Hemopatch group). The rates of B/C POPF (the primary endpoint) were 23.2% and 16.3% ($P=0.120$), while the number of patients with 1 or more complications (including patients with B/C POPF) was 34.8% and 24.4% ($P=0.049$) in the standard and Hemopatch groups, respectively. In patients with hand-sewn stump and main duct closure, the rates were 26.2% versus 10.0% ($P=0.014$) and 23.3% versus 7.7% ($P=0.015$) in the standard and Hemopatch groups, respectively. The NNT in these 2 subgroups was 6 and 6.4, respectively.

Conclusion: The results of the first randomized trial evaluating Hemopatch-reinforced pancreatic stump after DP to prevent type B/C POPF do not allow us to conclude that the risk of B/C POPF was lower. Based on the NNT, however, routine use of Hemopatch after DP may result in fewer complications (including POPF) overall, especially in cases with hand-sewn closure of the pancreatic stump or main pancreatic duct.

Registered at ClinicalTrials.at (INS-621000-0760).

INTRODUCTION

Postoperative pancreatic fistula (POPF) affects 13% to 41% of pancreatic resections overall and 15.5% to 60% of distal pancreatectomy (DP).[1–4] POPF is a source of substantial postoperative morbidity, a possible cause for delayed chemotherapy,[5] and a major financial burden for health care.[4,6]

Several procedures have been advocated for pancreatic stump closure after DP to decrease the prevalence and severity of POPF, including pancreat(ic)o-enteric anastomoses, stapled

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S.U. and A.F. contributed equally to this work.

Participating centers: Athens, Bochum, Bucharest, Graz, Innsbruck, Istanbul, Milan, Moscow, Munich, Munster, Naples, Pavia, Pisa, Rome, Verona, Zaragoza, and Vigo.

Availability of data and material

All data gathered and analyzed are available from the corresponding authors upon request.

All authors have contributed either to the conception, drafting, and critical revision of this manuscript and have given their approval of its contents. The authors acknowledge the help of Chadl Dziri, MD, FACS (Tunis University El Manar—Medical School of Tunis; Director of Honoris Medical Simulation Center—Tunis) in the analysis of data. None of the authors have any conflicts of interest, financial or otherwise, to disclose and declare that Industry had no role in data acquisition, analysis, or the writing of this article.

The secretarial work and statistical analysis were funded by the European Society of Trauma and Emergency Surgery.

Annals of Surgery Open (2021) 1:e033

Received: 24 September 2020; Accepted 24 December 2020

Published online 10 February 2021

DOI: 10.1097/AS9.0000000000000033

(vs hand-sewn) closure, over-sewing the stump, ligation of the main pancreatic duct, and reinforcement of the closure line with glue, autologous tissues or nonautologous absorbable or nonabsorbable materials.

Two recent meta-analyses highlighted the preventive role of patch coverage of the stump after DP.[7,8] Conversely, the recent consensus conference of the International Study Group on Pancreatic Fistula (ISGPS)[9] underscored the lack of evidence that any energy-based tissue sealant, chemical sealant device or combinations of these could impact the POPF.

The results of 5 completed randomized trials testing nonautologous patches added to the pancreatic stump (vs unprotected stump closure) showed divergent outcomes[3,10–13]: Two[3,10] found a statistically significant decrease in POPF according to whether synthetic reinforcement (Seamguard[10] or Peristrips[10] or polyglycolic mesh[3]) was used or not, while 3 others testing TachoSil[11–13] were unable to show any statistically significant difference (Table 1).

Hemopatch is a thin bovine-derived collagen pad coated with a polyethylene glycol monomer that has both hemostatic and tissue sealing properties that have been used in multiple surgical specialties.[14] To the best of our knowledge, there are only 2 publications on the use of Hemopatch in pancreatic surgery; 1 studied the effects of Hemopatch after pancreatoduodenectomy,[15] the other after distal pancreatectomy.[16] Both showed that the POPF rate was lower with the use of Hemopatch. Of note, however, the latter was a historical comparison in a retrospective cohort of 57 patients. Its use in the prevention of POPF has not yet been explored in a controlled trial.

