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Delayed Gastric Emptying After Pancreatic Surgery: A Review

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Abstract

Background: Delayed Gastric Emptying (DGE) after pancreatic surgery is a common postoperative complication. In literatures, the reported incidence of DGE after pancreatic surgery varies considerably and, in 2007, The International Study Group of Pancreatic Surgery (ISGPS) came up with a standard definition with grades of DGE. It has been associated with prolonged ICU and hospital stays, compromise in quality of life of patient, severe fatigue, and general malnutrition.

Pathogenesis and treatment: After a review of literatures on DGE after pancreatic surgery, it is clear that the pathogenesis has been speculated to involve several factors which are; gastric dysrhythmias, gastric atony, ischemic injury to antropyloric muscle mechanism, a decrease in circulating levels of motilin, preoperative diabetes, increased exposure of the newly created duodenojejunostomy environment to gastric volume, anastomotic disruptions at the pancreaticojejunostomy, and transient pancreatitis. Nevertheless, the true mechanism of DGE is still unclear. The treatment includes use of pharmacological drugs like motilin receptor agonists, drugs targeting gut hormones, ghrelin receptor agonist, and glucose dependent insulinotropic polypeptide. Several modifications to operative techniques have been suggested. However, the treatment and prevention strategies carried their own limitations.

Conclusion: ISGPS came up with a standard definition but it has not yet been accepted universally. DGE remains a serious problem and higher quality randomized trials with sufficient sample sizes are needed.

Keywords: DGE; Duodenojejunostomy; ISGPS; Pancreatitis; Pancreaticojejunostomy; Pancreatic Surgery

Introduction

Delayed Gastric Emptying (DGE) is especially common after pancreatic surgery, and can prolong ICU and hospital stays [1,2]. DGE, also known as gastroparesis, is the partial paralysis of the stomach whereby food remains for an abnormally long time. The vagus nerve controls the contractions of the stomach to move food down the small intestine for digestion, assimilation and absorption. DGE may occur when the vagus nerve; the nerve of Latarjet [3]; is damaged or the muscles of the stomach and the small intestine do not function properly. The recent advances in operative techniques, intensive care medicine, interventional radiology, and better patient selection and preparation, the perioperative mortality of pancreatic surgery in high-volume centers has decreased markedly over the past decades to less than 5% [4-8]. The management of post-operative morbidity has also improved [9,10]. However, DGE remains a troublesome postoperative complication after pancreatic surgery. It is described as a complication not only leading to patient discomfort, increased costs, greater number of hospital readmissions, compromise quality of life but also inheriting the risk of silent aspiration and aspiration pneumonia [11,12]. It is highly important for the pancreatic surgical team to improve gastric emptying and restore tolerance for enteral nutrition because the latter has the benefits of preserving intestinal integrity, preventing mucosal atrophy and avoiding bacterial translations, over parenteral feeding [13]. In addition, the primary complications cause by DGE include fluctuations in blood glucose due to unpredictable digestion times, especially in diabetic patients, severe fatigue and weight loss due to calorie deficit, intestinal obstruction due to formation of bezoars, bacterial infection due to overgrowth in undigested food, and general malnutrition [14]. This review will focus on the concise overview of DGE after pancreatic surgeries which includes its' current understanding of the pathogenesis, clinical manifestations and treatment.

Historical Background

DGE after pancreatic surgery was first clinically coined by Warshaw in 1985 [15]. Since that moment DGE was poorly defined in literature because several surgical centers use a different definition of DGE. Similarly, in 2002, Yong-Hyun Park, et al. [16] defined DGE as a either a nasogastric tube producing 300mL/day at the end of 10 days or its reinsertion because of vomiting or failure to tolerate a regular diet after 14th postoperative day while Makhija, et al. [17] defined DGE as the need of nasogastric tube for more than 7 days or withholding oral fluids for more than 7 days after surgery. Hence, valid comparisons of different study reports and operative techniques were not possible till the International Study Group of Pancreatic Surgery (ISGPS) developed an objective and generally applicable definition with grades of DGE based primarily on severity and clinical impact, in 2007 (Table 1).

DGE grade	NGT (nasogastric tube) required	Unable to tolerate solid oral intake by POD (postoperative day)	Vomiting gastric distention	Use of prokinetics
A	4-7 days or reinsertion > POD 3	7	+/-	+/-
B	8-14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+

Table 1: Consensus definition of DGE after pancreatic surgery.

