Langenbecks Arch Surg (2016) 401:161–167
DOI 10.1007/s00423-016-1374-7

ORIGINAL ARTICLE

Risk factors for delayed gastric emptying following distal pancreatectomy

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Received: 3 August 2015 / Accepted: 17 January 2016 / Published online: 27 January 2016

Abstract
Purpose Delayed gastric emptying (DGE) is a frequent complication after pancreatoduodenectomy and other types of upper gastrointestinal surgery with published incidences as high as 60 %. The present study examines the incidence of DGE following distal pancreatic resection (DPR).
Methods Between 2002 and 2014, 100 patients underwent conventional DPR at our department. DGE was classified according to the 2007 International Study Group of Pancreatic Surgery definition. Patients were analyzed regarding severity of DGE, morbidity and mortality, length of hospital stay, and demographic factors.
Results Overall incidence of DGE was 24 %. No difference in age, gender, or other demographic factors was observed in patients with DGE. Perioperative characteristics (splenectomy rate, closure technique of the pancreatic remnant, operation time, blood loss and transfusion, ICU, ASA score) were comparable. Major complications were associated with DGE (11/24 patients (46 %) vs. 19/76 patients (25 %) without DGE) and the rate of pancreatic fistula was significantly higher in the group of patients with DGE (14/24 patients (58 %) vs. 27/76 patients (36 %), $P=0.047$). In multivariate analysis, a periampullary malignancy was shown to be a significant factor for DGE development. DGE significantly prolonged hospital stay (14 vs. 22 days).
Conclusions DGE is a substantial complication not only after pancreatoduodenectomy, but it also occurs frequently after DPR. Prevention of pancreatic fistula might reduce its incidence, especially in patients with malign pathology.

Keywords Distal pancreatic resection · Distal pancreatectomy · Pancreatic left resection · Delayed gastric emptying · DGE

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Introduction

Delayed gastric emptying (DGE) is the most frequent complication following pancreatoduodenectomy (PD) with published incidences of up to 60 % [1, 2], while most studies report DGE frequencies between 11 and 35 % [3–8]. Although DGE is not life-threatening and self-limiting in most instances, it distinctly impairs patient comfort, delays hospital stay, and significantly contributes to health care costs [9]. Therefore, strategies are needed to identify risk factors to lower the incidence of DGE.

Since the first comparative study reporting DGE in pancreatic surgery by Warshaw et al. in 1985 [10], DGE has been extensively examined including studies with a high grade of evidence. Proposed causes for DGE after PD are hormonal dysbalances due to resection of the duodenum, ischemia and denervation of the stomach because of mobilization and lymphadenectomy and mechanical alterations [9]. The presence of other intraabdominal complications (fluid collections, pancreatic fistula) has also been related to DGE [3, 5, 11]. Focusing on the mechanical aspects of postresectional reconstruction, the value of pyloric preservation and the type of reconstruction (antecolic vs. retrocolic, Billroth II vs. Roux-en-Y) have been intensively examined with different results [2, 6, 12–14]. Apart from differing study designs, various definitions of DGE might be one reason for the inconsistent findings of these studies. Hence, the International Study Group of Pancreatic Surgery (ISGPS) definition by Wente et al., published in 2007 [1], was a major development in the scientific evaluation of DGE, allowing comparison of different studies from various pancreatic surgery centers for the first time.

DGE also develops after other types of upper gastrointestinal surgery including subtotal gastrectomy [15], esophagectomy [16], and hepatectomy [17, 18]. Especially after hepatectomy, no change to the mechanical structure of the gastrointestinal tract is made and the duodenum is not resected; hence, some of the classic risk factors for DGE are not relevant. While DGE after distal pancreatic resection (DPR) is seldom reported, in our clinical experience, it frequently occurs. The present study examines incidence and risk factors for DGE following DPR at our tertiary care center.

Materials and methods

Between 2002 and 2014, 100 patients underwent conventional DPR in our department. Due to the different impact of laparoscopic procedures on postoperative bowel motility [19, 20], laparoscopic DPRs were excluded from this study. Patient data were prospectively entered into a pancreatic resection database with the approval of the institutional ethics committee. Morbidity and mortality were consistently documented according to the Dindo-Clavien-classification [21].

