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ORIGINAL ARTICLE

Pancreatic Fistula and Delayed Gastric Emptying After Pancreatectomy: Where do We Stand?

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Abstract Pancreatic resection has become a feasible treatment of pancreatic neoplasms, and with improvements in surgical techniques and perioperative management, mortality associated with pancreatic surgery has decreased considerably. Despite this improvement, a high rate of complications is still associated with these procedures. Among these complications, delayed gastric emptying (DGE) and postoperative pancreatic fistula (POPF) have a substantial impact on patient outcomes and burden our healthcare system. Technical modifications and postoperative approaches have been proposed to reduce rates of both POPF and DGE in patients undergoing pancreatectomy; however, to date, their rates have remained unchanged. In the present study, we summarize the findings of the most significant studies that have investigated these complications. In particular, several studies focused on technical modifications including extent of dissection, stent placement, nature of anastomosis, type of reconstruction, and application of biological or non-biological agents to site of anastomosis. Moreover, postoperatively, drain placement, duration of drain usage, postoperative feeding, and use of pharmacological agents were studied to reduce rates of POPF and DGE. In this review, we summarize the most relevant literature on this fundamental aspect of pancreatic surgery. Despite studies identifying the potential benefit of technical modifications and postoperative approaches, these findings remain controversial and suggest need for further extensive investigation. Most importantly, we recommend that all surgeons performing these procedures base their practice on the most updated and highest available level of evidence.

Keywords Pancreatic surgery · Postoperative outcomes · Complications · Delayed gastric emptying · Postoperative pancreatic fistula

Introduction

Pancreatic resection became a feasible treatment of pancreatic neoplasms around the turn of the twentieth century with the reports of the first distal pancreatectomy by Trendelenburg in 1882 [1] and the pancreaticoduodenectomy in the Annals of Surgery in 1935 [2]. With improvements in both surgical techniques and perioperative patient management, the mortality associated with pancreatic surgery has decreased from 25 % to approximately 2 % [3]. Despite the dramatic improvement in mortality since the 1970s, pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy are still associated with a high rate of complications, ranging between 30 % and 50 % even at high-volume centers [4, 5]. In particular, the most frequent complications of pancreatic resection include delayed gastric emptying (DGE) and postoperative pancreatic fistula (POPF), followed by intra-abdominal abscess and sepsis [6, 7]. These complications impact outcomes and are associated with increased length of hospital stay, need for re-operation or percutaneous procedures, delayed initiation of adjuvant therapy, and in rare instances, can even lead to death [3]. Overall, these complications effect patient recovery and place significant financial burden on the healthcare system. Several studies have outlined the negative impact of these complications on both short- and long-term outcomes. In

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addition, a great deal of effort has gone into the study of technical features of the operations and postoperative management protocols to reduce these two complications. However, to date, the occurrence of POPF and DGE has remained unchanged over the past 50 years.

The goal of this review is to summarize the major studies that have attempted to reduce the rate of POPF and DGE or improve the management of these complications in patients undergoing pancreatectomy.

Postoperative Pancreatic Fistula: Definition and Classification

The leakage of pancreas exocrine secretions from the anastomosis or pancreatic transection line results in a POPF with a reported rate between 10 and 28 % [8, 9]. Historically, numerous definitions were used to report POPF. Recently, a unified definition of POPF was proposed by the International Study Group on Pancreatic Fistula (ISGPF) in 2005 and has gained widespread use in the literature. According to this definition, a POPF is defined as a drain amylase of over three times that of the serum amylase at or beyond postoperative day 3 (POD 3) [10]. In addition, the ISGPF classified POPF into three grades based on the relative impact of this complication [10, 11]: grade A POPF constitutes of a short-lived fistula with no clinical symptoms but with higher drain amylase levels with minimal clinical effect that requires no significant alterations in management protocols. Grade B fistula results in clinical symptoms and radiographic imaging may depict peri-pancreatic fluid collections. For this grade, the management includes at least one of the following: antibiotic administration, supplemental nutrition, placement of a postoperative percutaneous drain, or readmission to the hospital [12, 13]. Grade C fistula is the most severe class with patients being clinically unstable. It is associated with sepsis, organ dysfunction, and death; therefore, re-operation and exploration may be required [7, 12, 13].

Approaches to Reduce the Rate and the Grade of POPF

In general, two approaches have been attempted to improve outcomes: changes in surgical technique and modification of postoperative management. Studies performed on improving technique have focused on assessing the type of anastomosis and application of both biological and non-biological agents to the site of anastomosis. Postoperatively, the effect of drain placement, duration of drain usage, placement of stents, type of postoperative feeding, and use of pharmacological agents (somatostatin analogues) were studied.

Studies of Technical Modifications to Reduce the Rate of POPF

Extensive work has been performed that assessed various technical aspects to reduce POPF (Table 1). Pancreaticojejunostomy (PJ) after pancreatoduodenectomy (PD), which drains the pancreatic remnant into the gastrointestinal tract, is the most common method of reconstruction. In the conventional loop reconstruction, pancreaticojejunostomy is performed in an end to end or end to side manner utilizing the same jejunal loop that continues to the hepatojejunal and gastro- or duodenal-jejunal anastomoses. Therefore, there is a risk of breakdown of the anastomosis due to the activation of pancreatic enzymes by gastric and biliary secretions [13, 14]. In order to circumvent this problem, a Roux-en-Y (R-Y) reconstruction with isolated pancreatic drainage was evaluated to lower the risk of POPF development by isolating the pancreatic drainage from activating factors [15]. Isolation of pancreatic drainage is based on the concept that deviation of biliary from pancreatic secretions minimizes the risk of activation of pancreatic enzymes that can result in erosion [13]. Ke et al. performed a randomized controlled trial (RCT) that investigated the effect of Roux-en-Y reconstruction with isolated pancreatic drainage as compared to conventional loop reconstruction on the incidence of POPF [13]. The study found no significant difference in the incidence of POPF between the two methods of reconstruction (15.7 % vs. 17.6 %, $p>0.05$). However, patients who underwent Roux-en-Y reconstruction had decreasing severity of POPF and a reduced hospital stay and lower costs [13].

