

Stump closure reinforcement with absorbable fibrin collagen sealant sponge (TachoSil®) does not prevent pancreatic fistula after distal pancreatectomy: the FIABLE* multicenter controlled randomized study

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Background: evaluate the effectiveness of TachoSil® sponge on distal pancreatectomy remnant stump in reducing the rate and severity of post-operative pancreatic fistula (POPF)

Methods:

All consecutive patients requiring distal pancreatectomy were randomized in 45 centers. Principal endpoint: onset of "clinically relevant" POPF. Univariate and multivariate analyses searched for predictive factors.

Results

Of 270 patients randomized in 45 centers (134 with TachoSil®;136 without), 150/270(55.6%) sustained a POPF (74 clinically relevant;76 clinically silent (27.4% and 28.1%, respectively): no statistically significant difference (NS) was found between patients with (41(30.6%) *vs.* 33(24.3%) without TachoSil®(p=0.276), or overall POPF (73(54.5%) with *vs.* 77(56.6%) without TachoSil®(p=0.807), but more clinically relevant POPF after hand-sewn (32.3%) *vs.* mechanical closure (19.8%)(p=0.025) and, in case of splenic preservation, after splenic vessel ligation (15/32,46.9%) *vs.* vascular preservation (17/72,23.6%)(p=0.024). Hand-sewn pancreatic remnant closure (p=0.023) and splenic vessel ligation in splenic preservation (p=0.035) were independent predictive factors for the onset of clinically relevant POPF.

Conclusion: TachoSil® sponge reinforcement of the proximal remnant after distal pancreatectomy reduced neither the rate nor the severity of POPF.

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Stump closure reinforcement with absorbable fibrin collagen sealant sponge (TachoSil®) does not prevent pancreatic fistula after distal pancreatectomy: the FIABLE* multicenter controlled randomized study

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*FIABLE : Efficacité sur la survenue des **FI**stules p**A**ncréatiques et la tolérance de l'éponge de TachoSil® appliquée sur la tranche de

section pancréatique chez les patients ayant su**B**i une pancréatectomie dista**LE** pour tumeur.

This study was approved by the Committee for the Protection of Patients under the number CPP 08012, and registered with the European Clinical Trials Database EUDRACT under the number 2008-001253-17.

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Running title :

Pancreatic stump fistula prevention

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Introduction

While distal pancreatic resections are performed less frequently than other pancreatectomies (1), the rate of post-operative pancreatic fistula (POPF) is high, ranging from 5% (2) to 64% (3-5), according to the definition used (4).

Several procedures have been proposed to reduce the rate and/or severity of POPF after distal pancreatectomy (3): decreasing digestive tract secretions (6), main duct ligation (7), various techniques of division and/or stump closure (1,5,8-10), different types and durations of abdominal drainage (11, 12), and stump reinforcement with omentum, absorbable or non-absorbable mesh or biological glue (8, 13-18). While some reinforcement materials have a mechanical action, reducing the traction on the sutured edges, others act by enhanced healing (14). TachoSil®, a sponge composed of horse collagen, impregnated with human thrombin and fibrinogen, stabilized by albumin, combines enhanced healing while exercising a hemostatic role (19) and has been used to improve hemostasis and bilistasis on the surface of the divided liver (18).

Several uncontrolled studies seem to indicate that absorbable mesh reinforcement could reduce the POPF rate after distal pancreatectomy (13,14). One randomized study has shown that Seamguard ® or Peristrips Dry ® reinforcement of stapled stump closure was effective in decreasing the fistula rate (17). However,

to date, only one controlled trial has studied the role of TachoSil® for stump closure in distal pancreatectomy (19), concluding that TachoSil® did not reduce the overall POPF rate.

The goal of the present study was to report the results of a French multicenter randomized controlled study evaluating the role of the TachoSil® sponge in reducing the rate and the severity of pancreatic POPF after distal pancreatectomy, separating clinically silent from clinically relevant POPF.

