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SYSTEMATIC REVIEW AND META-ANALYSIS

Effectiveness of Tachosil® in the prevention of postoperative pancreatic fistula after distal pancreatectomy: a systematic review and meta-analysis

Felix J. Hüttner[1,2] · André L. Mihaljevic[1] · Thilo Hackert[1] · Alexis Ulrich[1] · Markus W. Büchler[1] · Markus K. Diener[1,2]

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Abstract
Purpose Postoperative pancreatic fistula (POPF) is a frequent and clinically relevant problem after distal pancreatectomy. A variety of methods have been tested in the attempt to prevent POPF, most of them without convincing results.
Methods A systematic literature search was conducted in PubMed, Embase and the Cochrane Library to identify clinical studies comparing pancreatic stump closure with the addition of Tachosil® to conventional stump closure. The identified studies were critically appraised, and meta-analyses were performed using a random-effects model. Dichotomous data were pooled using odds ratios, and weighted mean differences were calculated for continuous outcomes, together with the corresponding 95 % confidence intervals.
Results Four studies (two randomised controlled trials and two retrospective clinical studies) reporting data from 738 patients were included in the meta-analysis. Overall POPF, clinically-relevant POPF, mortality, reoperations, intraoperative blood loss and length of hospital stay did not differ significantly between conventional closure and additional covering of the pancreatic stump with Tachosil®. A sensitivity analysis of only randomised controlled trials confirmed the results.
Conclusions The application of Tachosil® to the pancreatic stump after distal pancreatectomy is a safe procedure but provides no relevant benefit in terms of POPF, mortality, reoperation rate, blood loss or length of hospital stay. Future research should concentrate on novel methods of pancreatic stump closure to prevent POPF after distal pancreatectomy.

Keywords Distal pancreatectomy · Postoperative pancreatic fistula · Surgical sealants · Tachosil®

✉ Markus W. Büchler
markus.buechler@med.uni-heidelberg.de

[1] Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

[2] Study Center of the German Surgical Society, University of Heidelberg, Heidelberg, Germany

Introduction

Distal pancreatectomy is the standard surgical treatment for tumours of the pancreas located to the left of the portal/superior mesenteric vein [1, 2]. Indications include pancreatic ductal adenocarcinoma, mucinous and serous cystadenoma, intraductal papillary mucinous neoplasms, neuroendocrine tumours and chronic pancreatitis [3, 4].

Even though the postoperative mortality of pancreatic surgery has decreased substantially in the past decades, postoperative morbidity remains high [5, 6]. Postoperative pancreatic fistula (POPF) is the most common and important complication after distal pancreatectomy, with rates of 0–60.9 % [7, 8]. Several methods have been tested in an attempt to reduce the high rates of POPF after distal pancreatectomy, e.g. hand-suture vs. stapler closure of the pancreatic remnant without showing a significant benefit for one of the strategies [9]. . Furthermore, assorted dissection devices and methods [10–12], seromuscular or falciform ligament patches [13–15], and/or various tissue sealants and meshes have been assessed in their efficacy to prevent POPF [16, 17]. However, there is still no consensus about the best method of stump closure for effective prevention of POPF [18, 19].

Fibrin sealants have been used extensively in hepatobiliary and pancreatic surgery [20], with some promising results [21–23]. However, in a recent systematic review and meta-analysis, Orci et al. suggested that fibrin sealants cannot be

recommended for routine clinical use in the setting of pancreatic surgery [24].

Tachosil®, a collagen patch coated with human fibrinogen and thrombin, is used to improve postsurgical haemostasis. A recent systematic review covering all fields of surgery suggested that Tachosil® is able to improve haemostasis and promote tissue sealing [25]. As a consequence, postoperative complications and length of hospital stay were reduced in patients treated with Tachosil® [25].

Materials and methods

This systematic review was performed in adherence to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. The selection, data extraction, and critical appraisal of all studies were conducted by two independent reviewers. In the case of disagreements between the two reviewers, a third reviewer was consulted to find a consensus.

Literature search

A systematic literature search was conducted in the databases PubMed, the Cochrane Library, and Embase up to January 2016 for relevant randomised and nonrandomised studies comparing conventional remnant closure (stapler or hand-sewn closure) after distal pancreatectomy to remnant closure with addition of Tachosil®. The search was not restricted by language or publication date. Reference lists of relevant studies and former reviews were searched manually, and the "related articles" function was used in PubMed.