A RCT by Nakeeb et al. compared the outcomes of isolated loop pancreaticojejunostomy (IRPJ) with those of pancreaticogastrostomy after PD, based on the theory that reducing the activation of pancreatic juice by biliary secretion will decrease the incidence and severity of POPF. The study that comprised 90 patients showed no significant difference in the incidence of POPF between the two groups (11.2 % vs. 6.7 %, $p=0.796$). However, there was a reduced incidence of steatorrhea ($p=0.029$) and early return to oral feeding ($p=0.029$) in patients who underwent IRPJ [16]. Tani et al. reported a randomized clinical trial which found no significant difference in POPF rates in patients who underwent isolated Roux-en-Y vs. conventional reconstruction after PD (33 % vs. 34 %, $p=0.909$) [17]. Similarly, a meta-analysis of three RCTs and four controlled clinical trials comparing conventional single loop vs. dual loop (Roux-en-Y) with isolated pancreaticojejunostomy reconstruction after PD reported no significant difference in the rates of POPF between the two methods (relative risk (RR)=0.91, $p=0.54$) [18].

The method of creation of the pancreaticojejunostomy has also been studied. A RCT compared two surgical techniques comprising of an end to side duct to mucosa vs. invagination pancreaticojejunostomy and found no significant difference in

Table 1 Effects of surgical interventions on POPF following pancreatectomy

Author	Type of study	No. of patients	Type of intervention	Results
Ke et al. (2013) [13]	Prospective randomized trial	216 • 107 • 109	Roux-en-Y reconstruction with isolated pancreatic drainage vs. conventional loop reconstruction	• Similar incidence of POPF (15.7 vs. 17.6 % in the Roux-en-Y group vs. conventional group) • Conventional group had higher incidence of grade B fistula, longer hospital stay, and higher hospital costs
Antila et al. (2014) [7]	Prospective randomized trial	16 • 8 • 8	Finnish binding pancreaticojejunal anastomosis vs. hand-sewn closure of pancreatic remnant in patients undergoing left pancreatectomy	• Higher incidence of POPF (60 %) in FBPJ group vs. hand-sewn group (13 %, $p<0.05$) • FPBJ technically feasible in only 28 % of patients undergoing LP
Nakeeb et al. (2014) [16]	Prospective randomized study	90 • 45 • 45	Isolated Roux loop pancreaticojejunostomy vs. pancreaticogastrostomy after PD	• No significant difference in rate of POPF between the two groups • Incidence of steatorrhea was lower in IRPJ group along with early oral feeding and maintenance of oral feeding in cases even where POPF developed
Lillemoe et al. (2004) [50]	Prospective randomized trial	125 • 59 • 66	Application of fibrin glue sealant at the pancreatic anastomosis vs. no application	• No significant difference in the incidence of DGE in the fibrin application group and the no fibrin application group (26 vs. 30 %, p=Not significant)
Winter et al. (2006) [34]	Prospective randomized trial	234 • 115 • 119	Placement of stent	• No significant difference in the incidence of POPF in patients who underwent stent placement and those who did not both in the soft/normal texture (21.1 vs. 10.7 %; $p=0.1$) and the hard texture (1.7 vs. 4.8 %; $p=0.4$) groups
Poon et al. (2007) [41]	Prospective randomized trial	120 • 60 • 60	External drainage of pancreatic duct with a stent after PD	• Stented group had significantly lower rates of POPF (6.7 vs. 20 %, $p=0.32$)
Motoi et al. (2012)	Randomized clinical trial	93 • 47 • 46	External pancreatic duct stent placement in patients undergoing PD	• Rate of clinically significant POPF were significantly lower in patient who had stent placed (3 (6 %) vs. 10 (22 %), $p=0.04$)
Pessaux et al. (2011)	Prospective randomized trial	158 • 81 • 77	External pancreatic duct stent placement in patients undergoing PD	• Reduction in the overall POPF rates in patient who received stent placement (20 (26 %) vs. 34 (42 %), $p=0.03$).
Diener et al. (2011) [44]	Randomized controlled multicenter trial	450 • 221 • 229 352 analyzed • 177 • 175	Closure of pancreatic remnant by a stapler vs. hand-sewn technique	• No significant difference between stapler device closure and hand-sewn closure in the development of POPF and death (32 vs. 28 %, $p=0.56$).
Bassi et al. (2003) [19]	Prospective randomized trial	144 • 72 • 72	Duct to mucosa vs. end to side pancreaticojejunostomy reconstruction after PD	• No difference in incidence of POPF between the two groups (13 % in duct to mucosa PJ vs. 15 % in end to side PJ, p=not significant)
Nakeeb et al. (2015) [20]	Prospective randomized study	107 • 53 • 54	Duct to mucosa vs. invagination pancreaticojejunostomy after PD	• No significant difference between the two techniques in incidence ($p=0.46$) or severity ($p=0.4$) of POPF.
Que et al. (2015) [33]	Meta-analysis of 8 randomized controlled trials	1211 • 607 • 604	Pancreaticogastrostomy vs. pancreaticojejunostomy after PD	• Significantly lower risk of POPF in PG group as compared to PJ group (RR 0.6853, $p=0.0024$)

Table 1 (continued)