The mild, moderate and severe forms of DGE after pancreatic surgery can be classified into grades A, B and C by their clinical impact. The necessity of NGT between POD4 and 7, or if NGT must be reinserted due to nausea and vomiting after removal by POD3 and the patient cannot tolerate solid food on POD7 but can resume solid diet before POD14, this condition is classified as grade A DGE. The need of NGT between POD 8 and 14, or if NGT must be reinserted after POD7, or if unlimited oral intake cannot be tolerated by patient by POD14 but can resume solid oral diet before POD21, this condition is classified as grade B DGE. The continuous dependency on NGT or reinsertion after POD14, or if patient cannot tolerate unlimited oral intake by POD21, this condition is classified as grade C DGE [18].

Pathogenesis and risk factors

DGE results in compromise of quality of life of a patient after pancreatic surgery, however, the true mechanism is still unclear, and its pathophysiology has not been elucidated, and hence, prevention will lack effectiveness. The pathogenesis of DGE after pancreatic surgery has been speculated to involve several factors [3,19-22]. It is believed to occur due to gastric dysrhythmias secondary to some intra-abdominal complications such as pancreatic fistula, intraperitoneal abscess, local inflammation, such as inflammation of pancreaticoenterostomy and edema from duodenojejunostomy [21,23]. Pancreatic fistulas have been showed to be associated with fatal consequences such as intra-abdominal bleeding and abscess [24]. Besides, one of the triggering factors is gastric atony after resection of the duodenal pacemaker and disruption of gastroduodenal neural connections [3,25,26]. This is due to the consequences of nerve damage, commonly the nerves of Latarjet [3,22], resulting from extended dissection of lymph nodes along the common hepatic artery. The ischemic injury to antropyloric muscle mechanism [22], during pancreas surgery, due to dissection of right gastric artery [27], has a part to play in the occurrence of DGE. This concept is supported by recent reports comparing standard pancreatic surgeries with addition of pyloric dilatation or pyloromyotomy suggested a decrease in DGE after these modified techniques (26% versus 7% and 25% versus 2% respectively) [28,29].

Moreover, it is considered that a decrease in circulating levels of motilin [25,30]; a polypeptide hormone which causes an increased motility of several portions of gastrointestinal tract, plays a vital role. A reduction in motilin levels is caused by resection of duodenum and proximal jejunum [31]. This is supported by the observation that patients undergoing distal pancreatectomy rarely develop DGE. The comparative studies of duodenum-preserving pancreatic head resection versus pancreatoduodenectomy suggest a lesser rate of DGE after duodenum-preserving pancreatic head resection [20,32,33]. In addition, preoperative diabetes was strongly and consistently associated with DGE. Several abnormalities are considered to contribute to it. They are namely autonomic neuropathy, enteric neuropathy involving excitatory and inhibitory nerves, acute fluctuations in blood glucose, incretin-based medications used to normalize post-prandial blood glucose and psychosomatic factors [16,34].

Furthermore, it is believed that a situation predisposing to DGE could result when the newly created environment of duodenojejunostomy is exposed to increased gastric volume due to external pancreatic juice drainage. This was supported by the 50% incidence of DGE in the retro group of the study by Tani, et al. [35] is comparable with the reported incidence of 33% after pancreatic surgery when retrocolic reconstruction was done and pancreatic juice was not allowed to enter the intestine because the pancreatic tube was exteriorized. The exteriorization of pancreatic juice markedly increases gastric secretion and deteriorated gastric motor activity, owing to a higher acid output caused by elevated gastrin levels [36]. On top of that preoperative biliary drainage has

been associated with low postoperative DGE incidence because bile reflux into stomach has been thought to be involved in the pathogenesis of DGE [16]. Besides, anastomotic disruptions at the pancreaticojejunostomy due to torsion or angulation of the reconstructed alimentary tract increases the incidence of DGE [37]. Therefore, technical approaches to pancreatic surgery have thought to play roles in the etiology of gastroparesis. Previous studies of surgical methods have claimed that classic Whipple versus pylorus-preservation, antecolic versus retrocolic gastric/duodenal reconstruction, pancreaticogastrostomy versus pancreaticojejunostomy reconstruction, duodenal preservation in benign disease, and even preservation of the right gastric artery can influence DGE. Nevertheless, these studies have been limited to a small sample size and the results have been mixed. This has resulted in the absence of a consensus regarding the influence of surgical technique in DGE [38].