The final PubMed search strategy was ((((((distal pancreatectomy[MeSH terms]) OR left pancreatectomy) OR distal pancreatectomy) OR pancr*) AND (((tacho*) OR tachosil) OR tachocomb)) without any further limitations. Similar search strategies were used for the Cochrane Library and Embase. The most recent search in PubMed was performed on 10 January 2016.

Study selection

Randomised trials and retrospective and prospective clinical studies comparing conventional remnant closure (stapler or hand-sewn closure) after distal pancreatectomy to remnant closure with addition of Tachosil® were considered eligible. Studies that applied additional methods of remnant closure, e.g. seromuscular patches or other sealants, were excluded from the analysis.

Titles and abstracts retrieved by the systematic literature search were screened by two independent reviewers. The full text of the article was obtained if one of the reviewers considered that an article was eligible. Full texts were assessed in detail for final inclusion in the review.

Outcome measures

The primary endpoint was POPF, preferably defined according to the International Study Group of Pancreatic Fistula (ISGPF) [27]. Clinically relevant POPF was defined as ISGPF grade B or C POPF. Further, outcome measures were postoperative mortality, haemorrhage/bleeding (defined as any bleeding complication in the postoperative course), reoperation and interventional radiology procedures. Intraoperative blood loss and length of hospital stay were also evaluated.

To assess the safety of Tachosil® in the randomised controlled trials, the rate of adverse events related to the application of Tachosil® was evaluated.

Data extraction

Data extraction was performed in duplicate by two independent reviewers. The extracted data included study characteristics, baseline data of the included patients, quality characteristics and the outcome measures described above for the individual treatment groups.

If a study reported on an additional method of remnant closure, e.g. in a three-armed design, only the two groups with conventional stapler or hand-sewn remnant closure and remnant closure with addition of Tachosil® were extracted.

Critical appraisal

For randomised controlled trials, the Cochrane Risk of Bias Tool was used for the assessment of methodological quality [28]. Critical appraisal was described qualitatively for nonrandomised studies. Furthermore, the GRADE approach was used to judge the overall quality of the evidence [29].

Statistical analysis

Meta-analyses of the individual outcomes were performed with RevMan (Version 5.3, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen). Weighted mean differences (MD) were pooled by the inverse variance method for continuous outcomes and presented together with the corresponding 95 % confidence intervals (CI). Dichotomous outcomes were presented as odds ratios (OR) with the corresponding 95 % CI calculated by the Mantel–Haenszel (M-H) method. To account for zero counts in both groups, mortality was presented as risk difference (RD) with the corresponding 95 % CI calculated by the M-H method. Due to the clinical heterogeneity, a random-effects model was chosen for the meta-analyses. To calculate means and standard

deviations from studies reporting only medians and ranges, the methods of Hozo et al. were applied [30]. For assessment of statistical heterogeneity, I^2 statistics were performed. Sensitivity analyses were conducted including only the randomized controlled trials to validate the results of the primary analysis.

Results

A total of 124 abstracts were identified by the systematic literature search. After exclusion of duplicates, review articles and non-relevant studies, four studies were included in the systematic review and meta-analysis. The study selection process is depicted in a PRISMA flow chart with reasons for exclusion at each stage (Fig. 1).

Study characteristics

Two retrospective studies [31, 32] and two randomised controlled multicentre trials [33, 34] evaluated the safety and efficacy of Tachosil® in stump closure after distal pancreatectomy. The included studies assessed a total of 738 patients. Tachosil® was applied in 388 of these patients, and conventional stump closure was performed in the remaining 350 patients. The retrospective studies were conducted in Italy and Norway and the randomised controlled trials in France and Italy. Whereas each of the retrospective studies was carried out at a single centre, the randomised controlled trials involved 19 [33] and 45 [34] centres respectively, including low-, medium- and high-volume centres.

All studies reported POPF rates according to the ISGPF definition together with exact grading.