Author	Type of study	No. of patients	Type of intervention	Results
				• Reduced severity of POPF after pancreaticogastrostomy • No difference in the incidence of DGE between the two techniques
Klaiber et al. (2015) [18]	Meta-analysis of 3 randomized controlled trials and 4 controlled clinical trials	802	Conventional single-loop vs. dual loop (Roux-en-Y) with isolated pancreaticojejunostomy reconstruction after PD	• No significant difference in POPF rates between the two groups (RR=0.91, p=0.54)
Yeo et al. (1995)	Prospective randomized trial	145 • 73 • 72	Pancreaticogastrostomy vs. Pancreaticojejunostomy after PD	• No significant difference in POPF rates between the two groups (12.3 % PG vs. 11.1 % PJ, p>0.05)
Duffas et al. (2005) [31]	Controlled randomized multicenter trial	149 • 81 • 68	Pancreaticogastrostomy vs. pancreaticojejunostomy after PD	• No significant difference in POPF rates (16 % PG vs. 20 % PJ, $p\geq$0.05) and severity between the two groups
Bassi et al. (2005) [28]	Prospective randomized study	151 • 82 • 69	Pancreaticojejunostomy vs. pancreaticogastrostomy after PD	• No significant difference in the incidence of POPF between PG (13 %) and PJ (16 %, p>0.05) • Significantly lower rate of multiple surgical complications (p=0.002), biliary fistula (p=0.01), DGE (p=0.03), and postoperative collections (p=0.01) in patients who received PG
Wellner et al. (2012) [27]	Randomized controlled trial	116 • 59 • 57	Pancreaticogastrostomy vs. pancreaticojejunostomy after partial PD	• No significant difference in the incidence of POPF between PG and PJ (10 vs. 12 %, p=0.775)
Topal et al. (2013) [26]	Multicenter randomized trial	329 • 167 • 162	Pancreaticogastrostomy vs. pancreaticojejunostomy after PD	• Significantly higher incidence of POPF in the PJ group (19.8 % in PJ vs. 9.0 % in PG, p=0.002) • Lower incidence of DGE in the PJ group (8 % in PJ vs. 15 % in PG, p=0.04)
Figueras et al. (2013) [32]	Randomized clinical trial	123 • 58 • 65	Pancreaticogastrostomy vs. pancreaticojejunostomy after PD	• Significantly higher incidence (20 of 58 in PJ vs. 10 of 65 in PG, p=0.014) and severity (p=0.006) of POPF in the PJ group as compared to PG
Olah et al. (2009) [43]	Randomized clinical trial	70 • 35 • 35	Closure of pancreatic remnant by stapler alone vs. stapler closure and covering with a seromuscular patch of jejunum following distal PD	• Higher overall pancreas-related complications in the stapling alone group (p=0.041) • No significant difference between the two techniques in the development of clinically relevant (grade B or C) POPF and fluid collection (p=0.0428)
Berger et al. (2009) [21]	Randomized prospective trial	197 • 97 • 100	Duct to mucosa pancreaticojejunostomy vs. invagination pancreaticojejunostomy after PD	• Significantly lower incidence of POPF in invagination PJ as compared to duct to mucosa PJ (12 vs. 24 %, p<0.05)
Buren II et al. (2014) [42]	Randomized prospective multicenter trial	137 • 68 • 69	PD with and without intraperitoneal drainage	• PD without drain placement associated with increased number of complications per patient (p=0.029), increase in number of patients with at least 1 grade 2 or more severe complication

Table 1 (continued)

Author	Type of study	No. of patients	Type of intervention	Results
				(p=0.0047), increased average complication severity (0.027), higher incidence of DGE (p=0.021), intra-abdominal fluid collection (p=0.033), and abscess (0.033), severe diarrhea (p=0.005), need for postoperative percutaneous drain placement, and increased duration of hospital stay • No significant difference in POPF rates between the two groups (p=0.155) • Study stopped early due to increase in mortality from 3 to 12 % in patients without drain placement
Carter et al. (2013) [46]	Randomized controlled trial	109 • 55 • 54	Stapled or sutured closure of pancreatic remnant after PD vs. stapled or sutured closured and addition of a falciform patch and fibrin glue	• No significant difference in POPF rates between the two groups (20 % in the SS group vs. 19 % in the FF group, p=1.000)
Peng et al. (2007) [22]	Prospective randomized trial	217 • 111 • 106	Binding Pancreaticojejunostomy vs. invagination pancreaticojejunostomy after PD	• Significantly lower POPF in binding PJ group (0 % in binding PJ vs. 7.2 % in invagination PJ, p=0.014)
Fernandez-Cruz et al. (2008) [25]	Prospective randomized study	108 • 53 • 55	Pancreaticogastrostomy with gastric partition after PPPD vs. conventional pancreaticojejunostomy	• Lower postoperative complications (23 % in PPPD-GP group and 44 % after PPPD-PJ, p<0.01) • Lower incidence of POPF in the PPPD-GP group as compared to PPPD- PJ (4 vs. 18 %, p<0.01)
Frozanpur et al. (2012) [36]	Prospective controlled clinical trial	58 • 29 • 29	Prophylactic transpapillary pancreatic stent following distal pancreatectomy vs. no stent after DP	• No significant difference in POPF rates between the two groups (p=0.122)
Montorsi et al. (2012) [51]	Multicenter randomized controlled trial	275 • 145 • 130	Standard surgical suturing or stapling with or without TachoSil (absorbable fibrin sealant patch) after distal pancreatectomy	• No significant difference between the two groups in POPF rates (62 % TachoSil vs. 68 % standard, p=0.267)
Tani et al. (2014) [17]	Randomized clinical trial	151 • 75 • 76	Isolated Roux-en-Y vs. conventional reconstruction after PD	• No significant difference in POPF rates (33 vs. 34 %, p=0.909) and number of patients with clinically relevant POPF (10 vs. 11, p=0.789) between the two groups
Suc et al. (2003) [52]	Prospective randomized trial	182 • 102 • 80	Temporary fibrin glue occlusion of the main pancreatic duct	• Duct occlusion did not significantly decrease the rate of POPF. (duct occlusion vs. control: 17 (17 %) vs. 12 (15 %), p>0.05)

the incidence of POPF between the two (13 % vs. 15 %, p>0.05) [19]. Moreover, another RCT compared the two aforementioned techniques finding no significant difference in the incidence and severity of POPF (p>0.05) [20]. In contrast, another RCT comparing invagination PJ with a duct to mucosa PJ reported significantly reduced rates of POPF in the invagination PJ group as compared to the duct to mucosa technique (12 % vs. 24 %, p<0.05). Higher rates of POPF were reported in patients with a soft gland vs. patients with hard glands [21]. Another prospective trial compared binding PJ with invagination PJ and reported significantly lower POPF rates in binding PJ (0 % vs. 7.2 %, p=0.014) [22]. A case-control study compared binding vs. conventional PJ and reported no significant

difference in incidence of POPF between the two techniques. However, median delay in healing of the pancreatic fistula was longer (p=0.003) and post-pancreatectomy hemorrhage was higher (p=0.023) in the binding PJ group [23]. Casadei et al., in a prospective study, compared Peng's binding pancreaticojejunostomy after PD with historical controls that underwent duct to mucosa pancreaticojejunostomy and concluded that this technique did not reduce the rate of POPF (BPJ vs. duct to mucosa: 43 (82.7 %) vs. 56 (81.2 %), p= 0.97) [24].