The goal of this multicenter double-blinded randomized clinical trial was to evaluate the efficacy, safety, and tolerance of Hemopatch affixed to the pancreatic stump in preventing types B and C POPF (B/C POPF) after DP.

METHODS

Patients

All patients undergoing DP for either benign or malignant disease, aged between 18 and 90 years old, with an American Society of Anesthesiologists (ASA) score less than 5, a Simplified Acute Physiology Score (SAPS II) less than 56, were eligible. Excluded were patients undergoing additional gastrointestinal resection(s), anastomosis or stoma, patients with acute necrotizing pancreatitis, immunosuppressed, incapable of giving informed consent, with any history of allergy to human thrombin and fibrinogen or collagen, or any other particular contraindication for DP or women in pregnancy or breast-feeding.

Intervention

Surgery could be performed either via laparotomy or laparoscopy, with or without splenectomy, and in case of splenic preservation, with (but preserving the short gastric vessels)[17] or without[18] ligation of the main splenic vessels. Surgeons could close the pancreatic stump according to personal preference, either manually or stapled, with or without selective main pancreatic duct suture closure.

The Hemopatch sponge was placed on the stump without sutures, overlapping the closure line by at least 2.5–3 cm on all sides (Figure 1). If more than 1 Hemopatch was needed, they were positioned side-by-side with minimal overlap.

Passive (without suction) external drainage was mandatory for at least 7 days with the drain positioned next to but not in contact with the pancreatic stump. Omentoplasty, fibrin sealant, fibrin injection into the main pancreatic duct or serosal patch with another adjacent organ, or hollow organ resection including gastric wedge resection were not allowed. Likewise, we did not include patients undergoing simple enucleation or intraabdominal anastomosis, including pancreatico-enterostomy.

Outcomes

The primary outcome was to evaluate the efficacy of Hemopatch in preventing clinically relevant (grades B/C) POPF according to the ISGPF definition [any measurable amount of drainage fluid, with amylase concentration greater than 3 times the upper limit of normal in the serum on or after postoperative day 3, irrespective of its color or aspect, exteriorized through a drain or retrieved during reoperation or via percutaneous (sonography or computed tomography-guided) aspiration],[19,20] compared with the absence of pancreatic stump coverage, called standard closure. Secondary endpoints included the safety and tolerance of Hemopatch in patients undergoing DP. Safety was judged by the number of patients with 1 or more complications, the rates of surgical site (SS) infection and wound dehiscence, fluid collection requiring treatment, deep organ space complications, hospital stay, reintervention (surgical, interventional radiologic or endoscopic), and death, irrespective of the cause, up to 30 days post-operative. Other secondary endpoints were duration of stay in intensive care and hospital.

Tolerance was measured by the adverse events (AE) occurring during the trial. An independent data and safety monitoring board (DSMB) monitored all AE within 24 hours of reporting. The DSMB then judged AE as "related to," "probably related to," "possibly related to," "probably not related to," or "not related to" the use of the product.

TABLE 1.

Randomized Studies on Nonautologous Pancreatic Stump Closure Reinforcement After Distal Pancreatectomy in the Literature

First Author	Journal/y	With/ Without	Material	% B/C POPF
Montorsi	Ann Surg/2012	145/130	TachoSil	8 vs14
Hamilton	Ann Surg/2012	54/46	Seamguard or peristrips	1.9 vs 20.0§
Sa Cuhna	Am J Surg/2015	134/136	TachoSil	30.0 vs 24.3
Shubert*	J Surg Res/2016	32/35	Seamguard vs Tissuelink	12.5 vs 22.9
Park	J HBP Sci/2016	48/53	Staples alone vs Fibrin +TachoSil	22.9 vs 28.3
Jang	JAMA Surg/2016	44/53	Polyglycolic mesh	11.4 vs 28.3§

*Study stopped prematurely.
§Statistically significant difference.