The most frequent indications for distal pancreatectomy were cystic neoplasms (33.5 %) such as intraductal papillary mucinous neoplasms, mucinous and serous cystadenomas. The remaining indications were pancreatic adenocarcinoma (28.3 %), pancreatic neuroendocrine neoplasms (24.4 %), chronic pancreatitis (4.7 %), metastasis or other carcinoma (2.4 %), and miscellaneous indications (6.6 %). The majority of the patients were female (62.3 %), and most patients underwent open surgery (66.7 %). However, surgery was laparoscopic in all patients described by Pavlik Marangos et al. [31] and open in all patients reported by Silvestri et al. [32]. One hundred and ninety-seven of the 738 distal pancreatectomies (26.7 %) were performed with spleen preservation, whereas 540 procedures were distal pancreatectomy with splenectomy (73.2 %); spleen resection or preservation was unrecorded for one patient (0.1 %) in the Italian RCT [33]. Because of the laparoscopic approach, remnant closure was performed by means of a stapler in all patients in the Norwegian study [31], whereas all patients in the Italian retrospective underwent hand-sewn stump closure with elective

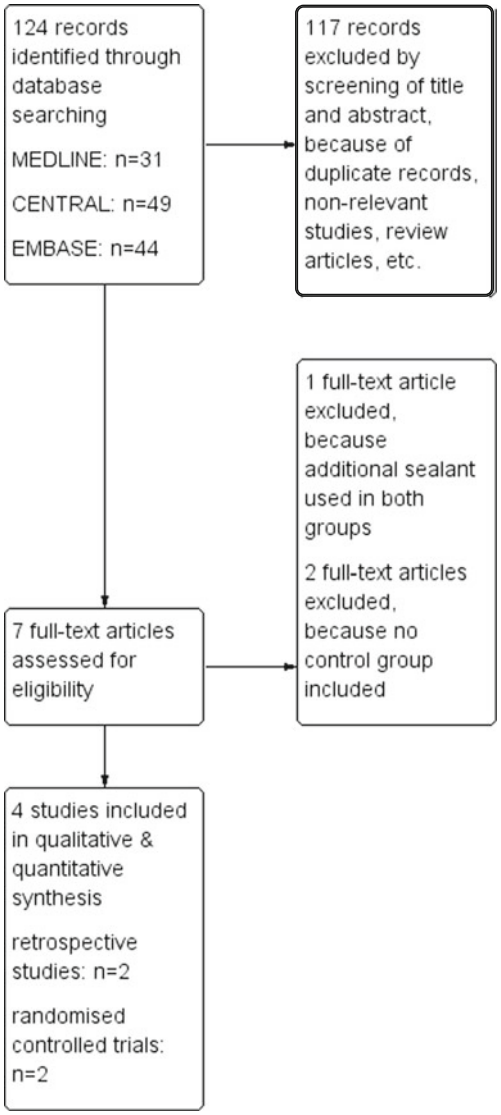

Fig. 1 PRISMA flow chart of study selection

closure of the pancreatic duct. In both randomised controlled trials, the means of remnant closure (stapler or hand-sewn) was decided individually by the surgeon. In total, 422 of the 738 patients underwent hand-sewn closure of the pancreatic remnant (57.2 %), 312 patients had stapler closure (42.3 %), three patients underwent a combination of both techniques (0.4 %) and the closure technique was unclear in one patient (0.1 %) from the trial by Montorsi et al. [33]. Table 1 summarizes the patients' baseline characteristics.

Risk of bias assessment for included studies

Both randomised controlled trials described random sequence generation with sufficient clarity. The means of allocation concealment remained unclear in the trial by Montorsi et al. [33], but central randomisation was used in the trial by Sa Cunha et al. [34]. Patients and outcome

Table 1 Patient characteristics

Study	Tachosil® group	Control group	Total
Pavlik Marangos 2012, Norway; retro [31]			
Gender (F/M)	49/24	32/16	81/40
Surgical access (open/laparoscopic)	0/73	0/48	0/121
Spleen preservation (Y/N)	20/53	10/38	30/91
Remnant closure (hand-sewn/stapler)	0/73	0/48	0/121
Montorsi 2012, Italy; RCT [33]			
Gender (F/M)	81/64	91/39	172/103
Surgical access (open/laparoscopic)	116/29	105/25	221/54
Spleen preservation (Y/N)	28/116[a]	29/101	57/217[a]
Remnant closure (hand-sewn/stapler)	101/42[b]	85/43[c]	186/85[d]
Silvestri 2015, Italy; retro [32]			
Gender (F/M)	20/16	21/15	41/31
Surgical access (open/laparoscopic)	36/0	36/0	72/0
Spleen preservation (Y/N)	1/35	5/31	6/72
Remnant closure (hand-sewn/stapler)	36/0	36/0	72/0
Sa Cunha 2015, France; RCT [34]			
Gender (F/M)	86/48	80/56	166/104
Surgical access (open/laparoscopic)	n.r.	n.r.	199/71
Spleen preservation (Y/N)	59/75	45/91	104/166
Remnant closure (hand-sewn/stapler)	80/54	84/52	164/106

