



Review

The using of sealants in pancreatic surgery: A Systematic Review



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ABSTRACT

Background: POPF derives from the pancreatic stump, which follows pancreatic resection and the pancreatoenteric anastomosis following pancreaticoduodenectomy. Since 1978 sealants have been used in pancreatic surgery to prevent pancreatic fistula after resection of the pancreatic head and tail or for the management of trauma and the treatment of low-output pancreatic fistula. Different types of fibrin sealants have been evaluated for their potential to reduce the occurrence of POPF.

Methods: A systematic search of the electronic literature was performed using PubMed, Cochrane Library, and Scopus databases to obtain access to all publications, especially clinical trials, randomised controlled trials, and systematic reviews concerning fibrin sealants pancreatic surgery. Searching for “fibrin sealants pancreas,” we found a total of 73 results on Pubmed, 61 on Scopus, and 14 on Cochrane Library (148 total results).

Results: Eighteen studies were found on literature, following the criteria already described, concerning the use of fibrin sealants in pancreatic surgery. All articles described were published in the period between 1989 and 2019. Most of these were single centre studies. A total of 1032 patients were enrolled in this review. In the studies, sealants were used to reinforce pancreatic anastomoses and for the occlusion of the main pancreatic duct.

Conclusion: CR-POPF is a fearful complication of pancreatic surgery; among the possible solutions to reduce the risk of onset, sealants were used on the pancreatic stump; today the sealants should be considered such as an option to reduce the CR-POPF, but the routine use in clinical practice has to be validated.

1. Introduction

The most critical determinant of postoperative morbidity and mortality related to pancreatic resection is POPF, which is the cause of mortality in 0–5% of patients undergoing pancreatic surgery [1,2]. It is defined as an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived enzyme-rich fluid [3]. Generally, POPF derives from the pancreatic stump, which follows pancreatic resection and pancreatoenteric anastomosis following pancreaticoduodenectomy. It is associated with significant sequelae such as sepsis, abscess, and haemorrhage, which lead to a prolonged hospital stay, increased healthcare costs, and possible mortality. Therefore, reducing the incidence of POPF has been suggested variations in surgical techniques of pancreatic anastomosis, the use of long-acting somatostatin analogues, and adhesive materials close to pancreatoenteric anastomosis site [1]. The anastomosis between the pancreatic remnant and the intestinal tract is still the surgical Achilles

heel after pancreatic head resection. Over 27% of patients develop a clinically relevant POPF [4].

In literature, several techniques for pancreatojejunostomy anastomoses, such as the duct-to-mucosa technique and the invagination of the entire pancreas's end into the jejunum, are described. Based on different studies, there is no significant difference between the two techniques regarding the leak rate. However, there was a slight decrease in clinically relevant fistula with the invagination approach [5].

Besides, Octreotide's use after pancreatic surgery remains controversial: a Cochrane review [6] shows a reduction in overall fistula rates using somatostatin-analogues after pancreatic surgery, without finding differences about relevant fistulae. Instead, pasireotide's use demonstrates a significant reduction in clinically relevant fistulas, leaks, and abscesses [7,8].

Since 1978 sealants have been used in pancreatic surgery to prevent pancreatic fistula after resection of the pancreatic head and tail or for the management of trauma and the treatment of low-output pancreatic

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fistula [9,10]. Different types of fibrin sealants have been evaluated for their potential to reduce the occurrence of POPF. However, because of the small numbers in some studies or the noncontrolled methodology, no conclusions can be drawn regarding whether fibrin sealant is useful or not [10].

2. Methods

This study was conducted on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and its quality was evaluated using the AMSTAR-2 tool [11,12]. This study was registered to Research Registry with the unique identifying number (UIN) 1116 [13]. A systematic search of the electronic literature was performed using PubMed, Cochrane Library, and Scopus databases to obtain access to all publications, especially clinical trials, randomised controlled trials, and systematic reviews concerning fibrin sealants pancreatic surgery. Searching for “fibrin sealants pancreas,” we found a total of 73 results on Pubmed, 61 on Scopus, and 14 on Cochrane Library (148 total results). We included only English publications, full-text documents, clinical trials, randomised controlled trials, systematic reviews. After excluding similar articles between three databases, we enrolled a total of 18 studies (Fig. 1).