In case of preoperative malnutrition, sip feeds were provided; parenteral nutrition was only administered when the oral route was inaccessible. No oral bowel preparation was used and oral fasting was limited to 2 h for liquids and 6 h for solids. A mid-thoracic epidural catheter was placed by default. In case of contraindications, no placement options or unsatisfactory catheter function, patient-controlled-analgesia with opioids was the alternative. Anesthesia was carried out according to guidelines (postoperative nausea and vomiting-prophylaxis if required, near-zero fluid balance and close glycemic control). DPR was performed via a left subcostal incision. After complete exploration of the abdomen, the pancreatic tail was mobilized and resection was performed by scalpel (closure with isolated ligation of the pancreatic duct followed by a slow absorbable USP 4-0 monofilament suture) or with a linear stapler (Ethicon TL 60 mm) at the discretion of the surgeon. In case of malignancy, regional lymph nodes and spleen were removed en-bloc with the distal pancreas by default. Two soft drains were placed at the pancreatic remnant before closure of the abdomen. These were removed on postoperative day (POD) 3 when no elevated amylase content (compared to serum amylase) was measured. A 14 French nasogastric tube (NGT) was placed and removed at the end of surgery by default. If NGT had to be left in place (e.g., need for prolonged respirator therapy), it was removed when the output fell below 500 ml/day. Liquid diet was allowed from the evening of the day of surgery, while from POD 1, solid food was offered and the diet was increased according to standard protocol (POD 1 fat reduced/easily digestible, POD 2 fiber reduced/easily digestible, POD 3 basic diet (no pulses/cabbage), POD 4 normal diet). If no bowel movement had occurred by POD 2, oral laxative (magnesium sulfate) was administered. Transition to a normal diet was discontinued in case of vomiting. All patients received perioperative antibiotic (aminopenicillin plus β-lactamase inhibitor) and weight-adapted thrombosis prophylaxis (continued for 4 weeks after hospital discharge plus elastic stockings) but no secretion inhibitor (octreotide) on a regular basis. Beginning on the evening of the day of surgery, scheduled mobilization and breathing therapy were carried out by physiotherapists.

DGE was recorded in accordance with the 2007 definition of the International Study Group of Pancreatic Surgery (ISGPS). DGE was classified in three grades based on the duration of the nasogastric tube, the need for reinsertion, the first day when solid food was tolerated, the occurrence of vomiting and the use of prokinetics [1]. Patients before 2007 were retrospectively graded according to the ISGPS definition based on their medical records.

Data were recorded and analyzed with Excel 2013 (Microsoft Corporation, Redmond, Washington, USA) and SPSS 23 (IBM Corporation, Armonk, New York, USA). Continuous and normal distributed variables were expressed as medians ± standard deviation and analyzed using Student's *t* test, whereas non-normal distributed data was expressed as medians and interquartile range and analyzed using the Mann-Whitney *U* test. Categorical data was expressed as proportions and compared with the Pearson χ^2 or the Fisher's exact test as appropriate. Factors with $P < 0.1$ in the univariate analysis were included in multivariate stepwise logistic regression analysis. The relative risk was described by the estimated odds ratio with 95 % confidence intervals. A P value <0.05 was considered statistically significant.

Results

Both groups were comparable in terms of age and gender (Table 1). Neither preoperative factors (nicotine or alcohol abuse, weight loss) nor diabetes or the use of octreotide had an influence on the frequency of DGE. DGE significantly prolonged the hospital stay (22 vs. 14 days, $P = 0.004$). Fifty patients required surgery for malignancies, of these, 16 developed DGE. A further 50 patients underwent DPR with a benign diagnosis, of these eight developed DGE (Table 1). Thus,

Table 1 Characteristics and hospital stay

		No DGE		DGE		*P* value
		n = 76		*n* = 24		
Age, years		56 ± 14		62 ± 17		0.105
>75a		5		7		*0.007*
Gender						0.36
Male		43	(57 %)	11	(46 %)	
Female		33	(43 %)	13	(54 %)	
Smoker		32	(42 %)	9	(38 %)	0.38
Alcohol		25	(33 %)	5	(21 %)	0.26
Weight loss		22	(29 %)	6	(25 %)	0.71
Octreotid	(post)	30	(39 %)	10	(42 %)	0.85
DM	pre	16	(21 %)	7	(29 %)	0.41
	post	18	(24 %)	9	(38 %)	0.2
Hospital stay, days						*0.004*
		14 (11–18)		22 (15–35)		
Diagnosis						
Malignant		34	(45 %)	16	(67 %)	0.061
Ductal adenocarcinoma		12		4		
Neuroendocrine carcinoma		8		5		
Metastases		7		3		
Infiltrating carcinoma		6		2		
Other		1		2		
Benign		42	(55 %)	8	(33 %)	
Pancreatitis		20		2		
Adenoma		8		2		
IPMN		4				
Trauma		3		1		
Other		7		3		

Data are expressed as mean ± SD, number (%), or median (interquartile range). Statistical significance indicated by italics

DGE was more common following cancer surgery ($P = 0.061$) than in patients with benign histology. Forty-six multivisceral resections were performed (no DGE $n = 35$; DGE $n = 11$) in which 67 organs were resected (Table 2). There was no statistical difference in the number or pattern of resected organs that contributed to the occurrence of DGE. No vascular resections (excluding splenic vessels) were performed. Intraoperative factors (splenectomy rate, closure technique, operation time, blood loss, transfusion) did not differ between patients who developed DGE and patients who did not. ASA score was not significantly different and despite the longer hospital stay because of DGE, the stay in the intensive care unit (ICU) was one day in both groups.