Retro retrospective study, *RCT* randomised controlled trial, *n.r.* not reported for individual groups

[a] Spleen preservation or resection unknown for one patient

[b] Closure hand-sewn + stapler for one patient, unknown for one patient

[c] Two patients hand-sewn + stapler

[d] Three patients hand-sewn + stapler, 1 patient unknown, not reported for individual groups, but randomisation stratified for open/laparoscopic

assessors were blinded in the French trial [34], while an open design was employed in the Italian trial [33]. Both trials presented adequate information on all patients with a CONSORT flow diagram illustrating the flow of participants. Concerning selective reporting, a published protocol was not available for any of the trials. However, the trial registration of the Italian trial (EudraCT 2008-005714-46) provided sufficient information on trial design and prespecified endpoints. The registration number given in the report of the French trial (EudraCT 2008-001253-17) was not found in the registry; thus, selective reporting remained unclear. Both trials were analysed according to the intention-to-treat principle and presented sufficient information on sample size calculation. Since both trials were supported by Nycomed S.p.A., the manufacturer of Tachosil®, the risk for funding bias remained unclear. The risk of bias of the randomised controlled trials is depicted in Fig. 2.

The Norwegian study [31] was a well-reported retrospective analysis of prospectively collected data. Owing to the retrospective, nonrandomised design, however, selection bias cannot be ruled out. Allocation to the treatment or the control group was mainly based on the date of treatment, because the authors started to use Tachosil® after distal pancreatectomy in 2005. Therefore, the control group consists primarily of patients treated between 1997 and 2005. This introduces some risk of bias for comparability of the study groups. Furthermore, no sufficient information was available on duration and completeness of follow-up.

The Italian study [32] was a similar retrospective analysis of prospectively collected data. Some degree of selection bias is probable, and the reason for selection of the 72 patients from a total of 221 patients undergoing distal pancreatectomy in the described study period remains unclear. Other unclear factors are how patients were allocated to the treatment or control group and whether patients in the two groups were recruited during the same period of time. Concerning the patients' characteristics, however, the two groups in the Italian study seem comparable. The duration of postoperative follow-up was described as 60 days for mortality and 30 days after discharge for complications. However, completeness of follow-up is not described. The endpoints were well defined and could be assessed adequately.

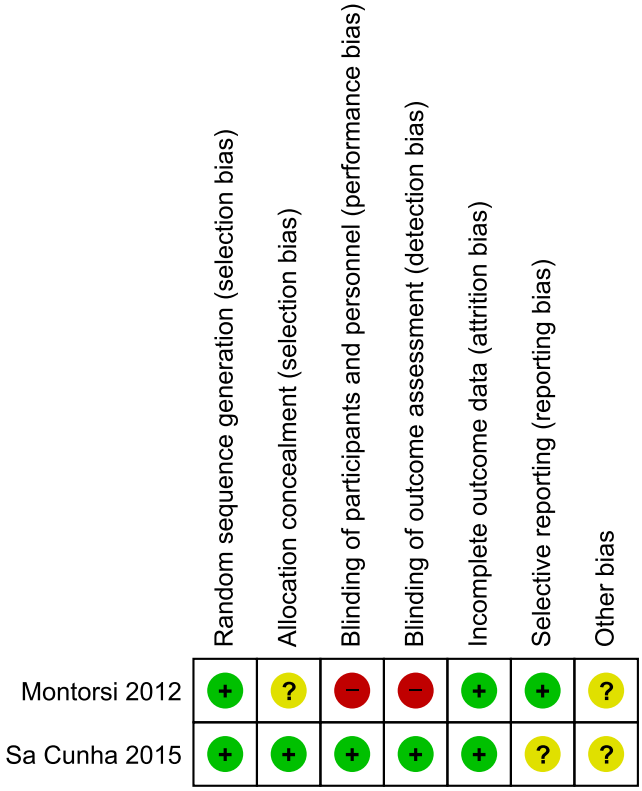

Fig. 2 Risk of bias summary graph

Applying the GRADE criteria [29], the overall quality of evidence summarised in this review is high. The review is based on the results of two well-conducted multicentre randomised controlled trials, without major sources of potential risk of bias, together with two retrospective studies that exhibit a moderate quality of evidence. Sensitivity analyses including only the randomised controlled trials did not change any of the results. The quality of evidence of the randomised controlled trials was not down-graded because we found no serious imprecision, no unexplained heterogeneity or inconsistency, and no indirectness.