Pancreaticogastrostomy is a less common method of pancreatic anastomosis [16]. Several clinical trials have been conducted to compare the outcomes of pancreaticojejunostomy with those of pancreaticogastrostomy in an attempt to determine the best method of pancreatic reconstruction after PD [25–33]. A prospective randomized trial comparing PG with PJ consisting of 145 patients found no significant difference in POPF rates between the two groups (12.3 % PG vs. 11.1 % PJ, p>0.05) and concluded that PG was not safer than PJ [30]. Similarly, a randomized multicenter trial comparing the two techniques found that the type of pancreatic reconstruction (PG or PJ) does not affect the incidence (16 % PG vs. 20 % PJ, p>0.05) or severity of POPF [31]. Another prospective randomized study consisting of 151 patients also found no significant difference in the incidence of POPF between PG (13 %) and PJ (16 %, p>0.05). However, a significantly lower rate of multiple surgical complications (p=0.002), biliary fistula (p=0.01), DGE (p=0.03), and postoperative collections (p=0.01) were associated with PG [28]. Another randomized trial found no significant difference in POPF, DGE, and intraluminal bleeding between PG and PJ in patients undergoing partial PD [27]. On the other hand, a multicenter randomized superiority trial including 167 patients who received PJ and 162 who received PG found a significantly higher incidence of POPF in the PJ group (19.8 % in PJ vs. 9.0 % in PG, p=0.002). This study found the incidence of DGE to be lower in the PJ group (8 % in PJ vs. 15 % in PG, p=0.04) [26]. Similarly, another RCT found higher rates of POPF in patients receiving PJ as compared to PG (p=0.014). The severity of POPF was also higher in the PJ group (p=0.006). Moreover, PG was associated with a lower hospital readmission rate due to complications, less weight loss, and better exocrine function [32]. Another prospective randomized study compared the outcomes of PG with gastric partition (pylorus-preserving pancreaticoduodenectomy (PPPD)-GP) after PPPD with conventional PJ and found lower postoperative complications (23 % in PPPD-GP group and 44 % after PPPD-PJ, p<0.01) and lower incidence of POPF in the PPPD-GP group as compared to PPPD-PJ (4 % vs. 18 %, p<0.01) [25]. A meta-analysis of eight randomized controlled trials comparing the two reconstruction methods after PD including a total of 1211 patients found a significantly lower risk of POPF in patients who underwent a PG as compared to PJ (RR 0.68, p=0.002). There was no significant difference in the incidence of DGE between the two groups [33].

Placement of stents in the pancreatic duct at time of pancreaticojejunostomy was investigated in several studies [34–40]. Winter et al. performed a prospective randomized trial on the use of stents to reduce the incidence of POPF [34]. The patients were randomized based on the texture of the gland and 115 received stents while in 119 stent was not placed in the pancreatic duct at the time of anastomosis. They did not find any statistically significant difference in rates of POPF in patients who underwent stenting when compared to those who did not, both in the soft/normal texture (21.1 % vs. 10.7 %; p=0.1) and the hard texture (1.7 % vs. 4.8 %; p=0.4) groups. They concluded that placement of stent does not decrease both the rate and severity of POPF [34]. Similarly, an RCT by Colon et al. on 179 patients demonstrated no added benefit of drain placement in reducing rate of complications after surgery [35]. Frozanpur et al. also reported a prospective controlled clinical trial that found no difference in the rates of POPF in patients who received prophylactic pancreatic duct stenting after distal pancreatectomy and those who did not (p=0.122) [36]. Motoi et al. on the other hand reported that the rate of clinically significant POPF were significantly lower in patients who had stent placed as compared to those that did not (stent vs. no stent=3 (6 %) vs. 10 (22 %), p=0.04). On sub-analysis, they found out that this observation was only true for patients with non-dilated ducts, and no significant difference was seen in patients with dilated ducts [37]. Pessaux et al. and Poon et al. also demonstrated a reduction in the overall POPF rates in patients that received stent placement (20 (26 %) vs. 34 (42 %), p=0.03), (4 (6.7 %) vs. 12 (20 %), p=0.032) [38, 41].

A randomized prospective trial compared the outcomes of PD with and without intraperitoneal drainage. Although no significant difference was found between the two groups in rates of POPF (p=0.155), the study reported that PD without drain placement was associated with an increased number of complications per patient (p=0.029), increase in number of patients with at least one grade 2 or more severe complication (p=0.0047), increased average complication severity (0.027), higher incidence of DGE (p=0.021), intra-abdominal fluid collection (p=0.033), intra-abdominal abscess (0.033), severe diarrhea (p=0.005), and need for postoperative percutaneous drain placement and increased duration of hospital stay. The study had to be stopped early due to increase in mortality from 3 to 12 % in patients without drain placement [42].

Closure of the pancreatic remnant following distal pancreatectomy has been attempted using several different techniques and the subsequent results on POPF development have been reported in literature [7, 43–45]. Regarding the distal pancreatectomy, Antila et al. performed a RCT comparing the Roux-Y binding pancreaticojejunal (Finnish binding pancreaticojejunal, FBPJ) anastomosis to a hand-sewn closure group of the pancreatic remnant. The technique used during an

FBPJ involved the insertion of the pancreatic remnant 2–3 cm inside the jejunal limb using seven peri-pancreatic sutures followed by tightening of the purse string suture and a Roux-en-Y entero-enteric anastomosis. Of note, the FBPJ was not technically feasible for 72 % of the cases. The results showed a higher incidence of clinically significant POPF in the FBPJ group as compared to the hand-sewn group (60 % vs. 13 %, $p<0.05$). Therefore, the routine use of FBPJ to close the pancreatic remnant was not recommended in patients undergoing left pancreatectomy [7]. A RCT was conducted at 21 European hospitals to assess whether closure of the pancreas after distal pancreatectomy by a stapler device would reduce the rates of POPF as compared to a hand-sewn technique. No significant difference was found between the two closure techniques in the occurrence of POPF and death (28 % in stapler closure vs. 32 % in hand-sewn closure, $p=0.56$) [44]. Similarly, another RCT compared closure of the pancreatic remnant after distal pancreatectomy with a stapler device alone or closure with a stapler and covering it with a seromuscular patch of jejunum. Although overall, pancreas-related complications including fistula were higher in the stapling alone group ($p=0.041$), there was no significant difference between the two techniques in the development of clinically relevant (grade B or C) POPF and fluid collection ($p=0.0428$) [43]. Another randomized controlled trial compared the closure of the pancreatic remnant after PD by a stapled or sutured closure (SS) technique vs. stapled or sutured closure and addition of a falciform patch and fibrin glue (FF). The study found no significant difference in POPF rates between the two closure techniques (20 % in SS group vs. 19 % in FF group, $p=1.000$) [46].

A retrospective analysis of 126 patients reported that identification of the pancreatic duct and suture ligation was associated with a reduced rate of pancreatic leak (9.6 % vs. 34 %, $p<0.001$). Moreover, not ligating the pancreatic duct was found to be the only factor associated with increased risk of pancreatic leakage during multivariate analysis ($p=0.001$) [47].