In addition, an association between postoperative pancreatitis and delayed gastric emptying has been reported in literatures [18]. The diagnostic criteria for postoperative pancreatitis after pancreatic surgery have not been well defined as amylase measurement is not sensitive enough. However, CT – as the gold standard for the diagnosis of acute pancreatitis – should at least detect the severe cases. The commonly accepted CT criteria for pancreatitis, is used [39]. CT could detect the pancreatitis in 60% of cases on day 2. This speaks for the very early onset of postoperative pancreatitis. The detection of pancreatitis in CT in 40% cases not until day 5 does not necessarily indicate it started then, because there is usually a delay of at least 1-2 days in other etiologies before pancreatitis changes can be observed in CT [40]. Interestingly, Murakami, et al. [41] found an association with delayed gastric emptying and acinar cell necrosis, lobular fibrosis, and inflammatory cell infiltrations in pancreatic specimen taken during pancreatic surgery. These are typical histopathologic changes in acute or chronic pancreatitis [42]. Hence, it might be possible that pancreatitis, either persisting from preoperative period, beginning postoperatively, or during the surgery right after transecting the pancreas with the release of multiple local and systematic mediators of inflammation is the trigger that later influences the gastric motility. Poor gastric motility is a well-recognized condition during pancreatitis [43]. Postoperative pancreatitis might be one important reason for the induction of delayed gastric emptying.

Epidemiology

The incidence of DGE is unclear. It is considered as the most frequent complication following the pancreatic surgeries with published incidences of up to 61%. While most studies, on the other hand, report DGE frequencies between 11% and 57% [18,44-47]. Initially, Pylorus-Preserving Pancreaticoduodenectomy (PPPD) was initially reported to be associated with a higher incidence of gastroparesis compared with standard Whipple procedure with antrectomy, but this statement was later revoked [3,48-50]. One report, stated that rate of DGE decreased from 17% to 6% over a ten-year period [51]. In univariate and multivariate analyses, gender was significantly associated with DGE, revealing significantly more women without DGE. This is supported by the findings of Fabre, et al. [52], although the pathophysiologic background is not evident.

Clinical manifestations

The awareness of the variety of clinical manifestations of patients with DGE, after pancreatic surgeries, is highly important. The most common symptoms include chronic nausea (93%), vomiting (68-84%), abdominal pain (46%-90%) [14]. Other symptoms may include myalgia, erratic blood glucose levels, gastroesophageal reflux, heartburn, lack of appetite, muscle weakness, night sweats, palpitation, morning nausea, spasms o stomach wall, weight loss and malnutrition. However, vomiting may not occur in all cases as patients may adjust their diets to include only small amounts of food [13]. Vomiting is uncommon in DGE grade A, according to ISGPS definition of DGE, whereas DGE grades B and C, there is usually vomiting. This perhaps indicate consideration of a trial of prokinetic drugs, such as erythromycin or metoclopramide, as used in idiopathic or diabetic gastroparesis [18].

Diagnosis

In clinical practice, distinguishing DGE from postoperative ileus and ruling out mechanical obstruction, is vital with respect to the management of DGE [53]. During the postoperative period after pancreatic surgery, DGE without mechanical obstruction can occur due to vagotomy [54-57]. The surgical team must be aware of clinical pitfalls as a technical problem at the anastomosis, for example, a stenosis or other mechanical obstruction, can lead to complete obstruction, which should not be classified as DGE. Therefore, DGE should be justified by abdominal imaging during postoperative periods [47].

Treatment

The treatment of DGE emphasize on close observation and timely monitoring. The maximum duration for a patient to return to oral feeding reported in literature is 6 to 7 weeks. The first steps include the use of Naso-Gastric Tube (NGT) and prokinetics. The time of removal of NGT was determined when drainage is less than 500mL/day. The pharmacological management includes usage of prokinetic drugs. Motilin receptors agonists like erythromycin have shown to decrease postoperative DGE. It binds to motilin receptors thereby triggering phase 3 of the gastric migratory motor activity complex. The prophylactic use of erythromycin has showed a reduction of 53% to 75% in incidence of DGE [58]. If DGE persists, endoscopic insertion of a jejunal feeding tube, followed by low dose (20mL/h) enteral feeding, is recommended.

Usually DGE will resolve within few days. However, routine placement of a jejunal tube during surgery cannot be recommended at present [58,59]. Another recommendation is the prophylactic use of somatostatin analogues after pancreatic surgeries, which has proved a decrease in DGE occurrence with authors opting for its' routine use [60]. Besides, hormones are modulators of powerful regulatory mechanisms of gastric motility and emptying. Thus, studies must be carried out to identify possible pharmacological interventions targeting gut hormones.