3. Results

Eighteen studies were found on literature, following the criteria already described, concerning the use of fibrin sealants in pancreatic surgery. All articles described were published in the period between 1989 and 2019 (Table 1).

Most of these were single-center studies. Three studies [1,11,12] were trial which enrolled animals (rats and pigs), for testing the efficacy of fibrin glue, so in these cases, it was not possible to establish the rate of POPF and mortality for the authors in our review. A total of 1032 patients were enrolled in this review. In the studies, sealants were used to reinforce pancreatic anastomoses and for the occlusion of the main pancreatic duct. Different kinds of sealants were analysed: Ethibloc, Neoprene, 2-octyl cyanoacrylate, Tachosil, Tissucol, Vitagel, Polyethylene glycolic acid, Tisseel, Vivostat, BioGlue, and Coseal. The POPF rate in all the studies, considering only clinical significantly POPF, had a rate of 3,9–40%.

Marzczell et al. [13] and Luu et al. [14] showed a mortality rate of 0% with the use of sealants [13,14].

Kwon et al. [15], in the study, compared two groups, on the one hand, patients treated with pancreaticojejunostomy covered with a fibrinogen/thrombin-coated collagen patch (TachoSil; Takeda Austria, Linz, Austria), plus the application of fibrin glue to the pancreaticojejunostomy site in distal pancreatectomy, on the other hand, the application of fibrin glue alone to the pancreaticojejunostomy site.