Methods

Patients

Patients requiring complete removal of the distal pancreas for benign or malignant tumors of the pancreatic body or tail were eligible for this randomized controlled trial. Inclusion criteria required: life expectancy of at least six months, written informed consent before randomization, no history of allergy to human thrombin and fibrinogen or collagen, no preoperative signs of chronic pancreatitis, and absence of indications for simple enucleation or intra-abdominal anastomosis, including pancreatoenterostomy (to eliminate fistula related to the breakdown of these anastomoses (19)). Patients were randomized to receive the sponge, or not, only after the distal pancreas had been removed, the stump was closed and the surgeon was sure that the TachoSil® sponge could be applied under satisfactory conditions.

Intervention

Surgery could be performed either via laparotomy or laparoscopy, with or without splenectomy, and in case of splenic preservation, with ligature (but preserving the short gastric vessels, as described by Warshaw (20)) or not of the splenic vessels. The pancreatic stump had to be closed, either manually or stapled, as per surgeon's choice. Selective main pancreatic duct closure (suture) was not mandatory but was recommended whenever feasible. The TachoSil® sponge was placed on the stump without sutures, overlapping the closure line by at least 2.5 cm and held there for at least 3 minutes to ensure that it stuck to the stump. Additional techniques such as abdominal drainage, omentoplasty and/or application of biological glue were left to the appreciation of the surgeon.

Definition of post-operative pancreatic fistula (POPF)

POPF was defined according to the International Study Group on Pancreatic Fistula (ISGPF) (21) as any measurable amount of drainage fluid, with amylase concentration greater than 3 times the upper limit of normal in the serum on or after post-operative day 3, irrespective of its color or aspect, exteriorized through a drain or retrieved during reoperation or via percutaneous (sonography or CT-guided) aspiration.

Definition of severity

This study was double blinded: neither the patients nor the independent committee whose role was to evaluate the severity of

POPF were aware of the allocations. Patients were categorized into two groups of POPF (17, 21, 22): one without any clinical signs suggestive of any postoperative complication including patients without any signs of POPF and patients with grade A severity (with no clinical impact (mainly no prolonged hospital stay)), categorized as being “clinically silent”, the other “clinically relevant” (with impact on the patient’s hospital course), including Grades B and C severity.

Judgment criteria

The primary endpoint was the onset of “clinically relevant” POPF. The secondary endpoints were: a) the overall POPF rate (ISGPF Grades A+B+C), b) interval between operation and the onset of POPF, c) median duration of post-operative stay in intensive care and/or resuscitative care units and overall hospital stay, d) number of post-operative complication(s) (other than POPF), e) adverse event(s) *i.e.* any potentially harmful manifestation related or not to the product under investigation, and f) mortality.

Follow-up

All patients underwent routine physical examination: daily during hospitalization and at three months (± 15 days) after operation, date at which the diagnosis of POPF and mortality were definitively determined.

Adverse events related to TachoSil®

All adverse events were reported immediately, examined and categorized by an independent data safety monitoring board (DSMB): the causality (not related, possibly related or probably related) was evaluated (23).

Statistical methods

Randomization was centralized by a vocal server and stratified according to the approach (laparotomy or laparoscopy). The α and β risks were fixed at 0.05 and 0.10, respectively, providing 90% power (one-sided test). Based on an expected decrease in the POPF rate from 30% to 15%, the number of patients necessary to satisfy these hypotheses was 262 patients (131 in each group). No intermediary analysis was planned. The predictive factors for the onset of “clinically relevant” POPF were analyzed by univariate and multivariate (step-wise regression) analyses. The log rank test was used to compare variables related to durations.

Results

Two hundred and ninety-seven patients underwent randomization in 45 centers between March 5, 2009 and March 10, 2011. As seen in the CONSORT flow chart (24), of these 297 patients, 27 were ultimately found to not correctly fulfill the entry requirements, and were not included in final analysis (figure 1).

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Of the 270 patients retained for analysis, 134 were allotted to receive the TachoSil® sponge, 136 were the control group. This was the intention-to-treat (ITT) population.