Postoperative pancreatic fistula

The overall POPF rate was 47.9 % in the Tachosil® group and 52.6 % in the control group. Meta-analysis revealed no significant difference (OR 0.88, 95 % CI 0.64–1.21; $p=0.44$; $I^2=0$ %). Similarly, the rates of clinically relevant POPF (grade B/C) were not significantly different, with 17.8 % in the Tachosil® group and 18.3 % in the conventional closure group (OR 0.98, 95 % CI 0.59–1.62; $p=0.94$; $I^2=30$ %). The results were confirmed by a sensitivity analysis including only the randomised controlled trials (overall POPF: OR 0.83, 95 % CI 0.59–1.18; $p=0.31$; $I^2=0$ %; grade B/C POPF: OR 0.92, 95 % CI 0.38–2.20; $p=0.85$; $I^2=71$ %). The results of the meta-analyses concerning POPF are illustrated in Fig. 3.

Secondary endpoints

Neither mortality (RD 0.00, 95 % CI −0.01 to 0.01; $p=0.80$; $I^2=0$ %) nor bleeding complications (OR 0.79, 95 % CI 0.38–1.65; $p=0.53$; $I^2=0$ %) differed significantly between patients treated with Tachosil® and patients with conventional stump closure (Fig. 4). The rate of reoperation was reported only in the trial by Montorsi et al. [33] and the study by Silvestri et al. [32] and did not differ significantly, with seven (3.9 %) reoperations in the Tachosil® group and nine (5.4 %) reoperations in the control group (OR 0.71, 95 % CI 0.26–1.92; $p=0.50$; $I^2=0$ %). The rates of interventional radiology procedures were also similar between the two groups, with 16 (11.0 %) interventions in patients treated with Tachosil® and 15 (11.5 %) interventions in patients with conventional stump closure (OR 0.95, 95 % CI 0.45–2.01; $p=0.90$; $I^2=$ n.a.) in the Italian trial [33].

The meta-analysis of length of hospital stay showed some degree of heterogeneity ($I^2=56$ %) due to a large variance between the individual studies with a median postoperative hospital stay of 5.5 days (range 2–35) in the study by Pavlik Marangos et al. [31] and 31.13 days (range 9–249) in the study by Silvestri et al. [32] for the conventional closure groups. However, no significant difference was detected in the length of postoperative hospital stay between the two groups (MD 1.01, 95 % CI −0.53 to 2.55; $p=0.20$; $I^2=56$ %; Fig. 5).

Estimated intraoperative blood loss was only reported by two studies [31, 33] and the meta-analysis showed no significant difference between patients treated with the addition of Tachosil® and those with conventional remnant closure (MD −33.90, 95 % CI −111.50 to 43.71; $p=0.39$; $I^2=0$ %; Fig. 5).

Safety

Both randomised controlled trials reported adverse events and their possible relation to the application of Tachosil®. None of the adverse events in either trial were judged to be directly associated with the application of Tachosil®.

Discussion

This is the first systematic review and meta-analysis assessing the value of Tachosil® in a specific surgical indication (i.e. distal pancreatectomy) with focus on clinically relevant outcomes. The underlying quality of evidence is high, based on two well-conducted multicentre randomised controlled trials and two further retrospective studies. Thus, strong recommendations for clinical practice are legitimate. No benefit of Tachosil® was found for any of the outcome parameters, comprising POPF, clinically relevant POPF, mortality, bleeding complications, reoperations, reinterventions, length of postoperative hospital stay and intraoperative blood loss. Since no