Recently, the most advanced option s motilin receptors agonist with non-macrolide properties (ABT-229 and mitemcinal GM-611). The development of synthetic non-peptide ghrelin receptor agonist (TZP-101 and TZP-102), competitive CCK-1 receptor agonist (Dexloxiglumide) and GLP-1 receptor antagonist (exendin 9-39) [61,62]. Focusing on prevention of insulin resistance may be effective in prevention of DGE because decreased insulin resistance has proved to be related to DGE. One of the important foci of perioperative management is Enhanced Recovery After Surgery (ERAS). ERAS protocol recommends metabolic control, starting pre-operatively with a short period of preoperative fasting and carbohydrate loading up to hours before surgery. Carbohydrate loading reduces postoperative insulin resistance and may therefore be effective in prevention of DGE [63]. Moreover, Glucose Dependent Insulinotropic Polypeptide (GIP) are incretin hormones which stimulates gastric emptying and responsible for most of the insulin secreted after a meal. In the past, it was once believed to slow gastric motility and delay gastric emptying [64]. However, results of a study with exogenous administration show a modest increase in gastric motility after intra-venous infusion. GIP at a low dose increases the emptying rate of the proximal part whereas no difference is seen with a high dose. The distal part of stomach empties slower with GIP at a low dose while a high dose increases the emptying of the distal part [65]. This effect may also be attributed to the incretin effect of GIP, which lowers blood glucose level leading to an enhanced gastric emptying. Nevertheless, the available pharmacological therapy carries limitations in terms of sustained efficacy and side effects. Prokinetic drugs like erythromycin carries the possibility of producing antibiotic resistance and cardiac toxicity. Besides, the overall physiology, pathophysiology and therapeutic potential of gut hormones are still not fully understood, which currently limits their development as drug targets for use in postoperative DGE. Moreover, the unfavorable pharmacokinetic profile and the weak biological effects of native GIP limit its effectiveness for the treatment of delayed gastric emptying. The complex dose-response relationship and the issue of selectivity appear to hamper the development of GIP analogues for specific use in delayed gastric emptying.

Furthermore, operative techniques during pancreatic surgeries can influence DGE. In 2015, a meta-analysis comparing Roux-en-Y and Billroth II reconstruction (Figure 1). after pancreaticoduodenectomy found that DGE frequency can be lowered when using Billroth II [66].

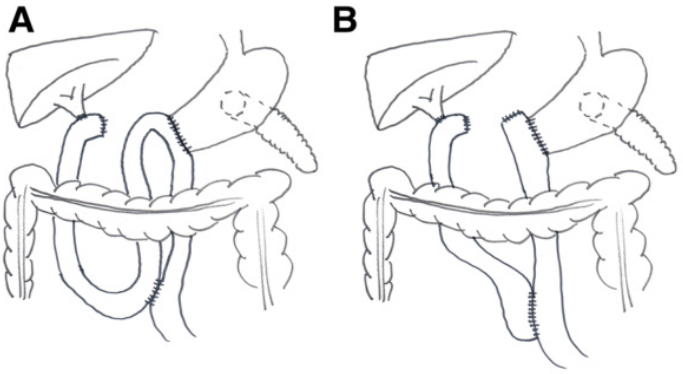

Figure 1: Schematic drawing of pancreatoduodenectomy with Billroth-II. **(A):** Reconstruction. **(B):** Roux-en-Y reconstruction.

However, the limitation of this study was the different understanding of the surgical reconstruction methods. Two studies compared conventional single loop reconstruction with Roux-en-Y reconstruction, while one study intentionally compared Roux-en-Y and Billroth II, again favoring Billroth II reconstruction [67]. Besides, antecolic reconstruction over retrocolic reconstruction of gastro-duodeno-jejunostomy is one of the most commonly recommended procedures from the perspective of reducing incidence of postoperative DGE (Figure 2). The incidence of DGE has been reported to be more than 30% for the retrocolic route compared with less than 15% for antecolic route, favoring antecolic reconstruction approach [68,69]. The antecolic reconstruction involves a region that is not in close proximity to areas that have risks of anastomotic leaks, such as pancreaticojejunostomy site or choledochojejunostomy site, thus minimizing possible negative effects of an infected collection and that the mechanical twisting and bending of the reconstructed digestive tract, which could compromise the venous draining of the jejunal loop, can be kept to a minimum. This reconstruction method has the benefit of eliminating gastric contents, promoted with gravity [70].