Two patients allotted to TachoSil® did not receive the sponge while three patients initially allotted to the control group, actually had the TachoSil® sponge, without any diagnostic or operative reason to back this choice. Therefore, as concerns the analysis as treated (*per protocol* group), exactly half (135) of the 270 randomized patients were assigned to each group. As the discrepancy between the two populations represents only 1.9% of the entire population, and according to the CONSORT recommendations (24), only the ITT analysis (134 *vs.* 136) is reported hereafter.

No statistically significant differences were found in patient demographics (gender, age or body mass index) (table 1).

The final pathology reports of the resected specimen showed that 128/270 patients (47.4 %) had benign disease while 142 (52.6 %) had malignant disease (p=0.223). Most cancers were pancreatic adenocarcinoma (26.7% of the whole population) (table 2).

No statistically significant differences were noted between the two groups as concerns the duration of operation, the number of patients admitted to and duration of patient stay in intensive care and/or resuscitation units or overall duration of hospital stay (Table 3), parenchymal consistency of the pancreatic remnant or the technical aspects of the operation (selective closure of the main

pancreatic duct, type of division and/or stump closure, laparoscopy or laparotomy, abdominal drainage or not, splenic preservation or not and, in case of preservation, ligation or not of the main splenic vessels (Table 4).

POPF

Of the 270 patients, 150 (55.6%) sustained a POPF (ISGPF Grades A, B and C) of which 74 (49.3%) were clinically relevant while 76 (50.7%) were clinically silent (27.4% and 28.1%, respectively, of the total number of patients) (table 5).

Comparison of patients with or without TachoSil®

Clinically relevant POPF

Forty-one patients (30.6%) had a clinically relevant POPF in the TachoSil® group *vs.* 33 (24.3%) in the control group (p=0.276) (Table 5). The odds ratio (OR) was 1.376 with a 95% confidence interval (95%CI) equal to [0.877-2.160]). The hypothesis that clinically relevant POPF occurred less often when TachoSil® was used, cannot be retained.

POPF (ISGPF Grades A, B and C)

No statistically significant difference was noted between patients with overall POPF in either group: 73 (54.5%) in the TachoSil® group *vs.* 77 (56.6%) in controls (p=0.807) (Table 5). The OR was 0.917, (95%CI: [0.613-1.372]). The hypothesis that any grade of POPF occurred less often after use of TachoSil® cannot be retained.

There was no statistically significant difference found between the two groups as concerns the interval between operation and the onset of clinical POPF (logrank test: p=0.957) or in the 10 patients undergoing surgical operation or drainage of an intra-abdominal collection after hospitalization: 7 *vs.* 3, respectively (p=0.217).

Prognostic factors of POPF

In univariate analysis, no statistically significant difference was found according to whether the POPF occurred in patients with benign (34/128) or malignant (40/142) disease (p=0.786).

The duration of operation was not statistically different in patients with or without clinically relevant POPF. Conversely, the duration of stay in intensive care and resuscitative care was longer (p=0.003 and p<0.001, respectively) for patients who sustained a clinically relevant POPF.

No statistically significant differences were noted in the rate of clinically relevant POPF according to whether or not: a) the pancreatic remnant consistency was normal (*vs.* chronic pancreatitis) (p=0.790); b) the main duct was sutured (p=0.130), c) drainage was performed (p=1.0), and in subgroup analysis, whether patients underwent splenic preservation or splenopancreatectomy (p=0.331). Conversely, there were statistically significantly more clinically relevant POPF when pancreatic remnant closure was hand-sewn (32.3%) *vs.* mechanical closure (19.8%)(p=0.025) and, in case of splenic

preservation, twice as many clinically relevant POPF when the splenic vessels were ligated (15/32, 46.9%) *vs.* vessel preservation (17/72, 23.6%) (p=0.024) (table 6).