Of the patients without DGE, 25 % suffered from major complications according to the Dindo-Clavien classification, while 46 % major complications occurred together with DGE ($P = 0.052$, Table 3). One patient died after a suicidal gunshot to the upper abdomen (unstoppable bleeding from gastric varices due to portal hypertension despite a portocaval emergency shunt in a second operation) and one patient with renal insufficiency died after multivisceral distal pancreatectomy including colectomy (intraabdominal abscess formation and peritonitis despite ileostomy in a second operation; overall mortality 2 %). Intraabdominal hemorrhage was a rare complication in both groups (4 vs. 5 %). Infectious complications showed a trend to association with DGE (wound infection 17 vs. 7 % and intraabdominal abscess formation 17 vs. 9 %), but only insignificantly. Pancreatic fistula (PF) occurred in 36 % (no DGE) and 58 % (DGE) of the patients, respectively. This was a statistically significant correlation. More high grade fistula (ISGPS grade B and C) were shown to occur simultaneously with DGE (41 vs. 24 %), but this correlation had no statistic difference.

Solid food was tolerated after a median of 6 days when no DGE developed, the NGT was then removed on the day of surgery (Table 4). When DGE developed, solid food was tolerated 3 days later (day 9) and the NGT was removed on day 1 after the index operation. Of the patients in the DGE group, 50 % developed DGE grade A, 46 % developed grade B, and only 4 % DGE grade C. In univariate risk factor analysis, the following four parameters qualified for further analysis: patient age, occurrence of pancreatic fistula, major Dindo-Clavien complications, and malign pathology. These parameters underwent multivariate logistic regression analysis (age was dichotomized), which revealed pancreatic fistula ($P = 0.018$) and malign diagnosis ($P = 0.024$) as significant risk factors contributing to DGE (Table 5).

Discussion

Although DGE has been extensively examined following PD [2, 6, 12–14, 22], its occurrence after DPR is only infrequently reported. As most of the proposed causes for DGE do not apply following DPR, the underlying causes might differ. Only two studies from Japan used the ISGPS definition following DPR: Yamamoto et al. examined 71 patients with T4 pancreatic body cancer, 13 of whom underwent celiac axis resection [23]. Some patients additionally underwent total gastrectomy or intraoperative radiotherapy and the incidence of DGE was 9 % (DPR) and 30 % (DPR with celiac resection). In 2014, Okada et al. reported on 37 patients, all with celiac axis resection (14 patients with preserved left gastric artery) with a DGE rate of 56.5 and 7.1 %, respectively [24]. Here, ischemic gastropathy was seen as the main contributing factor to DGE. Two papers regarding DPR reported DGE, but prior to the ISGPS definition, with an incidence between 0 and 18 % [25, 26]. To our knowledge, DGE (after introduction of the ISGPS-definition) following DPR has not been examined to date in a collective without extended arterial resection. Nevertheless, DGE occurs following DPR in our clinical

Table 2 Multivisceral distal pancreatectomies ($n = 46$): 67 resected organs (without spleen)

	n	Additional organ resections	
		n	Sites
No DGE			
Esophagus	2	1	1× (stomach + colon)
Stomach	14	7	2× adrenal gland; 1× (esophagus + colon); 2× (colon + adrenal gland); 1× (small intestine + colon); 1× (kidney + adrenal gland
Small intestine	7	3	1× (liver); 1× (stomach + colon); 1× (pancreatic head enucleation + colon)
Colon	11	6	1× (esophagus + stomach); 1× (stomach + small intestine); 2× (stomach + andrenal gland); 1× (pancreatic head enucleation + small intestine); 1× (kidney + adrenal gland)
Kidney	4	2	1× (stomach + adrenal gland); 1× (colon + adrenal gland)
Adrenal gland	10	6	2× (stomach); 2× (stomach + colon); 1× (stomach + kidney); 1× (colon + kidney)
Liver	3	1	1× (small intestine)
DGE			
Stomach	5	3	1× (adrenal gland); 1× (colon); 1× (liver)
Small intestine	2	1	1× (liver)
Colon	2	1	1× (stomach)
Kidney	1	1	1× (adrenal gland)
Adrenal gland	4	2	1× (stomach); 1× (kidney)
Liver	2	2	1× (stomach); 1× (small intestine)