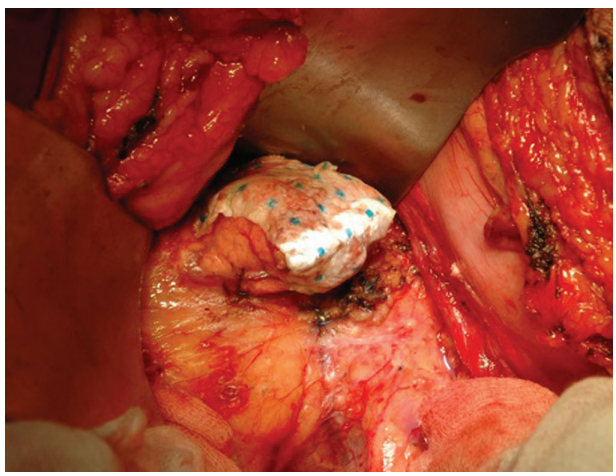

FIGURE 1. Hemopatch covering a hand-sewn pancreatic stump closure.

Evaluation of Severity of Complications

Severity was assessed according to the Clavien-Dindo classification,[21] separated into severe (grade III or greater) or not (grades I and II).

Randomization Methodology and Statistical Analysis

Data management and centralized online randomization were ensured by an independent organization (MedPass International, Paris). Patients were stratified according to the approach (laparotomy or laparoscopy) and randomized into 2 arms: standard stump closure and standard closure plus Hemopatch. Our null hypothesis in this superiority trial was that the risk of developing type B/C POPF was not statistically significantly different whether or not the Hemopatch was applied to the pancreatic stump. With a type I error set at 0.05 and a power of 0.90, we calculated that 322 patients would be necessary to reduce the B/C POPF rate from 30% to 15%.[11,13] To compensate for dropouts and protocol violations, we sought to include 360 patients with a planned intermediate analysis after the first 180 patients. Statistical analysis included Pearson's Chi-squared (or Fischer's exact test) method for categorical data, and Student's t-test for continuous data, as appropriate. The Mann Whitney or Kruskal Wallis test was used for comparisons of nonparametric data. For comparisons with stratification on prognostic variables, we used the Cochran-Mantel-Haenszel test.[22] As we performed an intermediate analysis, the limit of statistical significance was set at $P = 0.025$.

Clinical significance was determined according to the number of patients needed to treat (NNT) to avoid 1 B/C POPF (1/absolute risk reduction).[23]

This study was double-blinded: neither the patients nor the independent investigator of outcomes was aware of the allocations. Patients, however, upon request, could be informed of their allocation after the 30-day visit.

The initiator of this study was the European Society for Trauma and Emergency Surgery (ESTES). Either local ethic committees and institutional review boards of all centers approved the study, which was registered in ClinicalTrials (INS-621000-0760).

RESULTS

Patients were enrolled from March 1, 2016, to March 1, 2019.

After the planned intermediate analysis (91 assigned to standard closure, 88 to standard closure plus Hemopatch), the continuation of the study was approved on October 10, 2017.

Of 631 consecutive patients who were seen during the study period, 360 patients were randomized. After elimination of randomization errors, protocol violations (additional resections, absence of DP) for 328 patients remained. After patient withdrawal and elimination of patients with incomplete follow-up, full data were available for 315 patients (155 in the standard closure group; 160 in the Hemopatch group) (Figure 2). There were no cross-overs. No statistically significant difference was found in patient demographics (Table 2). Seventeen centers participated. The median number of patients included in each center was 18 (range 1–71). Centers performed a median of 15 DP/y (range 5–55) during the study period. A median of 77.5% (20%–100%) was performed via laparotomy.

The overall B/C POPF was 23.2% and 16.3% in the standard and Hemopatch groups, respectively ($P = 0.120$). The NNT to avoid 1 B/C POPF was $1/0.069 = 14.5$.

Operative Details

More than half [174 (55.2%)] operations were started via laparotomy, 126 (40.0%), laparoscopically, while 15 (4.9%) were performed via robotic-assisted surgery (Table 3). Twenty-three procedures (7.1%) started laparoscopically were converted to laparotomy; no robotic procedures required conversion. Finally, 197 procedures (62.5%) were completed via laparotomy, 118 (37.5%) minimally invasively (laparoscopic + robotic).