Of the 270 patients, 199 (74.7%) underwent laparotomy while 71 (26.3%) had a laparoscopic approach. No statistically significant difference was noted in the clinically relevant POPF rate between laparotomy *vs.* laparoscopy (30.2% (60/199) *vs.* 19.7% (14/71): (p=0.121). Spleen preservation was performed in 104 patients (38.5%), more often via laparoscopy (44/71: 62.0%) than via laparotomy (60/199: 30.2%), (p=0.001). When the spleen was preserved, 32 patients underwent the Warshaw technique (30.8%), 11 via laparoscopy *vs.* 21 via laparotomy, (p=0.322), with no statistically significant difference in the clinically relevant POPF rate according to route (4/11 via laparoscopy *vs.* 11/21 via laparotomy (p=0.470).

The variables entered into the multivariate analysis (p<0.10 in univariate analysis) included age, method of pancreatic remnant closure, splenic preservation (with or without splenic vessel ligation), performance of additional procedures or not: only hand-sewn closure of the pancreatic remnant (p=0.023) and the ligation of the splenic vessels after splenic preservation (p=0.035) were found to be independent predictive factors for the onset of clinical POPF.

Safety

According to the DSMB, 756 adverse events were considered to be “not related”, while 85 were considered as “possibly related” to the use of TachoSil ®. However, none of these adverse events were reported to be related to the onset of any post-operative complication.

Morbidity

Overall, there were 45 post-operative complications (table 7). Nevertheless, there was no statistically significant difference found between patients with or without TachoSil® or in patients sustaining POPF or not.

Mortality

One death occurred in the group randomized to TachoSil®, due to acute respiratory distress, while two deaths occurred in the group without TachoSil®, one related to shock associated with peritonitis and the other due to respiratory failure secondary to pulmonary embolism in a patient with infection and unexpected rapidly generalized cancer.

Discussion

Our results showed that the application of TachoSil® sponge on the proximal remnant after distal pancreatectomy reduced neither the rate nor the severity of POPF.

This is the second negative study on the use of TachoSil® in this indication (19). As highlighted recently (25,26), it is timely and highly relevant to publish well-conducted negative studies in order

to avoid publication and reporting bias, more and more prevalent today, and a real threat to the validity of decision-making for the care of our patients.

While the primary endpoint and the results were close to those in the only previous randomized study on the same topic with the same product (19), our study differed in that: a) we showed that TachoSil® was ineffective for exclusively clinically relevant POPF as well as for all grades of POPF, b) the evaluation of patient outcome for both the diagnosis of POPF and the causality of adverse events was double blinded, c) the power of making a false negative conclusion was twice as strong (our beta error (10%) was half that of the Italian study (20%)). Of note, as others (17, 22), our trial clearly distinguishes itself from the Italian study (19) in that we separated the clinically relevant from the clinically silent grade A POPF. Otherwise, the overall POPF (including Grade A+B+C) would have been 55.6%, still slightly less than the 65% reported in the Italian study (19).

In multivariable analysis, we found that hand-sewn closure of the pancreatic stump and ligation of the splenic vessels in case of splenic preservation were statistically significantly associated with an increased risk for clinically relevant POPF. This is of interest in the modern era where more and more distal pancreatectomies are being performed laparoscopically (5, 17): stapled stump closure and splenic vessel preservation are the preferred methods in laparoscopic distal pancreatectomy.

At least 18 observational (9), two randomized controlled trials (8, 9) and one meta-analysis (3) have compared hand-sewn to some other pancreatic stump closure procedure.

Both the systematic review of observational studies (9) and the meta-analysis of Knaebel *et al.* (3) were in favor of stapled closure. This is in agreement with our findings but contrasts with those of two high-volume institutional studies (1,5) that found that stapled stump closure was associated with a higher POPF rate, perhaps because of the crushing injury to the pancreatic parenchyma by the jaws of the linear stapler, and one other high-volume study (10) that did not find any difference. Likewise, the randomized studies of Bassi *et al.* (8) and Diener *et al.* (9) both showed a non-statistically significant difference in the POPF rate in favor of hand sewn stump closure. Of note, in all of these studies (1,3,8,9), the authors did not distinguish between clinically silent and clinically relevant POPF, as we did in our study.