The application of topical sealing agents has also been investigated. Several studies have assessed the effect of application of fibrin glue at the pancreatic anastomotic site [48, 49]. In a RCT performed by Lillemoe et al. comprising 125 patients, the pancreatic fistula rate in the fibrin glue arm of the study was 26 % vs. 30 % in the control group; however, this difference was not statistically significant ($p>0.05$) [50]. Possible reasons for this finding were identified to be poor adherence and degradation of the fibrin sealant due to the pancreatic enzymes. Another multicenter randomized controlled trial compared the outcomes of standard surgical suturing or stapling with or without application of TachoSil (an absorbable fibrin sealant patch) after distal pancreatectomy and found no significant difference between the two groups (62 % TachoSil vs. 68 % standard, $p=0.267$) [51]. Conversely, a significant reduction in the incidence of POPF after the application of a non-biological sealant 2 octyl-cyanoacrylate to the pancreaticojejunostomy site after PD was reported in a prospective study comprising of 75 patients who received dermabond and 49 historical patients as the comparison group (26 % vs. 22 %, $p=0.001$) [3].

In another study, Suc et al. investigated the effect of temporary pancreatic duct occlusion using fibrin glue and found no significant difference between rates of including POPF (occlusion vs. control=17 (17 %) vs. 12 (15 %), $p>0.05$) and other intra-abdominal complications [52].

Postoperative Approaches to Reduce the Rate of POPF

Apart from surgical techniques, effects of several non-surgical, postoperative management interventions on rates of POPF have been reported in literature (Table 2). The postoperative management of drain has also been studied. In particular, Kawai et al. reported that early removal of drains after PD was associated with a reduction in morbidity after surgery [53]. Moreover, Molinari et al. conducted an RTC to compare the effects of early (POD 3) vs. late (>POD 5) drain removal in patients undergoing PD who had <50,000 U/L amylase level in their drain on POD 1. In the POD 3 group, there was a significant decrease in the incidence of POPF (1.8 % vs. 26.3 %, $p=0.0001$), abdominal complications ($p=0.002$), pulmonary complications ($p=0.007$), median hospital stay ($p=0.018$), and hospital costs ($p=0.002$). The timing of drain removal was also significantly associated with the development of POPF ($p<0.001$). Authors concluded that early removal of drains on POD 3 can be done safely in patients who are at low risk of developing POPF [54].

The use of somatostatin and its analogues to inhibit pancreatic secretions have been reported in several studies with controversial results [55–59]. Sarr et al. reported, in their study on 275 patients, that the use of a potent somatostatin analogue vapreotide did not decrease rates of postoperative complications including anastomotic leak (26.4 % vs. 30.4 %, $p>0.05$) [57]. Similarly, Lowy et al. showed no significant difference in rates of clinically significant pancreatic leak in patients who received octreotide when compared to patients who did not (12 % vs. 6 %, $p=0.23$) [56]. Another prospective randomized trial also showed no significant difference in the median pancreatic juice output between patients who received octreotide and those in the placebo group ($p=0.538$) [60]. Yeo et al. reported a prospective randomized placebo-controlled trial in which no significant difference was found in the POPF rates between patients who received prophylactic octreotide and those who were in the saline control group (11 % vs. 9 %, $p>0.05$). The overall complication rates were also not significantly different in the two groups [61]. Contrastingly,

Table 2 Effects of non-surgical interventions on POPF following pancreatectomy

Author	Type of study	No. of patients	Type of intervention	Results
Bassi et al. (2010) [54]	Prospective Randomized Trial	114 • 57 • 57	Early (POD 3) vs. late (POD 5 and beyond) removal of drain	• Lower incidence of POPF in early drain removal (1.8 %) vs. late drain removal groups (26.3 %, p=0.0001, OR=20) • Significant association between POPF and timing of drain removal (p<0.001) • Decreased rate of abdominal complications (p=0.002) and pulmonary complications (p=0.007) • Decreased median hospital stay (p=0.018) and hospital costs (p=0.02) in early drain removal group
Yokoyama et al. (2014) [109]	Study design similar to a Randomized controlled study	60 • 30 • 30 (46 included in final analysis)	Enteral replacement of externally drained pancreatic juice (R group) vs. non-replacement of pancreatic juice (NR group) after pancreatoduodenectomy	• Significantly higher amylase secretion on POD 7 in the non-replacement group (p=0.044). • Higher incidence of > grade B POPF in the NR vs. R groups (33.1 vs. 9.1 %, p=0.046)
Allen et al. (2014) [12]	Randomized double blind trial	300 • 152 • 148	Perioperative subcutaneous pasireotide vs. placebo	• Significantly lower incidence of grade 3 or higher POPF, pancreatic leak or abscess in patients who received pasireotide (p=0.006)
Fernandez-Cruz et al. (2013) [60]	Prospective randomized trial	62 • 32 • 30	Subcutaneous octreotide vs. placebo	No significant difference between the two groups in median pancreatic juice output (p=0.538)
Yeo et al. (2000) [61]	Prospective randomized placebo-controlled trial	211 • 104 • 107	Prophylactic octreotide vs. saline control	No significant difference between the two groups in POPF rates (11 % in octreotide group, 9 % in control group, p>0.05)

Delgado et al. demonstrated that use of octreotide significantly reduced the rates of pancreatic fistula in their study population of 34 patients (0 % vs. 28 %, p<0.05) [62]. Closset et al. compared somatostatin with octreotide in patients undergoing PD and reported no significant difference between the two [63].

More recently, the use of pasireotide, a somatostatin analogue with a longer half-life and broader binding profile [64], was studied in an RCT to find its effects on development of POPF. The study, which included 300 patients undergoing pancreatic resection, showed a significant reduction in the rate of high grade (>3) POPF, leak, and abscess in patients who received perioperative pasireotide (9 % vs. 21 %; p=0.006) [12]. Similar findings were observed when sub-analyses were performed in the pancreaticoduodenectomy (n=220, 10 % vs. 21 %) and the distal pancreatectomy (n=136, 7 % vs. 23 %) groups [12].

An observational study reported the effects of implementation of early oral feeding as compared to routine enteral feeding through a nasojejunal tube (NJT) [65]. The study found no significant difference in the incidence of POPF between the two types of feeding strategies (12 % vs. 12 %, p=0.999). However, patients who received early oral feeding had early resumption of an oral diet and reduced length of hospital stay [65].

Delayed Gastric Emptying: Definition and Classification

Delayed gastric emptying is a common postoperative complication of pancreatic resection with an incidence between 14 and 61 % [66]. When this complication occurs, it is almost always associated with PD and patients undergoing distal pancreatectomy rarely develop it.