The rate of B/C POPF when the minimally invasive approach was used was 15/54 (27.8%) versus 15/64 (23.4%) in the standard and Hemopatch groups, respectively. This difference was not statistically significant ($P = 0.590$). However, when laparotomy (including conversions from laparoscopy to laparotomy) was used, the rates were 21/101 (20.8%) versus 11/96 (11.5%) (Table 3). The P value was 0.075.

There was no disparity in the proportion of B/C POPF according to whether the stumps were closed with staples or handsewn (21.1% vs 17.8%). In the stapled closure group (n = 180), the B/C POPF rates were 19/90 (21.1%) versus 19/90 (21.1%) without or with Hemopatch, respectively ($P = 0.855$) (Table 4). Of the 180 stapled stump closures, 28 were oversewn, 16 in the standard closure arm, 12 in the Hemopatch arm; 4 B/C POPF occurred, 3 in the standard group (18.8%), 1 in the Hemopatch group (8.3%): this difference was not statistically significant ($P = 0.415$). However, in the handsewn group, the B/C POPF rates were 17/65 (26.2%) versus 7/70 (10.0%) in patients without or with Hemopatch, respectively; the P value was $P = 0.014$ (Table 4). The NNT was 6 (95% CI: 3–29). Among the 125 patients who underwent main pancreatic duct closure, the rate was 14/60 (23.3%) versus 5/65 (7.7%) without and with the patch, respectively (9 patients with stapled closure, 116 handsewn). The P value was $P = 0.015$. The NNT was 6.4 (95% CI: 4–32).

Safety

The number of patients with 1 or more complications (including POPF) was 54/155 (34.8%) and 39/160 (24.4%) in the standard and Hemopatch groups, respectively ($P = 0.049$) (Table 5). No statistically significant difference was found between the 2 groups with respect to the rates of SS infection and wound dehiscence, fluid collections requiring treatment, deep organ space complications, severe Clavien/Dindo complications (grades III and over), reoperation (including interventional radiology or endoscopy), hospital stay or death, irrespective of the cause, within 30 days postoperative (Table 5).

One 88-year-old patient, a heavy smoker, died of respiratory failure on postoperative day 36; this patient was in the Hemopatch group and sustained a grade A biochemical leak. The DSMB reviewed his chart and declared that his death was not related to the product nor to the biochemical leak. As he was alive on day 30, he was included in the final analysis.

Tolerance

Adverse events (AE) were recorded 267 times in 137 patients: 49 AE were labeled as "serious" by surgeons, 7 possibly related to Hemopatch. All were reviewed by the DSMB; none were retained as being related to Hemopatch.

The rate of B/C POPF when the minimally invasive approach was used was 15/54 (27.8%) versus 15/64 (23.4%) in the standard and Hemopatch groups, respectively. This difference was not statistically significant ($P = 0.590$). However, when laparotomy (including conversions from laparoscopy to laparotomy) was used, the rates were 21/101 (20.8%) versus 11/96 (11.5%) (Table 3). The P value was 0.075.

Postoperatively, there was no statistically significant difference found in the median number of days in intensive care [1.5 (0–99) vs 1(0–15)] or in hospital [13 (4–142) vs 12 (5–71)] according to whether the patient received standard closure or Hemopatch ($P = 0.234$ and $P = 0.454$, respectively) (Table 5).