Neither splenic preservation nor splenectomy influenced the POPF rate in our study. Splenic preservation was found to be a significant predictive factor for POPF in two studies (19, 27), but no distinction was made according to whether the splenic vessels were preserved or not. Conversely, Kleef *et al*. (1) found a just significant higher rate (11.2% *vs.* 5.1% (p=0.048)) of POPF when splenectomy was performed.

Conversely, our higher rate of POPF after the Warshaw technique (20) is in accordance with Adam *et al.* (28).

This contrasts with one case-controlled study (29) and the Massachusetts General Hospital series (30), which found that the POPF rate did not differ statistically significantly whether splenectomy or the Warshaw technique (20) were performed. This is also in line with Jain *et al.,* who in a recent systematic review (31) was unable to show any statistically significant difference in the POPF rate between the Warshaw technique and preservation of the splenic vessels (p = 0.15). Here again, however, two of the studies (29,30) did not use the same definition of pancreatic fistula and, in three studies (29-31), no distinction was made as to the severity (21). One possible reason behind our findings could be that distinguishing between clinically relevant and clinically silent POPF unmasks the potential ischemic effects of splenic vessel ligation.

Our overall POPF rate was 55%, slightly lower that the Italian randomized trial (65%)(19), but considerably higher than that reported by Diener *et al.* in the DISPACT trial (9). However, we searched for this complication over a three-month period, compared to the 7 (30%) and 30 day (36%) analyses in the DISPACT trial. Moreover, 15% of their patients had chronic pancreatitis or pseudo-cysts, considered to be at low-risk for development of POPF.

One systematic review and meta-analysis (32) found that laparoscopic distal pancreatectomy had a statistically significant protective effect on the rate of POPF. This contrasts with the

results of our study as well as those of Cho *et al.* (33) who found that post-operative complications (including POPF) did not differ between laparoscopy and laparotomy. Of note, the meta-analysis (32) involved only observational studies and series were quite heterogeneous, while the Central Pancreas Consortium study (33) involved only expert centers, a potential selection bias.

Laparoscopy was performed in 71 of 270 patients in our study (26%), slightly more than the 20% in the Italian study (19). Splenic preservation techniques may be easier to perform laparoscopically: almost two thirds of splenic preservation operations (62.0%) were performed via laparoscopy in our study, higher than the 48% rate reported by Montorsi *et al.* (19). Our rate of splenic preservation was higher among procedures performed by laparoscopy than by an open approach (48% *vs.* 14%, $P < 0.001$), possibly in relation to the 47.4% proportion of benign disease in our study, and facilitating the temptation not to perform splenectomy and to spare splenic vessels with the minimally invasive approach (34). Conversely, it is possible that mandatory preservation of the short gastric vessels in the Warshaw technique (20) might be more difficult to perform laparoscopically explaining why 11/32=34.5% were performed via laparoscopy *vs.* 21/32=66% via laparotomy in our study.

In contrast to the results in our trial, several studies found that elective closure of the main pancreatic duct had a protective effect (7, 35). However, our study was not powered to determine the role of elective main pancreatic duct closure (secondary end-point in

our study) on prevention of POPF and to the best of our knowledge, there are no randomized controlled trials on this technical detail in the literature, only multivariate analyses (7, 35). Possible reasons for the discrepancy of results might be the variation in technical aspects of duct closure from one institution to another, and/or the small number of patients in the studies.

In spite of the outcomes of two randomized controlled studies (11,12), the debate as to the need of post-operative drainage (preventive effect on occurrence of clinical POPF or detection of POPF *vs.* its potential deleterious effects) has never been closed. Most surgeons in our series (95.6%) left a drain. In our study, there was no difference in the rate or severity of POPF whether patients had a drain or not.

Our study confirms that the use of TachoSil is safe, as it was not associated with any adverse events. This is in accordance with the Italian study (19) as well as a non-interventional multicenter prospective, surveillance study (36) in a total of 3098 patients recruited at 227 centers in 12 European countries.