In the vast majority of the cases, DGE is a self-limiting complication and its treatment is usually nutritional and fluid support. Despite the self-limiting nature, DGE results in prolonged hospital stays, increased hospital costs, and

strongly affects the quality of life of patients [67]. Several mechanisms regarding the physiology and pathogenesis of DGE have been hypothesized such as injury of the vagus nerve leading to gastric atony [68, 69], or the resection of the duodenum affecting both normal gastric motility and the concentrations of hormones as motilin and pancreatic polypeptide which play an important role in normal gastric motility [70–72]. Moreover, a meta-analysis by H. Qu et al. found preoperative diabetes, pancreatic fistulas, and postoperative complications to be associated with a higher risk of DGE while preoperative biliary drainage and antecolic reconstruction resulted in a lower risk of DGE [73]. Parmar AD et al. found pancreatic fistula, postoperative sepsis, and need for reoperation to be independently associated with DGE in a multivariate model including 711 patients undergoing PD or total pancreatectomy [67].

The International Study Group of Pancreatic Surgery classifies DGE into three different grades. Grade A, DGE is defined by nasogastric intubation lasting longer than POD 3, reinsertion of nasogastric tube after the POD 3, or intolerance of solid diet by POD 7. Grade B DGE constitutes of nasogastric intubation lasting for 8 to 14 PODs, the need to re-insert the nasogastric tube after POD 7 or intolerance to a solid diet by POD 14. Grade C DGE comprises of nasogastric intubation lasting for more than POD 14, reinsertion of nasogastric tube after POD 14, or intolerance of a solid diet by POD 21 [74].

Several interventions regarding the surgical technique and the postoperative management of the patients have been reported in the literature to reduce the rate of DGE.

Technical Approaches to Reduce the Rate of DGE

Various surgical techniques have been investigated in studies to examine their effect on development of DGE (Table 3). The pylorus-preserving pancreaticoduodenectomy (PPPD) was introduced in 1977 by Traverso and Longmire and has raised great interest as a more physiologic modification of a standard pancreaticoduodenectomy. In addition, some have speculated that it may decrease the rate of DGE [75–77]. Literature comparing classic PD with PPPD is abundant; however, it is mostly comprised of retrospective studies and only a limited number of large-scale RCTs is available.

After a PPPD, the two reconstruction methods employed are either an antecolic or a retrocolic anastomosis. Therefore, the question arises if the method of reconstruction has any effect on the incidence of DGE. Initially, retrospective reports indicated that antecolic reconstruction was associated with a lower incidence of DGE [78, 79]. In 2006, Tani et al. reported a RCT that compared the incidence of DGE in patients who underwent either an antecolic or a retrocolic reconstruction during a PPPD [80]. The study comprised of 40 patients and reported a significantly high incidence of DGE in patients receiving a retrocolic reconstruction as compared to those who underwent an antecolic duodenojejunostomy (50 % vs. 5 %, p=0.0014). Moreover, patients with antecolic reconstruction had a shorter duration of postop NG drainage, shorter length of hospital stay, and early ability to tolerate a solid diet [80]. Another trial was subsequently carried out comparing an antecolic duodenojejunostomy with a vertical retrocolic duodenojejunostomy during PPPD. This trial consisted of 116 patients, larger than the previous trials, and found no significant difference in the incidence of DGE between patients who received an antecolic or a vertical reconstruction during PPPD. However, the postoperative weight recovery was significantly better in patients with vertical retrocolic duodenojejunostomy. Eshuis et al., similarly in their study on 246 patients, demonstrated no significant difference between the two techniques (retrocolic group vs. antecolic group: 45 (36 %) vs. 41 (34 %); p=0.89) [81].

Some have proposed that DGE is linked to division of the right gastric artery, or the left gastric vein leading to ischemia or congestion around the pylorus ring, respectively [82, 83]. Therefore, a RCT was conducted to compare a new surgical approach where only the pylorus ring was resected with preservation of the remainder of the stomach with a pylorus-preserving pancreaticoduodenectomy. This trial included 130 patients who were randomized to either receive a pylorus resecting or a pylorus-preserving PD. The results reported a significantly decreased incidence of DGE in the pylorus resection group as compared to PPPD (4.5 % vs. 17.2 %, p=0.0244). There was also a significant delay observed in the C-acetate breath test at 1, 3, and 6 months postoperatively in patients who underwent a pylorus-preserving PD [84].

Another variant of PD is the subtotal stomach-preserving PD (SSSPD) that comprises of removal of the duodenum and pylorus ring, has been performed in Japan since the 1990s, in patients with periampullary lesions in an attempt to maintain the pooling ability of the stomach while reducing the incidence of DGE. An RCT comparing SSSPD and PPPD comprising of 100 patients with periampullary lesions reported a lower incidence of DGE in the SSSPD group as compared to PPPD (12 % vs. 20 %, p=0.41) that was not found to be statistically significant [85]. Another RCT conducted in Japan compared antecolic reconstruction with retrocolic reconstruction in patients treated with a SSPD, and found a significant decrease in the incidence of DGE in the antecolic reconstruction group (20.8 % vs. 50 %, p=0.0364). Also, a higher incidence of grades B and C DGE was observed in the retrocolic group (27.3 % vs. 4.2 %, p=0.0234) [86].

The literature has variable findings and while several studies suggest that the incidence of DGE is higher [87–90] in patients undergoing PPPD as compared to classic PD, others report it to be contrary [79, 91–93]. Henegouwen et al. reported that that blood loss (1580 ml vs. 1247 ml; p<0.001) and