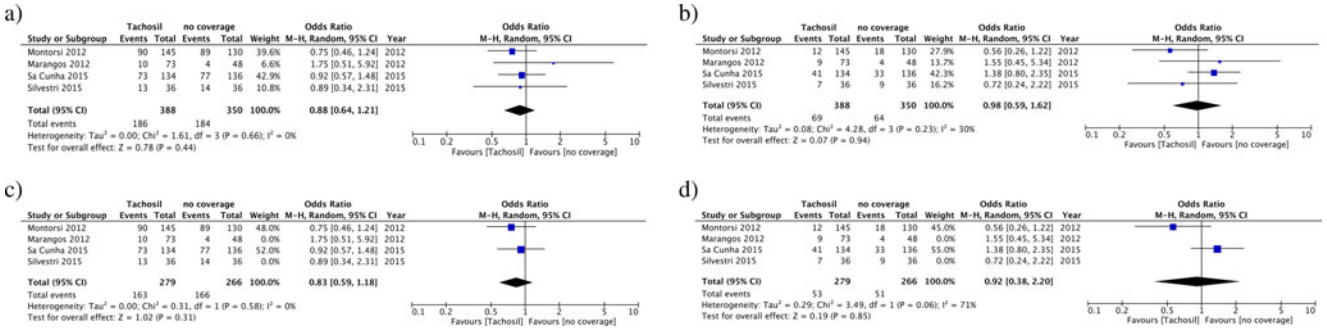

Fig. 3 Forest plots for **a** POPF (all grades), **b** clinically relevant POPF (grade B/C), **c** sensitivity analysis of POPF (all grades) only RCTs and d sensitivity analysis of clinically relevant POPF (grade B/C) only RCTs. *POPF* postoperative pancreatic fistula according to the ISGPF definition27, *RCT* randomised controlled trial, *M-H* Mantel-Haenszel method, *95 % CI* 95 % confidence interval

adverse events directly related to the application of Tachosil® were observed in the randomised controlled trials, Tachosil® seems to be safe for application on the pancreatic remnant.

High rates of the primary endpoint POPF were found, with a mean of 50.2 % in all four studies and 60.4 % if only randomised controlled trials were considered. This confirms that POPF still presents a substantial problem, especially after distal pancreatectomy [6]. The strict application of the ISGPF criteria [27] in a prospective study design with structured follow-up visits results in these considerable rates, whereas in the retrospective studies, the rates were substantially lower (21.1 %). This underlines the importance of prospective assessment and well-defined endpoints in clinical trials [35]. The higher rates of POPF than in previous randomised controlled trials such as the DISPACT trial [9] may be explained by the longer follow-up periods (2 and 3 months, respectively [33, 34] compared to 30 days in the DISPACT trial [9]). Furthermore, differences in surgical experience and baseline characteristics (e.g. underlying disease) of included patients might be responsible for the higher rates in the current trials. Whereas the overall POPF rate was higher than in previous trials in distal pancreatectomy, the rate of clinically relevant POPF was comparable, at approximately 19.1 % in the trials included in this meta-analysis [33, 34] and approximately 20.5 % in the DISPACT trial [9]. The differing rates of hand-sewn and stapled closure in the included trials and studies introduce some degree of clinical heterogeneity. However, as shown by the DISPACT trial and other studies, no substantial bias is