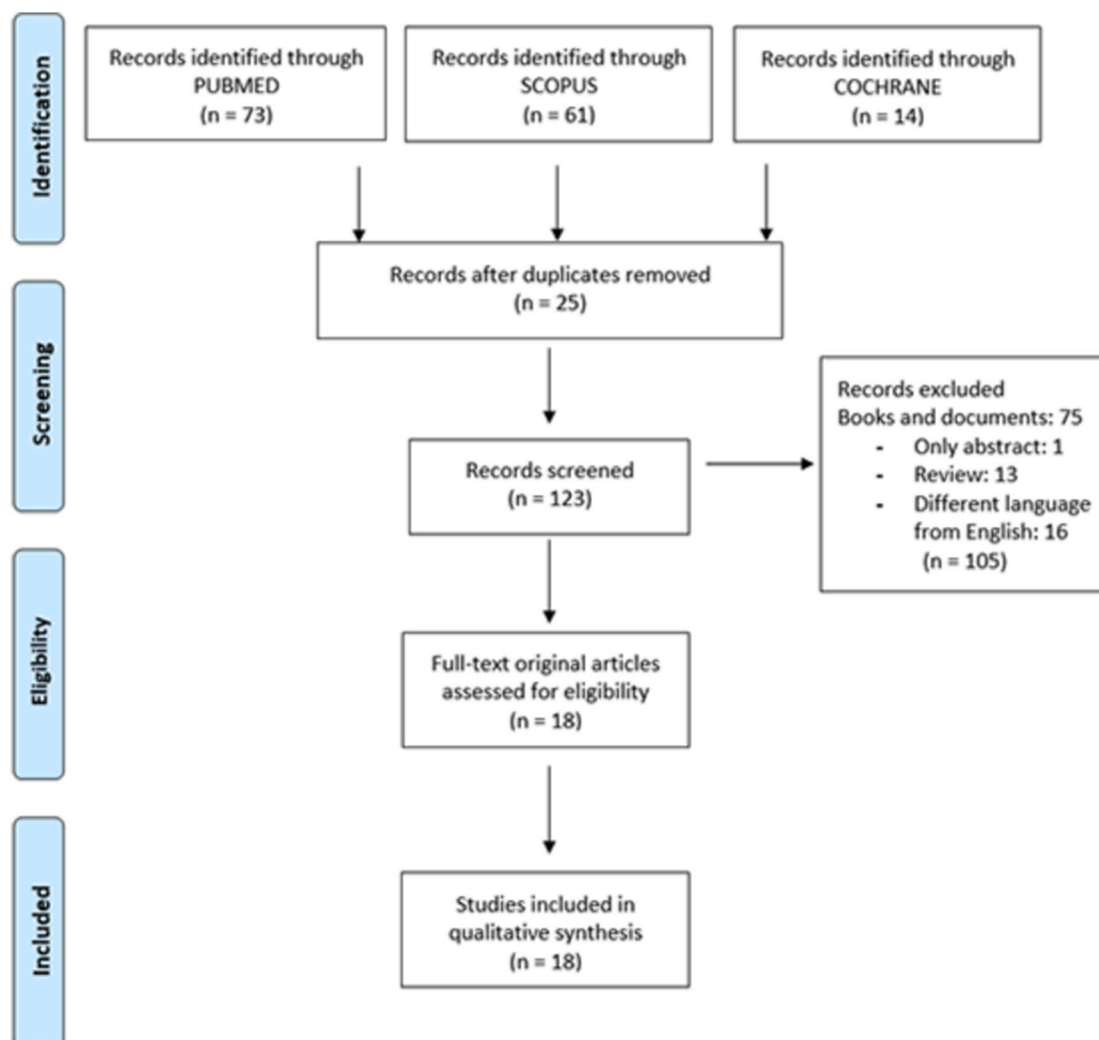


Fig. 1. PRISMA flow diagram on fibrin sealant in pancreatic surgery.

Table 1
Characteristics of the studies enrolled in the review.

Authors	Year	Country	Setting	Design	Patients treated with sealant, n	Type of sealant	POPF (%)	Mortality %
Gebhardt C.	1990	Germany	Single center	Clinical trial	–	Ethibloc	–	–
Plusczyk et al.	2001	Germany	Single center	Clinical trial	Inbred rats	Ethibloc	–	–
Ohwada et al.	1998	Japan	Single center	Clinical trial	56	Fibrin glue (Beriplast; Behring, Marburg, Germany)	26.8%	1,8%
Di Carlo et al.	1989	Italy	Single center	Clinical trial	51	Neoprene	3.9%	5,8%
Mazzaferro et al.	2019	Italy	Single center	Clinical trial	51	Neoprene	B: 9.8% C: 2%	2%
Schindl et al.	2018	Austria	Multicenter	Clinical trial	71	Fibrin coated collagen patch	23%	1,4%
Barakat et al.	2012	USA (Houston, TX)	Single center	Clinical trial	75	2-OCA (2-octyl cyanoacrylate)	3.5%	0%
Montorsi et al.	2012	Italy	Multicenter	Randomised controlled trial	145	Tachosil	8%	–
Lee et al.	2020	South Korea	Single center	Clinical trial	Experimental mice	Penicillin G	–	–
Kwon et al.	2019	South Korea	Single center	Prospective randomised trial	124	TachoSil	6,4%	1,6% and 0%
Suc et al.	2001	France	Multicenter	Prospective randomised trial	102	Tissucol with thrombin	16,7%	9%
Martin et al.	2012	Australia	Single center	Prospective randomised trial	32	Tisseel	40%	0%
Carter et al.	2012	USA	Multicenter	Prospective randomised trial	50	Vitagel	20%	0%
Kuhlbrei et al.	2019	Germany	Single center	Test in vitro	Pigs	Bioglue and Coseal	–	–
Kuramoto et al.	2013	Japan	Single center	Clinical trial	31	Polyethylene glycolic acid	29%	–
Marczell et al.	1991	Austria	Single center	Clinical trial	44	Tisseel	4,5%	0%
Luu et al.	2019	Germany	Single center	Clinical trial	66	Vivostat	27%	0%
Cunha et al.	2015	France	Multicenter	Controlled randomised study	134	Tachosil	30,6%	0,75%

POPF resulted higher in the control group than in the first one (37,1% vs 25,8%), and the mortality rate was 1,6% for the control group compared with the 0% of the first one [15]. Another comparison study was one by Mazzaferro et al. [16]. In their study, 51 patients underwent pancreatic duct occlusion (PDO) with neoprene-based glue, and 49 patients underwent pancreaticoduodenectomy with pancreaticojejunostomy. Except for the tumour stage and albumin levels, the two cohorts were similar. POPF grade B–C occurred in 11,8% of patients treated with Neoprene versus 16,3% of patients with PJ anastomosis. A rate of 2% of mortality resulted in the fibrin sealants group for intracranial haemorrhage, liver failure, and sepsis versus the 0% of the second group. At 1- and 3-years diabetes occurred in 13,7% and 36,7%, (versus 4,2% and 12,2%), in the Neoprene group that require an insulin treatment in the long-term in 58,3% of cases. All patients of the control group who developed diabetes in the long-term were insulin-dependent [16].