Table 3 Effects of surgical interventions on DGE following pancreatectomy

Author	Type of study	Total no. of patients	Type of intervention	Results
Yeo et al. (1999) [104]	Prospective randomized trial	114 • 56 • 58	Standard PD with enbloc removal of peri-pancreatic lymph nodes vs. radical PD with standard resection along with a distal gastrectomy and retroperitoneal lymphadenectomy	• Higher incidence of DGE in patients with radical resection (16 vs. 4 %, p=0.03)
Yeo et al. (2002) [105]	Randomized controlled trial	299 • 146 • 148	Standard PD vs. radical (standard plus distal gastrectomy and extended retroperitoneal lymph node resection)	• Higher rates of DGE (16 vs. 6 %, p=0.006) and POPF (13 vs. 6 %, p=0.05) in the radical group
Tamandl et al. (2014) [110]	Prospective randomized study	64 • 36 • 28	Antecolic vs. retrocolic reconstruction of the duodenojejunostomy after pylorus-preserving PD	• Incidence of DGE on POD 10 17.6 % in the antecolic group vs. 23.1 % in the retrocolic group. (p=0.628) • No significant difference between the two approaches
Kurahara et al. (2011) [86]	Prospective randomized controlled study	46 • 22 • 24	Retrocolic vs. antecolic reconstruction after pancreatoduodenectomy	• Significantly higher incidence of DGE in the retrocolic group compared to antecolic reconstruction (50 % vs. 20.8 %, p=0.0364). • Higher incidence of grade B/C DGE in the retrocolic group (27.3 vs. 4.2 %, p=0.0234)
Kawai et al. (2011) [84]	Prospective randomized controlled trial	130 • 66 • 64	Pylorus ring resection vs. pylorus preservation during pancreatoduodenectomy	• Significantly decreased incidence of DGE in intervention group (4.5 vs. 17.2 %, p=0.0244) • Significant delay in C-acetate breath test at 1, 3, and 6 months postoperatively in pylorus-preserving PD
Matsumoto et al. (2014) [85]	Prospective randomized comparison	100 • 50 • 50	Pylorus-preserving pancreatoduodenectomy (PPPD) vs. subtotal stomach-preserving pancreatoduodenectomy (SSPPD)	• No significant difference in incidence of DGE between PPPD and SSPPD (20 vs. 12 %, p=0.414)
Mack et al. (2004) [103]	Prospective, randomized controlled trial	36 • 20 • 16	Gastric decompression and enteral feeding by a double-lumen gastrojejunostomy tube	• 25 % controls had prolonged gastroparesis as compared to none in the intervention group (p=0.03) • Significantly longer hospital stay in controls (p=0.01)
Tani et al. (2006) [80]	Prospective, randomized controlled trial	40 • 20 • 20	Antecolic vs. retrocolic duodeno-jejunostomy during pylorus-preserving pancreaticoduodenectomy	• Significantly high incidence of DGE in retrocolic approach as compared to antecolic (5 vs. 50 %, p=0.0014) • Significantly shorter duration of postoperative NG drainage, early ability to take solid foods, and significantly shorter hospital stay in patients with antecolic route
Tien et al. (2009) [111]	Prospective randomized trial	247 • 123 • 124	Modified Roux-en-Y gastrojejunostomy reconstruction with placement of a jejunostomy feeding tube vs. conventional gastric bypass (control group)	• No significant difference in incidence of DGE between the two groups • Grades of DGE were significantly lower in the modified group as compared to the control group (p=0.01)
Shimoda et al. (2013) [99]	Prospective randomized trial	101 • 52 • 49	Billroth II vs. Roux-en-Y reconstruction for the gastrojejunostomy during subtotal stomach-preserving pancreaticoduodenectomy	• Significantly lower incidence of DGE in the Billroth group vs. the R-Y group (5.7 vs. 20.4 %, p=0.028) • Significantly shorter duration of hospital stay in the Billroth group
Imamura et al. (2014) [112]	Prospective randomized clinical trial	116 • 58 • 58	Antecolic vs. vertical retrocolic duodo-jejunostomy during pylorus-preserving pancreaticoduodenectomy	• No significant difference between the two groups in incidence of DGE.

Table 3 (continued)

Author	Type of study	Total no. of patients	Type of intervention	Results
				• Better weight recovery in the vertical retrocolic group at 12 months post operatively
Gangavatiker et al. (2011) [66]	Randomized controlled trial	72 • 35 • 37 (68 included in final analysis)	Antecolic vs. retrocolic gastro/duodeno-jejunostomy during pancreaticoduodenectomy (Whipple/pylorus-preserving PD)	• No significant difference in the incidence of DGE between the two groups • Age significantly associated with occurrence of DGE
Tran et al. (2004) [95]	Prospective, randomized multicenter analysis	170 • 83 • 87	Pylorus preserving pancreaticoduodenectomy vs. standard Whipple procedure	• No significant difference in operation time, volume of blood loss, length of hospital stay, mortality, morbidity, and incidence of DGE between the two groups
Eshuis et al. (2014) [81]	Randomized control trial	246 • 125 • 121	Antecolic vs. retrocolic route of gastroenteric anastomosis after PD	• No significant difference in incidence of DGE in retrocolic group and antecolic group (45 (36 %) vs. 41 (34 %); p=0.89)
Srinarmwong et al. (2008) [113]	Randomized control trial	27	Standard Whipple's vs. PPPD	• DGE was more common in patients undergoing PPPD
Wellner et al. (2012) [27]	Randomized controlled trial	116 • 59 • 57	Pancreaticogastrostomy vs. pancreaticojejunostomy after partial PD	• DGE (27 vs. 17 %, p=0.246) and intraluminal bleeding (7 vs. 2 %, p=0.364) more frequent with PG but no statistically significant difference

operative time (6 h vs. 4.8 h; $p<0.001$) was higher for the PD group and while incidence of DGE was higher in the PPPD group, there was no significant difference in between the two groups (37 % vs. 34 %; $p>0.005$) [88]. Contrastingly, Sadowski et al. reported a higher rate of DGE in patients undergoing classic PD when compared to PPPD in their prospective study (57 % vs. 20 %; $p=0.05$) [91]. Tran et al. and Seiler et al. reported no significant difference in the incidence of DGE between classic PD and PPPD groups [94, 95].

During the construction of the gastroenterostomy or duodenoenterostomy, factors related to the technique of the construction have been associated with development of DGE. Development of edema or kinking at the anastomotic site at either the efferent or afferent limb or any potential obstruction in this area could not only contribute to the development of DGE but also cause a rise in biliary and pancreatic outflow pressures resulting in an increased risk of sepsis and fistula formation. Therefore, the creation of an enteroenterostomy between the afferent and efferent limbs distal to the gastroenterostomy or duodenoenterostomy could decrease the chance of kinking at the anastomosis site and also direct the pancreatic and bile secretions away from the stomach. Such an enteroenterostomy was described by Braun over 100 years ago [96, 97]. Nikfarjam et al. published a study where 20 patients underwent a standard antecolic gastroenterostomy while the subsequent 24 patients underwent the same procedure along with the addition of a Braun enteroenterostomy (BEE) [96]. Results showed a significantly lower incidence of DGE in the BEE group vs. the standard reconstruction group (4.2 % vs. 35 %, $p=0.008$). Moreover, 85.7 % of patients in the standard reconstruction group who developed DGE had a grade C DGE. There was no significant difference between the two groups in the development of POPF [96]. Similarly, a recent retrospective review comparing patients who underwent PPPD with BEE vs. patients who underwent PPPD without BEE was performed. The results showed a significantly lower incidence of DGE in patients who underwent PPPD with BEE as compared to those who underwent PPPD without BEE (4 % vs. 21 %, $p<0.01$) [98].