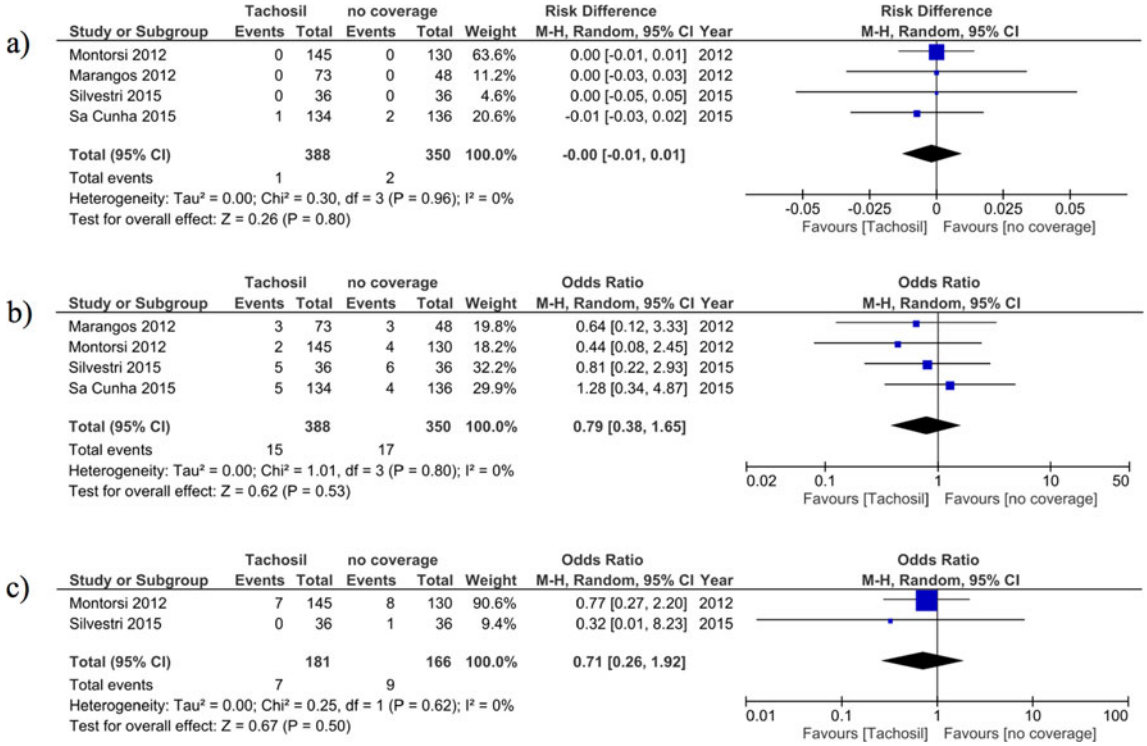

Fig. 4 Forest plots for **a** mortality, **b** bleeding complications and **c** reoperations. *M-H* Mantel-Haenszel method, *95 % CI* 95 % confidence interval

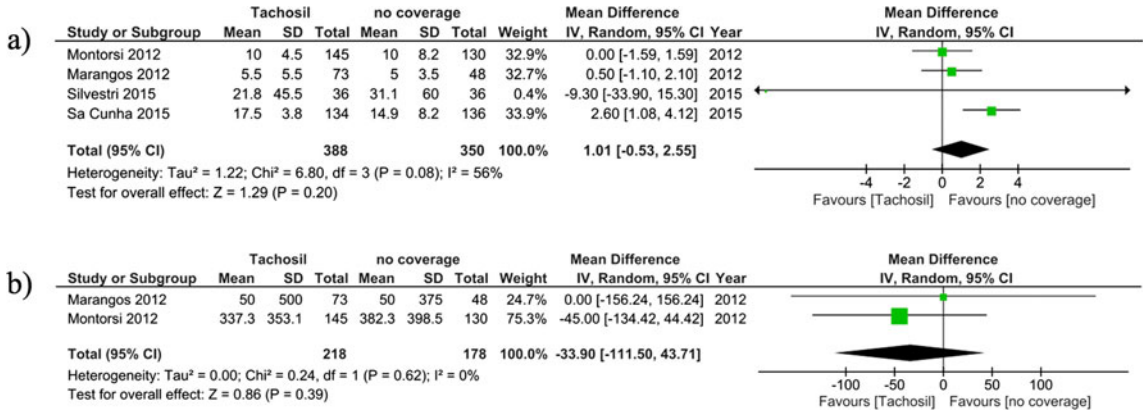

Fig. 5 Forest plots for **a** length of hospital stay and **b**) intraoperative blood loss. *IV* inverse variance method, *SD* standard deviation, *95 % CI* 95 % confidence interval

introduced by these clinical differences, since hand-sewn and stapled closure lead to similar rates of both overall POPF and clinically-relevant POPF [9]. Neither the Norwegian study in which all patients underwent stapled closure [31] nor the Italian study in which all patients underwent hand-sewn closure [32] found a significant difference in overall or clinically relevant POPF between the treatment groups. Furthermore, Montorsi et al. conducted a multivariate analysis investigating risk factors of POPF. Only male sex and spleen-preserving resection proved to be significantly correlated with the risk of POPF, whereas type of stump closure (stapled vs. hand-sewn) did not correlate with the risk of POPF [33]. In contradiction, hand-sewn pancreatic remnant closure and spleen-preserving resection with splenic vessel ligation were significant predictive factors for the onset of POPF in the multivariate analysis of the French randomised controlled trial [34]. The finding that hand-sewn closure was a negative predictive factor for POPF in this trial [34] is even more conflicting in the light of the meta-analysis by Orci et al. [24], which showed a significantly reduced POPF rate in a subgroup analysis of patients undergoing hand-sewn remnant closure with the application of a fibrin sealant. Unfortunately, a subgroup analysis for hand-sewn versus stapled closure was not possible in the present meta-analysis since no individual patient data or fistula rates for these subgroups have been presented in the included trials [33, 34]. This represents a potential limitation of the current study. However, the variety in surgical techniques and policies between the various centres contributing to this analysis reflects real-life practice in pancreatic surgery, and Tachosil® did not provide any benefit in this setting.