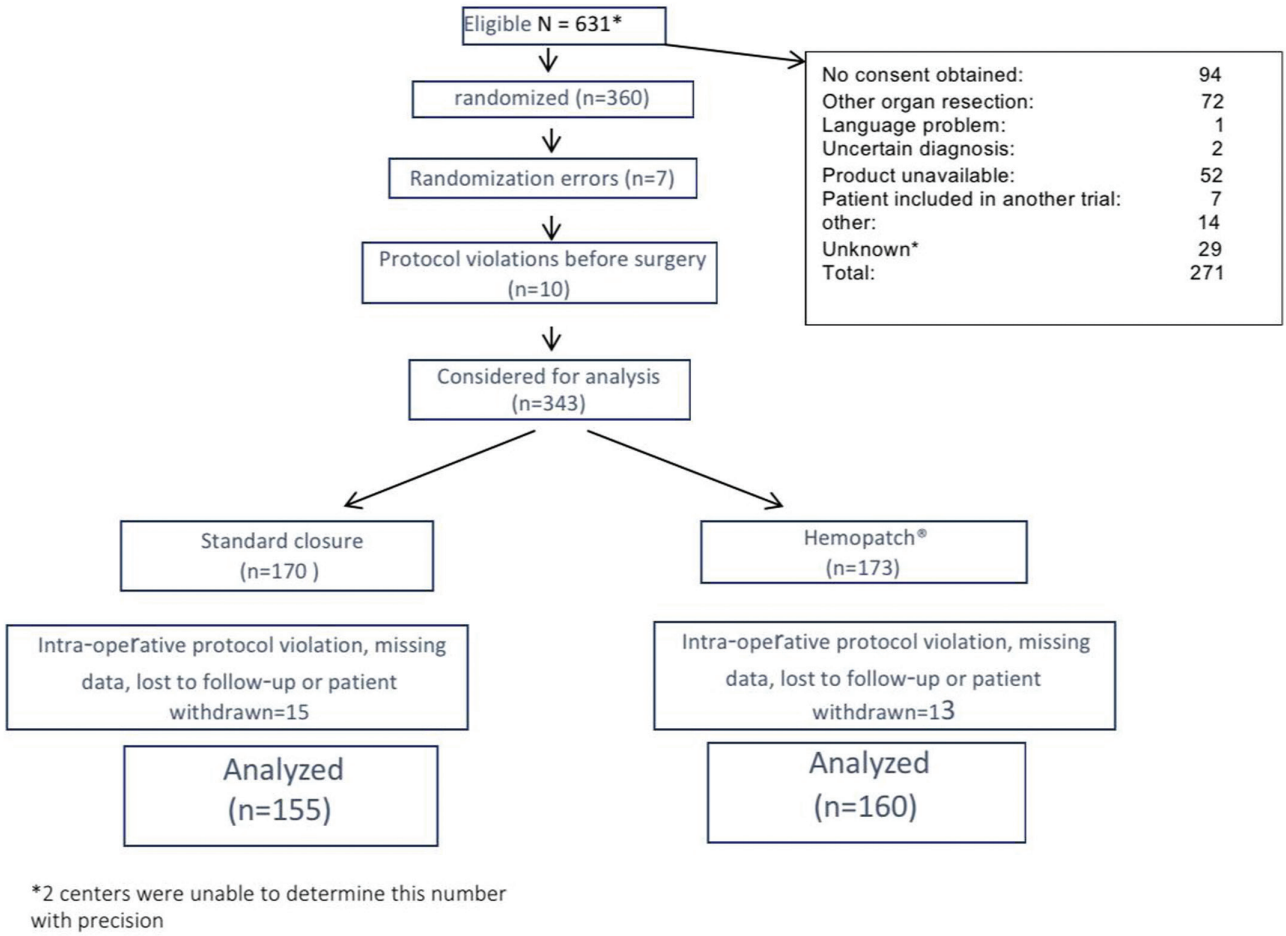

FIGURE 2. CONSORT flow chart.

Center and Volume Effect

A fairly strong center effect was found. According to the strict definition of the ISGPF, 1 center would have had a much higher B/C POPF rate than the others (28.1% vs 17.6%, respectively; $P = 0.058$). Analysis of data from that center found that drains were inserted and irrigated with "prophylactic" intent in more than 63% of their patients. The patient was allowed to leave the hospital with the drains in place, and this led to 27 patients who had the drain in place at postoperative day 21 at home. Of these patients, and in accordance with Marchegiani et al,[24] 6 were classed as type A because their amylase count was less than 3× the upper limit of the serum level, and they were asymptomatic.

TABLE 2.