Billroth II reconstruction for gastrojejunostomy or duodenojejunostomy with a Braun anastomosis provides two routes for the passage of gastric contents to the jejunum as compared to Roux-en-Y (R-Y) reconstruction. A randomized controlled study from Japan compared the effect of Billroth II vs. R-Y reconstruction of the gastrojejunostomy during SSSPD. The study showed a significantly reduced incidence of DGE in patients with Billroth II reconstruction as compared to R-Y reconstruction (5.7 % vs. 20.4 %, $p=0.028$). Moreover, the duration of hospital stay was significantly shorter in patients with patients who received a Billroth II reconstruction [99].

Patients with periampullary carcinomas are frequently malnourished [88, 100–102]. DGE is a common complication after PD, which affects the nutritional status of the

Table 4 Effects of non-surgical interventions on DGE following pancreatectomy

Author	Type of study	No. of patients	Type of intervention	Results
Yeo et al. (1993) [106]	Prospective, randomized, placebo-controlled trial	118 • 58 • 60	IV erythromycin 6-hourly from third to tenth postoperative days vs. equal volume of 0.9 % saline	• 37 % reduction in incidence of DGE in the intervention group
Kollmar et al. (2008) [114]	Prospective, randomized, double-blinded placebo-controlled trial	67 • 35 • 32	Prophylactic octreotide	• No effect on gastric emptying and incidence of POPF
Ohwada et al. (2001) [82]	Prospective randomized controlled trial	31 • 14 • 17	Low-dose erythromycin 8 hourly from POD 1 to 14 vs. H-2 receptor antagonists and gastrokinetic drugs after Billroth-I pylorus-preserving PD	• 75 % reduction in incidence of DGE in the intervention group • Decreased duration of nasogastric drainage • Early resumption of oral intake
Shan et al. (2005) [115]	Prospective randomized controlled trial	23 • 11 • 12	Somatostatin prophylaxis	• Incidence of DGE 82 % in intervention group vs. 25 % in the control group ($p<0.01$) • Somatostatin increased the half time of solid phase emptying • Somatostatin reduced fasting plasma motilin levels and caused prolonged suppression of plasma motilin as compared to the control group

patient and often requires gastric decompression. Therefore, a randomized controlled trial comparing the routine placement of a double-lumen gastrojejunostomy tube (GJT) for enteral feeding (via the jejunal port) and gastric decompression (via the gastric port without a nasogastric tube) during PD vs. routine care following PD was carried out. The study found no prolonged gastroparesis in patients who had received a GJT whereas 25 % of controls experienced prolonged gastroparesis ($p=0.03$). Moreover, patients with a GJT placed had a shorter duration of hospital stay and reduced hospital costs as compared to controls [103].

In 1999, Yeo et al. published a RCT comprising of 114 patients [104] to either undergo standard PD with en bloc removal of peri-pancreatic lymph nodes or a radical resection which included a distal gastrectomy and removal of retroperitoneal lymph nodes along with a standard resection. This study was not aimed at studying DGE after PD and although there were no significant differences in clinico-pathological characteristics of these patients including intraoperative blood loss, transfusion requirements, location, and size of the primary tumor and lymph node or positive margin status, the incidence of DGE was higher in the radical vs. the standard resection group (16 vs. 4 %, $p=0.03$) [104]. Subsequently, Yeo et al. published another randomized controlled trial comparing the same surgical techniques and concluded that although mortality was similar between patients who undergo standard pancreaticoduodenectomy vs. radical pancreaticoduodenectomy, the morbidity is increased in the radical group with higher rates of both DGE (16 % vs. 6 %, $p=0.006$) and POPF (13 % vs. 6 %, $p=0.05$) [105].

Postoperative Approaches to Reduce the Rate of DGE

Various non-surgical interventions and their effects on the incidence of DGE have been reported in literature (Table 4). One hypothesis for the pathogenesis of DGE is gastric atony due to reduced levels of circulating motilin [71]. Erythromycin, a macrolide antibiotic, acts as a motilin agonist [106]. A randomized controlled trial in 1993 compared the effects of administrating intravenous erythromycin (200 mg every 6 h) from postoperative day 3 to postoperative day 10 vs. administering 0.9 % saline. The results showed a reduction of 37 % in the incidence of DGE in the erythromycin group. Similarly, another randomized controlled trial comparing the effect of erythromycin administration from POD 1 to 14 vs. gastrokinetic drugs, and H2 receptor antagonists showed a 75 % reduction in the incidence of DGE for the erythromycin group. The patients who received erythromycin also had a reduced duration of nasogastric tube drainage and early resumption of oral diet [82].

Somatostatin and its analogues may be used after a PD in an attempt to reduce postoperative complications arising from pancreatic leakage since somatostatin reduces pancreatic exocrine and endocrine secretions [107]. However, it was identified in a study that patients who received

somatostatin prophylaxis after PPPD had a much higher incidence of DGE of around 80 %, whereas the incidence of DGE remained the same in patients who underwent conventional PD [108]. Subsequently, a randomized controlled trial was carried out to confirm this observation where 23 patients were randomized to either somatostatin prophylaxis or no somatostatin prophylaxis after PPPD. The study showed a significantly higher incidence of DGE in patients who received somatostatin prophylaxis as compared to those who did not (82 % vs. 25 %, $p<0.01$). Somatostatin increased the half time of solid phase emptying, reduced fasting plasma motilin levels, and caused prolonged suppression of plasma motilin as compared to the control group. Another randomized controlled trial compared the effect of octreotide, a long-acting somatostatin analogue, on the development of DGE. The study included 67 patients who were randomized to either the octreotide group or the control group. The results showed no significant difference in the incidence of DGE between the two groups. Moreover prophylactic octreotide did not reduce the incidence of POPF formation.

Conclusion

Both DGE and POPF cause considerable morbidity in patients undergoing pancreatic resection and while a substantial decrease has been observed in the mortality from the procedure, the morbidity still remains high. While multiple randomized control trials have shown a variable degree of efficacy of using both surgical and non-surgical interventions to reduce the rates of these complications conflicting results have been observed. There is still a need for further large-sample randomized trials to better understand the pathophysiology of these complications, in order to treat prevent them.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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