Concerning the different grades of POPF, the retrospective study by Silvestri et al. showed a significantly lower rate of grade C POPF in the Tachosil® group [32], whereas Pavlik Marangos et al. observed grade C POPF only in the group treated with Tachosil® [31]. The observed differences can be explained by the small sample sizes and retrospective nature of these studies and hence could not be corroborated by the randomised controlled trials [33, 34].

The analysis of length of postoperative hospital stay presented moderate heterogeneity. This can be explained by differences in discharge policies among hospitals and countries. Furthermore, differing frequencies of laparoscopic surgery between the included studies may partly explain the heterogeneity; for example, all patients in the study by Silvestri et al. [32] underwent open surgery, whereas all patients in the study by Pavlik Marangos et al. [31] were treated laparoscopically. Laparoscopic surgery is known to lead to faster recovery and reduced length of hospital stay, although high-quality evidence is lacking for laparoscopic pancreatic surgery [36].

The results of this systematic review are of high internal validity since the underlying quality of evidence was good according to the GRADE approach. The meta-analyses are based on two well-conducted randomised controlled trials and two retrospective controlled studies. All studies used the universally accepted ISGPF definition of POPF, leading to good comparability of the individual results for the primary endpoint. Especially the randomised controlled trials evinced high methodological quality, thus minimising the potential risk of bias. Sensitivity analyses including only the randomised controlled trials did not change the results of any of the meta-analyses. This corroborates the robust findings of the primary analyses. Furthermore, the inclusion of low-, medium- and high-volume centres in the randomised controlled trials reflects real-life practice in pancreatic surgery and allows generalizability of the results. A potential risk of bias is present in that both randomised controlled trials were supported by Nycomed, the manufacturer of Tachosil® at the time of the trials. However, neither of the trials reported beneficial results for the addition of Tachosil®, so the likelihood of industry bias, which usually leads to exaggeratedly positive reporting of outcomes [37], can be considered low.

In addition, another recent multicentre, randomised controlled trial investigating Tachosil® in 101 patients undergoing

distal pancreatectomy with stapled closure could not show any clinical benefits for the Tachosil® group with an overall POPF rate of 62.4 % and a rate of clinically relevant POPF of 25.7 % [38]. This reinforces the findings of the present meta-analysis. The trial was not included in this meta-analysis because an additional fibrin sealant was used in both, the control group and the Tachosil® group, which represented an exclusion criterion for this systematic review.

Tachosil® has proven beneficial in several fields of surgery [39], e.g. in the treatment of air leakage after pulmonary lobectomy [40, 41] or in achieving haemostasis during partial nephrectomy [42]. However, its use in distal pancreatectomy cannot be recommended based on the results of this systematic review. A recent in vitro study showed that both the fibrin and collagen components of Tachosil® are degraded rapidly by pancreatic enzymes [43], which might explain the negative trial results. Furthermore, some of the previous trials, e.g. in liver surgery, showed significant effects for surrogate parameters such as time to haemostasis without presenting any benefit in clinically or patient-relevant endpoints such as postoperative complications or length of postoperative hospital stay [44]. This implies the need for future trials evaluating medical devices such as Tachosil® with focus on clinical efficacy and effectiveness instead of efficacy for surrogate parameters such as the ones mentioned above.

In conclusion, Tachosil® should not be used to prevent POPF or reduce its severity after distal pancreatectomy as it is costly and ineffective for this indication. Nevertheless, surgeons still might use Tachosil® and comparable devices in special situations (e.g. haemostasis in laparoscopic surgery) on an individual basis as it proved to be a safe procedure. Since the quality of the underlying evidence of this systematic review is good, future research should focus on novel methods of sealing the pancreatic remnant to prevent POPF. Furthermore, specific options for treatment of POPF after distal pancreatectomy should be evaluated in future trials.

Authors' contributions Study conception and design: F. J. Hüttner, A. L. Mihaljevic, M. K. Diener and M. W. Büchler

Acquisition of data: F. J. Hüttner, A. L. Mihaljevic and M. K. Diener

Analysis and interpretation of data: F. J. Hüttner, A. L. Mihaljevic, T. Hackert, A. Ulrich, M. K. Diener and M. W. Büchler

Drafting of manuscript: F. J. Hüttner, A. L. Mihaljevic and M. K. Diener

Critical revision of manuscript: T. Hackert, A. Ulrich and M. W. Büchler

Compliance with ethical standards

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Conflicts of interest None.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For a systematic review and meta-analysis, no formal informed consent is required. However, as stated in the individual reports of the underlying studies, informed consent was obtained from all individual participants included in the underlying studies.

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