Patient Demographics

	Standard	Standard + Hemopatch	Total	*P*
Male/female	56/99	67/93	123/192	0.296
Age [mean (SD)]	60.8 (13.8)	61.4 (14.2)	61.1 (14.0)	0.719
BMI (median, range)	24.8 (22.2–29.0)	24.6 (22.4–27.8)	24.7 (22.2–29.0)	0.387
ASA				0.881
1	21	18	39	
2	88	93	181	
3	45	47	92	
4	1	2	3	
Type of tumor				0.497
Benign	40	44	84	
Malignant	66	75	141	
Beuroendocrine	49	41	90	

ASA indicates American Society of Anesthesiologists score; BMI, body mass index.

Before adjustment, Hemopatch had no statistically significant effect on the B/C POPF rate in this center [13/34 (41.2%) vs 10/30 (33.3%)] for patients treated without or with Hemopatch, respectively ($P = 0.869$). However, when we amended as stated, Hemopatch had a positive effect as the adjusted B/C POPF rate was 13/34 (38.2%) when Hemopatch was not used, and 5/30 (16.7%) when it was; the difference was not statistically significant but exhibited a tendency at $P = 0.055$. Once this correction was made, there was no statistically significant difference found in the duration of stay in ICU or in hospital between this center and the other 16 centers.

Five centers performed ≤10 DP/y: there was no statistically significant difference in the B/C POPF rate between these centers and those performing >10/y, with or without the use of Hemopatch.

DISCUSSION

This is the first randomized study on the use of Hemopatch affixed to the pancreatic stump with the goal of reducing the B/C POPF rate after distal pancreatectomy. The overall B/C POPF was lower in the Hemopatch group, 23.2% and 16.3% in the standard and Hemopatch groups, respectively: the difference was not statistically significant ($P = 0.195$). The number of patients with 1 or more complications (including POPF) was lower in the Hemopatch group (34.8% vs 24.4%) ($P = 0.049$). The difference in the B/C POPF rates was 17/65 (26.2%) versus 7/70 (10.0%) ($P = 0.014$) in patients when stump closure was hand sewn, and 14/60 (23.3%) versus 5/65 (7.7%) in patients when the main pancreatic duct was oversewn ($P = 0.015$).

TABLE 3.

Intraoperative Details

		Standard n = 155	Standard + Hemopatch® n = 160	Total N = 315	*p* value
Approach					
Laparotomy[a]	B/C POPF	21	11	32	0.075
	Total	101	96	197	
Minimally invasive[b]	B/C POPF	15	15	30	0.590
	Total	54	64	118	
Intraoperative data	Duration (minutes) (median, range)	240 (60–580)	240 (74–424)	240 (60–580)	0.222
	N patients requiring blood transfusion	7 (4.5%)	12 (7.5%)	19	0.266
Parenchymal texture					
Normal, friable or intermediate	B/C POPF	34	24	58	0.111
	Total	142	145	287	
Hard	B/C POPF	4	2	6	0.730
	Total	13	15	28	

[a]Including conversions from laparoscopy to laparotomy.

[b]Laparoscopic + robotic.

TABLE 4.

Clinically Relevant (B/C) POPF Rate According to Stump Closure Technique

		Standard	Standard + Hemopatch®	Total	*p* value
Closure technique					
	Handsewn (n = 135)	17/65 (26.2%)	7/70 (10.0%)	24/135 (17.8%)	0.014
	Stapled (n = 180)	19/90 (21.1%)	19/90 (21.1%)	38/180 (21.1%)	0.855*
Total	N = 315	36/155 (23.2%)	26/160 (16.3%)	62/315 (19.7%)	0.120

*Yates correction.

POPF indicates postoperative pancreatic fistula.

TABLE 5.