There are several possible weaknesses in our study. First, 45 centers participated in this multicenter study, possibly explaining the relatively high overall fistula rate and the wide range of techniques used. However, this is representative of real life surgery. Second, our low proportion of malignant disease (53.%) in relation to the literature (1, 3, 19) potentially represents a selection bias, but this also reflects the multicenter character of our study,

and the fact that general hospitals as well as specialized pancreatic surgery centers participated in our study.

Conclusion

While the concept of reinforcing the stump closure with a resorbable collagen sponge after distal pancreatectomy appeared interesting, our results confirm those from the only other previous controlled trial on this topic: the inability of this adjunctive method to reduce the rate of POPF, whether overall or, as shown in our study only, the rate of clinically relevant POPF. However, it is well known that several studies, especially when the results are negative, are necessary before strong and methodologically sound conclusions can be drawn as to the usefulness or futility of therapeutic decisions (37,38). As one controlled randomized trial (17) has shown a positive effect of non-absorbable mesh reinforcement on the pancreatic stump after distal pancreatectomy, further studies are needed with different types of material used for reinforcement.

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Table 1: Demographic data

		Experimental group (Tachosil®) (N=134)	Control group (no Tachosil®) (N=136)	p	Total number of patients (intention to treat) (N=270)
		n (%)	n (%)		n (%)
Sex				0.384	
	Male	48 (35.8)	56 (41.2)		104 (38.5)
	Female	86 (64.2)	80 (58.8)		166 (61.5)
Age (years)				0.571	

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		Experimental group (Tachosil ®) (N=134)	Control group (no Tachosil ®) (N=136)	p	Total number of patients (intention to treat) (N=270)
	m±sd	60.3 (14.1)	61.3 (13.4)		60.8 (13.7)
	Min ; Max	23.0 ; 85.0	20.0 ; 85.0		20.0 ; 85.0
Body mass index (kg/m²)				0.737	
	m±sd	25.7 (4.6)	25.8 (4.6)		25.8 (4.6)

(m±sd)= mean +/- standard deviation

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Table 2: Disease.

		Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
		n (%)	n (%)		n (%)
Type of tumor				0.223	
	Benign	69 (51.5)	59 (43.4)		128 (47.4)
	Malignant	65 (48.5)	77 (56.6)		142 (52.6)
Disease					
	Adenocarcinoma	28 (20.9)	44 (32.4)		72 (26.7)

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	Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
Other carcinoma	0	4 (2.9)		4 (1.5)
Mucinous cystadenoma	13 (9.7)	13 (9.6)		26 (9.6)
Serous cystadenoma	11 (8.2)	8 (5.9)		19 (7.0)
Metastasis (yidney)	4 (3.0)	6 (4.4)		10 (3.7)
Chronic pancreatitis*	8 (6.0)	7 (5.1)		15 (5.6)
IPMN**	25 (18.7)	19 (14.0)		44 (16.3)

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	Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
Endocrine tumor	40 (29.9)	26 (19.1)		66 (24.4)
Miscellaneous	5 (3.7)	9 (6.6)		14 (5.2)

*Intra operative diagnosis in patients operated on for pancreatic tumor

**IPMN: intraductal papillary mucinous neoplasm

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Table 3: Interval between the beginning and the end of operation, in intensive care, between the date of operation and discharge

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	Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
From the incision to the last suture of closure: hours (m±sd)	3.9 (1.7)	3.7 (1.6)	0.197	3.8 (1.6)
In intensive care: days (m±sd)	2.2 (7.4)	2.1 (3.9)	0.193	2.1 (5.9)
Operation discharge from hospital: days (m±sd)			0.324	

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	Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
	17.5 (13.8)	14.9 (8.2)		16.2 (11.4)

(m±sd)= mean +/-standard deviation

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Table 4: Technical conditions of the operation

		Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (%) (intention to treat) (N=270)
		n (%)	n (%)		n (%)
Consistence pancreatic remnant				0.342	
	normal	127 (94.8)	124 (91.2)		251 (93.0)
	hard*	7 (5.2)	12 (8.8)		19 (7.0)
Elective main duct suture		133**	135**	0.463	268**
	no	56 (42.1)	63 (46.7)		119 (44.4)
	yes	77 (57.9)	72 (53.3)		149 (55.6)