Furthermore, Barakat et al. [17] compared two groups of patients who underwent pancreaticoduodenectomy: one treated with Dermabond and the other without sealants. No significant difference was observed between groups about the overall rate of complications. The incidence of POPF was significantly lower in the Dermabond group than in the second one (2,6% vs. 22%). In the sealants group, POPF developed late (POD 6 and 8) and, apart from a case of POPF grade A, other patients had clinically relevant leakage. A rate of 12,2% of patients of the second group had relevant POPF. The mortality rate was significantly lower in the first group; indeed, in the control one, four patients died of post-operative complications not related to POPF and massive bleeding from the gastrojejunal anastomosis [17].

Ohwada et al. [18] reported outcomes of patients treated with two techniques: the sealing (56 patients) and the sandwich techniques (55 patients). The mortality rate was 0% for sealing and 3,6% for the sandwich group; besides, the morbidity rate was 33,9% for the sealing

group versus 21,8% for the sandwich one. POPF occurred in 26.8% of the sealing group patients and 9% in the sandwich group [18].

About Tisseel, Martin et al. [19] did not evidence significant differences between groups of people treated with this sealant versus patients treated without sealants. The mortality rate was 0% for both groups, and POPF was 40% for the Tisseel group and 43,8% for the second one [19]. Kuramoto et al. [20] evaluated the efficacy of applying the polyethylene glycolic acid felt pasting method to PJ anastomosis for the reduction of POPF after PD. The overall incidence of POPF was 29% in the PGA group and 48,5% in the control group [20]. Suc et al. [21] described that patients underwent total pancreatectomy without anastomosis, and patients underwent PJ anastomosis. The mortality rate was 9% for patients treated with duct occlusion. The causes of death were pancreatic fistula, multiple fistulae, biliary fistula, haemorrhage, heart failure, and pleuropulmonary infection acute hepatic failure due to isoflurane [21].

The efficacy of Tachosil was evaluated by Montorsi et al. [22], who showed a 62% POPF in patients treated with this sealant versus 68% of patients treated with the standard surgical procedure of distal pancreatectomy. Clinically relevant fistulas were observed in 8% of patients treated with sealant and 14% of the second group. Furthermore, the morbidity rate was 25% in the Tachosil group versus 24% in the standard one [22]. Martin et al. [19], evaluated the use of autologous falciform ligament patch with fibrin glue for pancreatic stump reinforcement with the pancreas' closure utilising staples and or sutures alone. The incidence of POPF was the same for the two groups, and 30-day mortality was 0% for both groups [19]. The study of Di Carlo et al. [23] reported postoperative complications in 33,3% of patients and 5,8% of mortality for hepatic failure and pulmonary embolism. Only two patients (3,9%) developed pancreatic fistula with low output and a spontaneous resolution within one month [23].

4. Discussion

The pancreatoduodenectomy is a procedure that remains burdened by significant morbidity, mainly related to postoperative pancreatic fistula [24]. The incidence of Postoperative Pancreatic Fistula (POPF) is 5%–30%, and pancreatic texture, diameter and position of Wirsung duct, blood loss, body mass index, and pancreatic disease etiology were identified risk factors. In the 1980s, pancreatic duct occlusion was explored as an alternative to pancreaticojejunal anastomosis [16,23,25]. The use of medical tissue adhesive represents an attractive option to suturing or stapling since they can accomplish several tasks, such as homeostasis and sealing air leakages. They do not represent any risk of needlestick injury to medical staff. The closure of the pancreatic duct with a chemical substance was proposed by Gebhardt [26] in 1978. He occluded the pancreatic duct with Ethibloc (Ethicon, Norderstedt, Germany) in patients with severe chronic cephalic pancreatitis. Prolamine (Ethibloc) is an alcoholic amino acid solution that has some advantages as an occlusive gel. It can solidify rapidly, microbiologically indifferent, disintegrates within two weeks, and causes only mild oedema [26,27].