Postoperative Course

	Standard	Standard + Hemopatch	Total	
	n = 155	n = 160	N = 315	*P*
No. patients with one or more complications (including patients with at least one complication and B/C POPF)	54 (34.8%)	39 (24.4%)	93 (29.5%)	0.049
SSI	2 (1.3%)	2 (1.3%)	4	0.975
Fluid collections requiring treatment/prolonged stay/rehospitalization	22 (14.2%)	22 (13.8%)	44 (14.0%)	0.910
Deep organ-space SSI	8 (5.1%)	7 (4.4%)	15	0.975
Clavien/Dindo*				0.489
Minor (I/II)	50 (32.3%)	39 (24.4%)	89 (28.3%)	
Major (III and higher)	24 (15.5%)	24 (15.0%)	48 (15.2%)	
Reoperations§	11 (7.1%)	15 (9.4%)	26 (8.3%)	0.463
Death	0	1	1	
Duration stay ICU (median, range)	1.5 (0–99)	1 (0–15)	1 (0–99)	0.234
N patients who did not go to ICU	59 (38.1%)	68 (42.5%)	127	0.422
Duration hospital stay, median (range)	13 (4–142)	12 (5–71)	12.5 (4–142)	0.454

*Number of patients with 1 or more complications (except POPF) (only the most severe grade was counted).

§Including surgery, interventional radiology, endoscopy.

ICU indicates intensive care units; POPF, postoperative pancreatic fistula; SSI, surgical site infection.

However, we would emphasize the clinical significance that is not influenced by subgroup analysis: the NNT for prevention of 1 B/C POPF was 6 and 6.4 when Hemopatch was used to reinforce handsewn stump closure or after main duct closure, respectively, meaning that with routine use of Hemopatch in these settings, 1 B/C POPF will be avoided for every 6 to 7 patients.

The cost of 1 Hemopatch is 140 euros or 168 USD (4.5 cm × 4.5 cm) and 240 euros or 288 USD (4.5 cm × 9 cm); in other terms, spending 840 to 1536 euros (according to the size) for routine use will avoid 1 B/C POPF for every 6 to 7 DP in these 2 settings. According to Maggino et al,[6] hospital costs of B/C POPF are 2.3 times higher than those of an uncomplicated resection. While the cost of DP varies considerably from 1 country to another, and 1 center to another, these savings go along the same lines as the Monte Carlo simulation study by Ramirez et al,[15] who, in an observational study of 26 pancreatoduodenectomies, found that Hemopatch reduced the severity of B/C POPF and via a reduced mean stay in hospital and intensive care, led to a substantial savings of $11,109.00 per patient undergoing surgery. In our study, the number of patients with 1 or more complications [fluid collection requiring treatment, reintervention (surgical, interventional radiologic or endoscopic), SS infection and wound dehiscence, deep organ space complications and death, and POPF] was lower in the Hemopatch group (34.8% vs 24.4%) ($P = 0.049$). There was no statistically significant difference in the duration of stay in ICU. The duration of hospital stay was shorter in the Hemopatch group but the difference did not reach statistical significance, most likely because our study was not powered

for these outcomes, and each participating center had varied protocols for ICU and hospital discharge.

One reason why Hemopatch might work is that it completes less than optimal hemostasis of the stump (because of its hemostyptic properties) precluding the need for intensive or repetitive electrocoagulation that might cause necrosis and then be a potential source of fistula.[14] Another argument might be that because of its sealant property, Hemopatch can seal off microfractures that occur either with sharp division or with the stapling device, especially in "thick" (>3 cm) pancreases,[10] a factor known to increase the POPF rate.[25,26]

In our study, 33.0% of distal pancreatectomies were completed laparoscopically. This is more than the average of European and Asian surgeons (24% and 18% of surgeons for at least 75% of procedures), but less than that of North and South American surgeons (43% and 44%, respectively), as found by the recent worldwide survey on current practice[27] involving 721 responding surgeons (14 years of experience) representing 6 continents and 68 nations. The rates of B/C POPF were 27.8% versus 23.4% in the standard and Hemopatch groups when the minimal invasive (laparoscopic + robotic) approach was used, respectively ($P = 0.590$). Of note, when stump closure was performed via laparotomy, the rates were 20.8% versus 11.5%, with a P value of 0.075. Although not quite statistically significant, these results might indicate that it is easier to place the Hemopatch via laparotomy. This is consistent with the decrease in B/C POPF when the pancreatic stump was closed handsewn (26.2% vs 10.0%) ($P = 0.014$) found in our study because many surgeons prefer handsewn closure when DP is performed via laparotomy. Of note, there was no difference in results according to whether the operation was performed in high- or low-volume institutions, although the participating surgeons performed a median of 15 distal pancreatectomies per year (range 5–55) during the study period.