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		Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (%) (intention to treat) (N=270)
Pancreatic remnant closure		134	136	0.803	270
	hand-sewn	80 (59.7)	84 (61.8)		164 (60.7)
	mechanical (staples)	54 (40.3)	52 (38.2)		106 (39.3)
				0.769	
Drainage	no	5 (3.7%)	7 (5.1%)		12 (4.4)
	yes	129 (96.3%)	129 (94.9%)		258 (95.6%)

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		Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (%) (intention to treat) (N=270)
Splenic preservation (total)				0.080	
	no	75 (56.0)	91 (66.9)		166 (61.5)
	yes	59 (44.0)	45 (33.1)		104 (38.5)
(with ligation splenic vessels)				0.668	
	no	42 (71.2)	30 (66.7)		72 (69.2)
	yes	17 (28.8)	15 (33.3)		32 (30.8)

* hard= consistence of chronic pancreatitis; ** two missing data

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Table 5: Post-operative pancreatic fistula (POPF) according to treatment group

		Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
		n (%)	n (%)		n (%)
Overall POPF (ISGPF definition*)				0.807	
	POPF	73 (54.5)	77 (56.6)		150 (55.6)

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		Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)	p	Total number of patients (intention to treat) (N=270)
	Absence of POPF	61 (45.5)	59 (43.4)		120 (44.4)
Clinically patent POPF				0.276	
	POPF	41 (30.6)	33 (24.3)		74 (27.4)
	Absence of POPF	93 (69.4)	103 (75.7)		196 (72.6)

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*ISGPF definition: definition of the International Study Group of Pancreatic Fistula (grade A+B+C)

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Table 6: Post-operative pancreatic fistula (POPF) according to technical conditions of the operation

		Clinically patent POPF (n=74)	Absence of clinically patent POPF n =196)	p	Total number of patients (intention to treat) (N=270)
		n (%)	n (%)		
Consistence pancreatic remnant				0.790	
	normal	68 (27.1)	183 (72.9)		251
	hard*	6 (31.6)	13 (68.4)		19
Elective main duct suture		74	194**	0.130	268**
	no	27 (22.7)	92 (77.3)		119
	yes	47 (31.5)	102 (68.5)		149

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		Clinically patent POPF (n=74)	Absence of clinically patent POPF n =196)	p	Total number of patients (intention to treat) (N=270)
Pancreatic remnant closure		74	196	0.025	270
	hand-sewn	53 (32.3)	111 (67.7)		164
	mechanical (staples)	21 (19.8)	85 (80.2)		106
Drainage				1.0	
	no	3 (4.1)	9 (4.6)		12 (4.4)
	yes	71 (95.9)	187 (95.4)		258 (95.6%)

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		Clinically patent POPF (n=74)	Absence of clinically patent POPF n =196)	p	Total number of patients (intention to treat) (N=270)
Splenic preservation (total)				0.331	
	no	42 (25.3)	124 (74.7)		166
	yes	32 (30.8)	72 (69.2)		104
(with ligation splenic vessels)				0.024	
	no	17 (23.6)	55 (74.4)		72
	yes	15 (49.9)	17 (53.1)		32

* hard= consistence of chronic pancreatitis; ** two missing data

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Table 7: Post-operative complications

Complications (number of complications other than POPF)*	Total	Experimental group (Tachosil®) (n=134)	Control group (no Tachosil®) (n=136)
Intra-abdominal bleeding	9 (7 associated with POPF)	5	4
Pneumonia	6	3	3
Deep SSI	6	4	2
Thrombophlebitis	4	3	1
Pulmonary embolism	4	4	0
Sepsis (including patients with shock)	3	2	1
Peritonitis	2	1	1