Moreover, Plusczyk et al. [11] induced a temporary obliteration of the pancreatic duct, in inbred rats, by using Ethibloc to introduce atrophy of the exocrine pancreas for treatment of chronic pancreatitis and to protect the anastomosis following Roux-Y pancreaticojejunostomy [11]. As described in previous experimental studies [28], the administration of Ethibloc could lead to fulminant acute hemorrhagic pancreatitis with disruption of the pancreatic ducts' epithelial lining cells and periductal leukocyte infiltration 15 days after the administration. The study showed severe tissue damage, an acute inflammatory response, and a significant increase in serum p-amylase levels after the use of Ethibloc. Retrograde intraductal infusion of Ethibloc caused temporary but compromising microcirculatory deterioration with almost complete ischemia of the pancreas [11]. The occlusion of the pancreatic duct with fibrin sealants, in Marczell et al.'s [13] study, significantly reduced the perioperative mortality and the postoperative complication rate of pancreatoduodenectomy (PD). Despite these results, it seems that prolamine, due to its viscosity, does not yield uniformly favourable long term results. It could also lead to interstitial fibrosis with subsequent high-grade sclerosis of the exocrine pancreatic parenchyma with an essential alteration of the endocrine cell function [13]. About this, Suc et al. [21] described a study in which ductal occlusion was performed with fibrin glue (Tissucol). The results did not show a significant decrease in the rate of intra-abdominal complications. The failure of fibrin glue ductal occlusion on the pancreatic fistula rate could be explained by increasing secretion of pancreatic juice in the secondary canals or on the suture line when the main pancreatic duct was blocked. Besides, occlusion of the main duct might be incomplete or not last long [21].

The most used surgical glues nowadays are fibrin-based adhesives and cyanoacrylates [32].

Fibrin glue is a surgical hemostatic agent derived from plasma coagulation proteins. It consists of two principal components: fibrinogen and coagulation factor XIII and thrombin dissolved in calcium chloride. When mixed, these two components mimic the blood coagulation's final stages, resulting in a fibrin clot formation. Sometimes, aprotinin, an antifibrinolytic agent, is added to the fibrin glue product to delay lysis of the adhesive material, particularly in high fibrinolytic activity areas. The fibrinogen and thrombin, components of fibrin glue, are usually applied in equal volumes, and maximal adhesive strength is generally achieved 3–5 min after application. The adhesive or mechanical strength of fibrin glue is a function of the fibrinogen concentration. Thrombin concentration affects the rate of fibrin clot formation: a high thrombin concentration results in clot formation within a few seconds and is appropriate when immediate hemostasis is desired [30,31]. Fibrin glue can once be sprayed, prevent leakage of pancreatic juice from sealed small ducts or the pancreatic stump's necrotic edge.

The review of Deng et al. [30] reported fibrin sealant use in four

studies for pancreatic anastomosis reinforcement after pancreatoduodenectomy and the comparison between two groups, which fibrin sealant use and the other with no fibrin sealant use [4,16,23,32]. Moreover, two studies analysed the application of fibrin sealants to pancreatic duct occlusion after pancreatoduodenectomy between fibrin sealant use and no fibrin sealant use [21,32]. The results showed that fibrin sealants might have little to no difference in the postoperative pancreatic fistula rate of mortality compared to control. The impact of fibrin sealants on POPF rate and mortality was unclear when fibrin sealant was applied to pancreatic anastomosis reinforcement or pancreatic duct occlusion after pancreatoduodenectomy. One study showed more participants developing diabetes mellitus at three- and 12-months' follow-up when fibrin sealants were applied to pancreatic duct occlusion after pancreatoduodenectomy. None of the other studies reported severe adverse events related to fibrin sealants.

Finally, the cost of fibrin sealants was relatively high; it cost approximately USD 500 per case using 5 mL [30]. Because simply spraying fibrin glue over the closed pancreatic stump to seal it off (the "sealing" technique) did not seem satisfactory for preventing pancreatic fistula, Ohwada et al. [18] used, as an alternative, the "sandwich" technique. It consists of spraying fibrin glue on the pancreatic remnant before suturing the cut end. In their study, this approach leads to fewer pancreatic fistula than to spray it on the already sutured end [18].

To suppress exocrine pancreatic secretion, Di Carlo et al. [23] in 1989 used the Neoprene injection in the Wirsung duct to induce progressive fibrosis of the exocrine tissue without affecting the islets of Langerhans. The study demonstrated that this approach is timesaving as compared with the classical Whipple procedure. Its chemical-physical properties chose Neoprene: it can be sterilised, is stable over time, is manageable, and allows a more homogeneous filling of the main and secondary ducts in comparison with other compounds. The injection of Neoprene into the Wirsung duct through the catheter must be done without direct contact with the surrounding tissue cause of its caustic compound due to its high pH. From this study resulted that the incidence of the pancreatic fistula was reduced. They observed only two fistulas (4%), which spontaneously resolved in a short time [23].