Drains were mandatory for 7 days in our study, the idea being to ensure detection of amylase and lipase in any intraperitoneal fluid collection. Although it may be argued that this could have influenced the outcome, either by increasing[28] or decreasing[29] the occurrence of B/C POPF, it is likely that as drainage was mandatory in *both* groups, the eventual positive or negative effect of mandatory drainage would have been the same in each of the allotted arms and any (unknown) effect on the outcome of our study would have been eliminated by the randomization process.

The 30-day visit, required in our study, was not recorded for 11 patients in our study. However, as we had information (a) for 7 of these patients between 20 and 26 days, (b) for at least 2 more patients who were in the same hospital, the centers knew that these patients had not sustained any complications; after consultation with the local surgical team, we calculated the B/C POPF rates these 9 patients as if they had fulfilled the 30 day requirement. Of note, in certain countries, it is not allowed by law to contact patients about their follow-up once the trial has been closed.

Weaknesses and Strengths

One weakness of our study was the relatively high drop-out rate of 38 patients, which together with 7 protocol violations left 315 patients for per-protocol analysis. Our final sample size does not allow us to come to any formal conclusion as to efficacy with respect to the overall B/C POPF rate. Nonetheless, there are situations in which a personalized appreciation of statistically nonsignificant results may influence and perhaps change practice.[30] Moreover, well-conducted "underpowered" studies can be part of larger systematic reviews and meta-analyses necessary for appropriate decision-making.[31,32] This why the results of hand-sewn stump closure and main pancreatic duct closure are important. While it might be argued that the analysis of the effect of Hemopatch in these 2 categories is akin to subgroup analysis, we emphasize that the clinical significance (NNT) is not influenced by such statistical considerations. As 15% to 45% of surgeons worldwide[27] close the pancreatic stump handsewn, we believe this information is important.

We did not measure the thickness of the pancreas at the level of the staple line. We know that thicker pancreases have a higher B/C POPF rate (if special precautions are not taken)[25,26] and this makes stapled closure a bit more difficult and sometimes impossible.[9] However, as for the effect of drains, it is plausible to assume that the variation in parenchymal thickness was evenly distributed between the 2 arms because of randomization and that this did not influence the outcome with respect to the efficacy of Hemopatch in these settings.

We acknowledge that the power calculation of our study was based on a review of the literature, and not a pilot study, which may have identified a lower rate of POPF in the participating institutions or the trend toward greater impact for patients undergoing open surgery with a hand-sewn stump closure technique.

As stated, the NNT for the overall population was 14.5. However, the 95% CI was large (6 to ∞). Conversely, for hand sewn closure with Hemopatch added, the NNT to avoid 1 B/C POPF was only 6 (95% CI: 3–29), and the NNT to avoid 1 B/C POPF when the main pancreatic duct was suture-ligated with Hemopatch added was 6.4 (95% CI: 4–32). These outcomes comfort our results, and the clinical signification was that routine use of Hemopatch after DP would result in fewer complications in these 2 settings.

In conclusion, this randomized trial, admittedly slightly underpowered, was unable to show a statistically significant difference in the B/C POPF after DP, but the clinical impact was that there were fewer patients with 1 or more postoperative complications (including B/C POPF) (24.4% vs 34.8%) ($P = 0.049$) (Table 5) in the Hemopatch versus standard groups, respectively. As can be seen in Table 5, this difference was essentially related to fewer Clavien/Dindo minor complications (24.4% vs 32.3% in the Hemopatch vs standard groups, respectively). Although there were substantial differences in B/C POPF rates after DP when the pancreatic stump was reinforced with Hemopatch in patients with hand sewn stump closure and the main pancreatic duct was ligated selectively, no causality can be inferred, and a specific controlled trial on this particular subset of patients is warranted.

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Appendix

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