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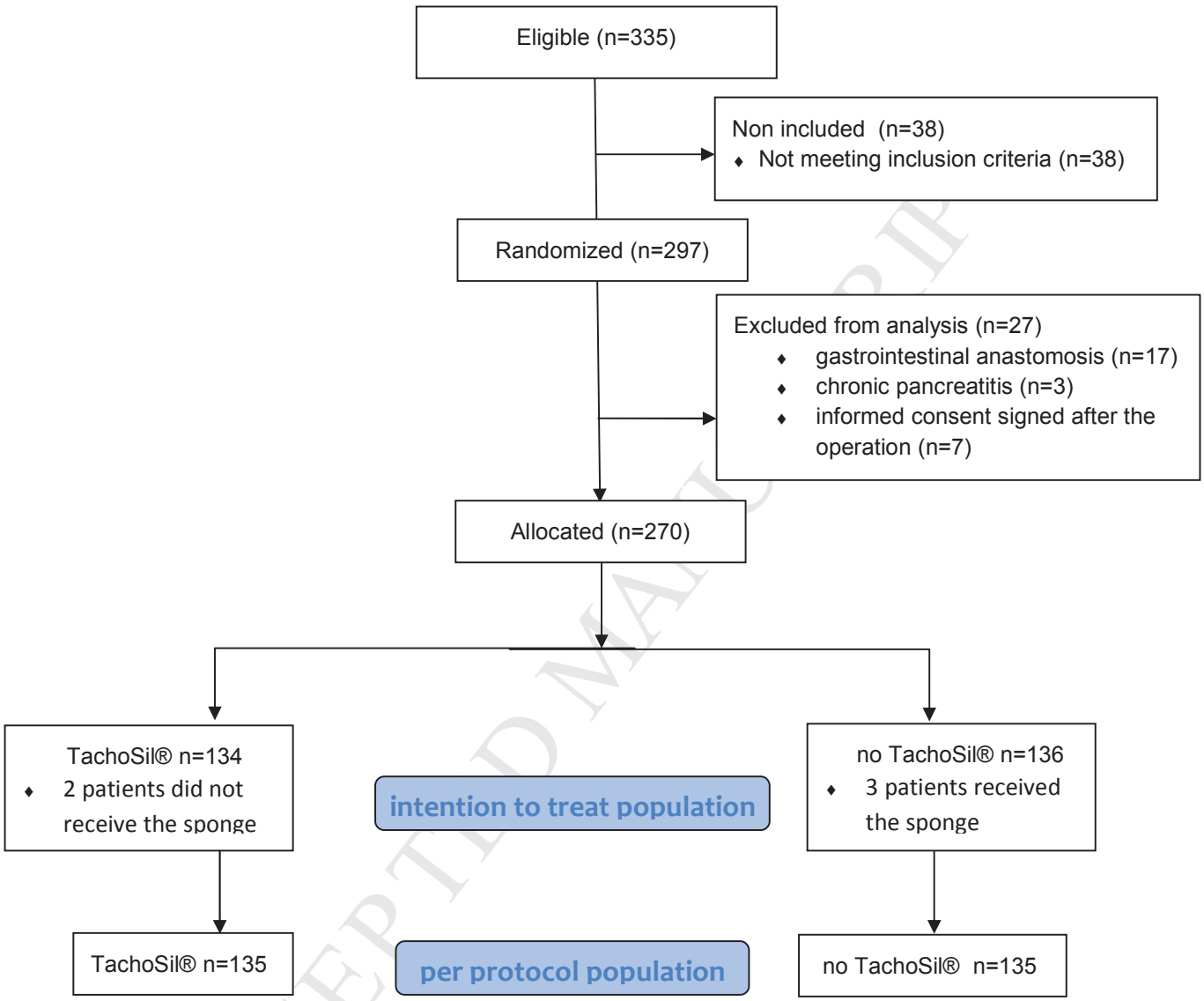
Renal failure	2	2	0
Intestinal obstruction	2	1	1
Respiratory distress/failure	2	1	1
Pleural effusion	1	0	1
Splenic infarction/necrosis	1	0	1
Organ perforation	1	1	0
Wound disruption	1	0	1
Arrhythmia	1	0	1
Total	45	27	18

POPF: Post-operative pancreatic fistula according to the International Study Group of Pancreatic Fistula definition;

*Patients could have one or more complications

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Figure 1: Flow Diagram of the randomization and population analysis



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