Moreover, no pancreatic inflammatory complications developed after Neoprene injection confirm that this agent induces only fibrosis of the exocrine tissue. The elimination of incompletely drained pancreatic parenchyma areas induces complete pain relief and makes the recurrence of the disease unlikely. The islets function is not significantly damaged by Neoprene-induced pancreatic fibrosis for up to 3 years after surgery [23].

Neoprene 671 is a low viscosity, liquid rubber of pH 12.4. Upon contact with the more acidic pancreatic juice, this product is polymerised and precipitated [33]. Peculiar of neoprene latex is the ability to depolymerise in contact with the pancreatic juice's basic pH, hardening into a semisolid cast of Wirsung duct [13,26]. Despite these attractive features, the scientific evidence of Neoprene based pancreatic duct occlusion (PDO) efficacy is lacking.

In their study, Mazzaferro et al. [16] enrolled 100 patients undergoing radical pancreatoduodenectomy for various cancers of the pancreatoduodenal region. Patients with high fistula risk scores and therefore at high risk for POPF were treated with PDO using a neoprene glue. A parallel cohort of control patients operated during the same period and considered at low risk of POPF received conventional pancreatic-jejunal reconstructions (PJA). The primary endpoint of the study was to compare in the two cohorts the 30-day complication rate according to Dindo-Clavien Classification (DCC). Other endpoints of the study were evaluating the new-onset insulin-dependent diabetes along with the follow-up and patient survival outcomes. The two cohorts were similar for most clinical characteristics, except for baseline albumin levels and tumour stage, more advanced in the study group receiving PDO than controls.

Complications at 30 days occurred in 13 patients of the study cohort and 12 controls. In particular, the rate of chemical pancreatitis was 0%,

even in those who underwent rescue PDO. On the one hand, they did not observe worsening morbidity and mortality after duct occlusion in patients at high risk of POPF than the parallel cohort at low risk of fistula receiving PJA. So, the efficacy of duct occlusion with Neoprene was confirmed. On the other hand, post-surgical new-onset diabetes incidence was higher in neoprene-PDOs than in the PJ anastomosis cohort. Most likely, neoprene-induced fibrosis was responsible for a significant reduction of the preoperative versus postoperative levels of insulin and C-peptide in Neoprene-occluded patients compared with control. Based on this study, PDO with neoprene-based glue was considered a safe and potentially efficacious procedure [16].

A study by Schindl et al. [4] evaluated a fibrin-coated collagen patch's ability to reduce the risk of postoperative POPF in patients undergoing pancreatoduodenectomy with pancreatojejunostomy. After surgery, biochemical leakage or POPF occurred in 85 of 142 patients: 45 of 71 in the patch group and 40 of 71 in the control group. There was no significant difference in surgical complications and drain fluid concentrations of total amylase, pancreas-specific amylase and lipase during the postoperative observation period between the groups [4].

Matrix-bound sealants are composed of a carrier such as collagen or gelatin to stimulate endogenous coagulation, with or without additional active components. In most studies in pancreatic surgery, sealant patches were used to cover the pancreatic stump after distal pancreatic resection. In a non-randomised single-centre study of 54 patients undergoing pancreatoduodenectomy [34], half of the patients received a fibrin sealant patch layered on to the pancreatojejunostomy, and the other half served as controls. The POPF rate was 7% in the entire cohort, with one grade B and two grade A POPFs in the control group and one grade A fistula in the patch group. Although the differences between groups were not significant, they suggested a possible advantage of fibrin sealant patches in the prevention of POPF. In contrast with a previous study [35], the authors supposed that pancreatojejunostomy by invagination of the pancreatic stump into the jejunum and Ticron-pledged sutures makes a homogeneous anastomotic surface able to support the adhesion of TachoSil® (Nycomed, UK Ltd.) and optimises the sealing effect, so it could be considered a good surgical technique, not inferior to pancreaticogastrostomy [34].

The popularity of sealant patches in pancreatic surgery is mainly related to the assumption that these products may reduce the overflow of pancreatic juice from the anastomosis during the first few days after surgery and reduce biochemical leak and its sequelae such as inflammatory retention and late haemorrhage. The lack of success of fibrin sealant patches placed on the pancreatojejunostomy may be explained by the finding that both liquid and carrier-bound forms of fibrin were rapidly and grossly degraded by the enzymatic activity of leaking pancreatic juice, may decrease both the adhesive strength and sealing properties of fibrin sealant, paving the way for POPF regardless of whether a patch is used [4].