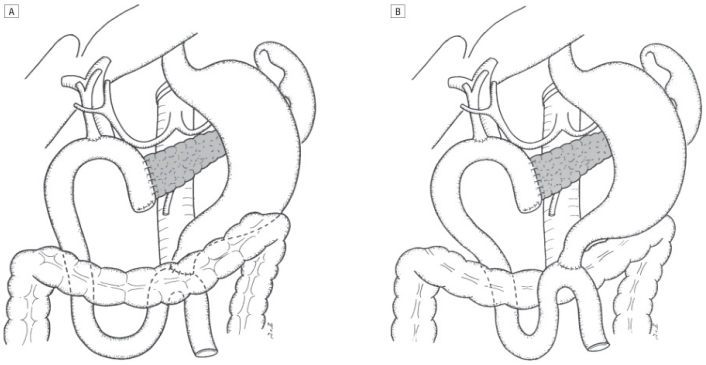

Figure 2: (A): Pylorus-preserving Whipple procedure with retrocolic duodenojejunostomy. vs **(B):** Antecolic duodenojejunostomy.

However, there are studies which have revoked the idea that technical approach during pancreatic surgeries have a role to play in incidence of DGE. It is stated that DGE cannot be influenced by either Billroth II or Roux-en-Y reconstruction. The single loop (conventional reconstruction) and Roux-en-Y (dual loop) reconstruction show no difference [71]. Moreover, it was reported, by recent studies, that the route of gastro-duodenojejunostomy reconstruction after pancreaticoduodenectomy does not affect postoperative incidence of DGE [72]. A recent meta-analysis also found that Braun's entro-enterostomy had significantly lower rate of clinically relevant DGE (grades B and C), however, there was no difference in the incidence of overall DGE (grades A, B and C) [73]. Besides, since the incidence of DGE was reported to be related to pylorospasm, modifications like pyloric dilatation and pylorus resection were introduced [29]. More recently, the concept of pyloric ring resection was introduced to preserve the reservoir function of the stomach and simultaneously tackle the problem of pylorospasm without the need for pyloromyotomy or pyloric dilatation [74,75].

In addition, therapy of DGE can be done based on the definition with grades of DGE developed by ISGPS. Usually there is no marked change in management of DGE grade A other than by minor disturbances in the return to intake solid food. The treatment with prokinetic drugs and parenteral or enteral nutritional support is necessary for DGE grade B. This sometimes may lead to the reinsertion of the NGT. Hence, DGE grade B is associated with prolonged postoperative hospital stay and compromised quality of life of the patient. Besides, some form of nutritional support is required in patients with DGE grade C. It is claimed that DGE grade C is linked with other postoperative complications, such as pancreatic fistula or intraabdominal abscess. The need of radiologic imaging or on occasion relaparotomy may be required for further evaluation of patients with DGE grades B and C [18].

Conclusion

Finally, via this review we conclude that the prognosis of DGE after pancreatic surgery is poor because of the lack of sufficient studies with respect to the pathogenesis and risk factors. ISGPS definition of DGE has been used in majority of studies published after 2010. There is wide variation in reported incidence rates despite standardization of the definition by ISGPS. There are evidences that postoperative complications, pancreatic fistulas and preoperative diabetes were strongly and consistently associated with DGE. Abdominal imaging can differentiate between postoperative DGE and mechanical obstruction, once diagnosed, specialized treatment should be prompted. The development of pharmacological treatment like motilin receptors agonists with non-macrolide properties has proved more effective in DGE management. Operative techniques like pyloric dilatation, Billroth II reconstruction and Braun's entro-enterostomy have been found to be associated with decreased incidence of DGE but these results are mostly based on retrospective data and hence should be interpreted with caution. Although superiority of antecolic reconstruction with regards to DGE has been shown in retrospective studies, the randomized trials have failed to demonstrate a clear advantage. Thus, it is very difficult to draw any reliable conclusion from available literatures to categorically prove or reject the benefit of surgical modifications like pyloric dilatation, Billroth II reconstruction, Braun's entero-enterostomy and antecolic reconstruction. Pyloric ring resection seems to be the most promising surgical modification but needs to be tested in high quality randomized trials with sufficient sample size. Therefore, DGE remains a serious problem and the solution remains elusive despite constant efforts by pancreatic surgeons.

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