Compared to fibrin sealants, the medical glue 2-octyl cyanoacrylate (2-OCA) is also readily applicable to the resection surface. Aggressive pancreatic enzymes do not degrade it due to its long-lasting tissue bonds. Cyanoacrylate is an acrylic resin that rapidly polymerises in the presence of water, forming long, strong bonds that join surfaces together. The compound 2-OCA is a nontoxic bacteriostatic medical glue that has been widely used to approximate skin edges. In 2013, Barakat et al. [17] had published their first results on the topical application of 2-OCA to pancreatojejunal anastomosis after pancreatoduodenectomy. They reported a highly significant reduction of POPF for the 2-OCA group compared to patients without 2-OCA application. The synthetic tissue sealant consisting of a blend of two monomers, 2-OCA and butyl-lactoyl-cyanoacrylate, OMNEX, creates a flexible physical seal after polymerisation, independent of the body's clotting mechanism. During a period of approximately 36 months, the sealant eventually degrades via hydrolytic chain scission, breaking down into smaller absorbable fragments. In total, they found six biochemical leaks, five clinically relevant cases of POPF.

Another option of reinforcement of the resection surface is coverage by autologous tissue, mostly done using the liver's falciform or teres ligament. Furthermore, some trials have focused on optimising pancreatic drainage over the papilla of Vater by prophylactic endoscopic stenting of the pancreatic duct or in a more recent trial by preoperative endoscopic injection of botulinum toxin into the sphincter of Oddi. However, stenting did not reduce the POPF rates in the randomised controlled trial, and botulinum toxic injection showed promising results in the pilot study. However, a controlled trial is still missing for this approach [36]. The use of several different methods to secure the pancreatic remnant, including duct ligation, ultrasonic dissection, fibrin glue, patches and meshes, pancreatoenteric anastomosis, and handsewn and stapler closure, possibly associated with pericardial buttress, attests to the ongoing controversy.

Another kind of fibrin sealant is Tachosil (Nycomed GmbH, Linz, Austria), a topical absorbable fibrin sealant patch consisting of a collagen fleece coated with human fibrinogen and thrombin, the usefulness of which as an adjunct to standard surgical techniques has been shown in liver, renal, pulmonary, and cardiovascular surgery. An *in vitro* study indicated that the patch retains proper adhesive strength even after prolonged contact with amylase-rich pancreatic juice, suggesting that it might be applied to the pancreatic tissue [37]. The trial of Montorsi et al. [22] about the application of TachoSil (Nycomed GmbH, Linz, Austria) on the pancreas stump after distal pancreatectomy (DP) showed that its use did not result in a significant reduction in the overall pancreatic fistula rate after DP. The rate of clinically significant fistulas resulted similarly to that reported in other studies with a non-significant reduction in the group of patients treated with TachoSil. The subsequent increase of amylase in drainage fluid probably reflects the degradation of TachoSil by pancreatic enzymes [22]. Cunha et al. [38] showed that Tachosil sponge's application on the proximal remnant after distal pancreatectomy reduced neither the rate nor the severity of POPF. It seemed to be ineffective for clinically relevant POPF and all grades of POPF in accordance with their research [38].

Kwon et al. [15] investigated the efficacy of fibrin sealant patches on pancreatic-enteric anastomosis during PD, splitting patients into two groups: the one treated with pancreatojejunostomy and fibrinogen/-thrombin collagen patch (Tachosil; Takeda Austria, Linz, Austria) on the anastomosis site and the second treated with only fibrin glue after pancreatojejunostomy. The study reported a clinically relevant POPF rate of 6,5% in both groups; in addition, no significant differences were found between the two groups concerning postoperative outcomes. However, no statistically significant superiority was seen in the use of fibrin sealant patches regarding the incidence of POPF after pancreaticoduodenectomy with pancreatojejunostomy [15].

The variety of biological tissue requires the development of specific adhesives with particular properties making the task of obtaining products with multiple potential applications a difficult one. When it comes to surgical adhesives, it will be challenging to find a model that fits all uses [29].

BioGlue were bio-absorbable sealants widely used to reduce the rate and severity of POPF after DP. These sealants were mainly used in cardiovascular and thoracic surgery for sealing graft anastomoses and bronchial closures. BioGlue consisted of glutaraldehyde and bovine serum albumin molecules that cross-link with each other and with tissue protein. Coseal, also, was another kind of sealant containing glycol polymers that cross-link rapidly with each other proteins of the target tissue. Experiments *in vivo* and *in vitro* in German Landrace pigs [12] demonstrated that both substances, when in contact with active pancreatic proteolytic enzymes, lasted up to 7 days due to their chemical cross-linking. Unfortunately, biogluetreated animals developed more frequently systemic inflammation, maybe for the compounds released from the polymerised product and direct interaction with immune cells [15].

To reinforce the pancreatic stump, Carter et al. [39] suggested using an autologous falciform ligament patch with fibrin glue (Vitagel), which

was deposited around the periphery of the patch. They compared fibrin with one of the staples or sutures with the results that there were no significant differences among the two groups. These results could be caused by the lack of vascularisation of the falciform ligament patch; the pedicled patch may have some vascularity element, which might give the remnant a buttress of live tissue. At the same time, a pedicled flap may prove a hindrance, being dislodged. Furthermore, patients treated with fibrin glue might have a delayed onset of pancreatic fistulae due to the additional physical barrier [39]. Furthermore, Kuramoto et al. [20] described the use of polyethylene glycolic acid (PGA) in conjunction with fibrin sealant in PJ anastomosis to reinforce not PJ anastomosis but the pancreatic remnant in order to have a tight fixation to the jejunum. This method significantly seems to reduce the incidence of POPF in patients with a soft pancreas [20].

Luu et al. [14] suggested an automated biotechnological process enabling preparations of autologous fibrin sealant, the Vivostat System (AFS, Vivostat, Allerød, Denmark), fibrin is made by patient blood. It seems to be useful to prevent severe complications such as septic haemorrhage and intensive care treatment. Vivostat System consists of three parts: the Processor Unit, which processes patient's blood and prepares concentrated fibrin I solution with a disposable preparation unit; the Applicator Unit, which stores AFS and controls the delivery of AFS to the spray pen and the Disposable Set, which components needed for preparation and application of AFS. Vivostat is a body-owned product, so foreign body reaction and toxic tissue damage are not expectable compared to conventional fibrin sealant, which contains bovine ingredients [17].

A novel approach toward preventing POPF was described by Lee et al. [1] through the intrapancreatic injection of penicillin G. They found a significant improvement in the hardness and suture holding capacity of the pancreas. At the same time, it seems that Penicillin G activated HPSCs to produce various fibrotic materials. Penicillin G induced reversible fibrosis, which does not permanently damage the pancreas and is normalised seven days after injection. The anastomotic site becomes compacted and adhesive as a result of fibrosis. However, the problem is that it is approximately 5–7 days after surgery when the pancreatic-enteric anastomotic site becomes adhesive and hardened by fibrosis. There is a gap between when the POPF is frequently encountered and when fibrosis is fully activated. Penicillin G could play a role in reducing this gap by speeding up the fibrotic process [1]. It could be an alternative to minimise and prevent POPF, even if its actual effectiveness and safety should be validated by further study.

5. Conclusion

CR-POPF is still today a fearful complication of pancreatic surgery; among the possible solutions to reduce the risk of onset, sealants were used on the pancreatic stump; today, the sealants should be considered such as an option to reduce the CR-POPF, but the routine use in clinical practice has to be validated with other clinical trials.

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Ethical approval

No patients are involved in this study.

Consent

This article is a systematic review, obtained by analyzing the papers published in the literature on the major databases. There were no contacts with patients and no consent was necessary.

Author contribution

Francesco Serra, MD: DESIGN OF THE REVIEW AND SUPERVISOR OF ENTIRE MANUSCRIPT.

Isabella Bonaduce, MD: REVIEW OF THE LITERATURE AND DATA COLLECTION.

Elena Giulia Rossi MD: DATA COLLECTION.

Nicola De ruvo, MD: AUTHOR OF THE DISCUSSION.

Nicola Cautero, MD: REVIEW OF THE LITERATURE.

Roberta Gelmini, Full Professor: SUPERVISOR OF ENTIRE MANUSCRIPT.

Trial registry number

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102244>.

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