Data are expressed as number

Table 3 Intraoperative characteristics and postoperative outcome

	No DGE		DGE		*P* value
	$n = 76$		$n = 24$		
Splenectomy	53	(70 %)	15	(63 %)	0.45
Closure (stapler)	15	(20 %)	2	(8 %)	0.14
Time of operation (min)	271 ± 99		264 ± 71		0.75
Red blood cell transfusion (units)	0 (0–3)		1.5 (0–4)		0.32
Blood loss (ml)	500 (200–1000)		650 (250–1450)		0.41
Days ICU	1 (1–4)		1 (0–2)		0.45
ASA score	2 (2–3)		3 (2–3)		0.15
Clavien classification					
Minor (°1–2)	57	(75 %)	13	(54 %)	
Major (°3–5)	19	(25 %)	11	(46 %)	0.052
Mortality	1	(1 %)	1	(4 %)	0.42
Surgical complications					
Intraabdominal hemorrhage	4	(5 %)	1	(4 %)	1.0
Pancreatic fistula	27	(36 %)	14	(58 %)	*0.048*
°A	9	(12 %)	4	(17 %)	
°B	16	(21 %)	9	(38 %)	
°C	2	(3 %)	1	(4 %)	
Minor/major	9/18	(12 %/24 %)	4/10	(17 %/41 %)	0.12
Wound infection	5	(7 %)	4	(17 %)	0.21
Intraabdominal abscess formation	7	(9 %)	4	(17 %)	0.45

Data are expressed as mean ± SD, number (%), or median (interquartile range). Statistical significance indicated by italics

Table 4 DGE and DGE-related parameters

	No DGE		DGE		*P* value
	n = 76		*n* = 24		
Tolerate solid diet (days)	6 (5–7)		9 (8–12)		*0.001*
Nasogastric tube (NGT)					
NGT duration (days)	0 (0–1)		1 (0–2)		0.12
NGT reinseration	0	(0 %)	7	(29 %)	*<0.0001*
Vomiting	6	(8 %)	20	(83 %)	*<0.0001*
Use of prokinetics	20	(26 %)	19	(79 %)	*<0.0001*
DGE °A			12	(50)	
DGE °B			11	(46)	
DGE °C			1	(4)	

Data are expressed as number (%) or median (interquartile range). Statistical significance indicated by italics

experience, although with a lower frequency compared to PD. In the study period between 2002 and 2014, the DGE rate after PD was 53 % at our department (DGE grade A 27 %, DGE grade B 10 %, DGE grade C 16 %), which is more than twice the frequency of DGE that we observe subsequent to DPR. Moreover, the severity of DGE after DPR is less pronounced with only 12 % of cases presenting clinically relevant DGE (grade B and C) compared to 26 % DGE grade B/C after PD. The ISGPS definition shows a trend of overestimating DGE in grade A [5], which is why some authors just report clinical relevant DGE B/C [12, 27] when specific treatment is indicated. Of the factors defining DGE (NGT duration, NGT reinsertion, inability to tolerate solid food, vomiting, and the use of prokinetics) NGT duration showed no difference between the no DGE and the DGE group. Possibly, this parameter does not correlate with DGE following DPR as well as it does after PD. At our department, the standard use of NGT after DPR has decreased over time. At present, NGT is removed directly after the end of surgery and is only reinserted when needed. NGT duration should only be used together with the other factors when grading DGE following DPR. Although the standard care protocol stipulates normal diet for POD 4, even in the no DGE group was normal diet not tolerated until POD 6. This shows that even in uneventful courses, factors do exist which influence the diet (time of first stool, patient wish for prolonged liquid diet, prolonged nausea without vomiting). In a review evaluating the ERAS guidelines in pancreatic surgery [28], the onset of normal diet was in part achieved even later (POD 11–24) [29].

In the therapy of DGE, it is important to distinguish between DGE and postoperative ileus (POI). While DGE and POI both present with vomiting, they can be distinguished by the absence of bowel movements. Other signs of POI, such as abdominal distension and possible bacterial translocation with elevated inflammation parameters, are also not present in DGE, as it is limited to the stomach. The value of factors beneficial in POI, such as peridural analgesia or opioid avoidance, has not been proven in the treatment of DGE. Nevertheless, we advocate standard use of both as part of our standard pancreatectomy protocol. Furthermore, it is important to rule out mechanical obstruction, which will not respond to prokinetic medication and in which no spontaneous resolution can be expected. A mechanical obstruction in the upper gastrointestinal tract can be excluded by endoscopy or imaging ("barium" swallow or computed tomography). When no mechanical obstruction is present and DGE does not respond to prokinetic medication (erythromycin [9]), we recommend endoscopic placement of a jejunal feeding tube followed by low dose (20 mL/h) enteral feeding. Usually, DGE will then resolve within days. Most of the risk factors attributed to cause DGE after PD do not arise following DPR. There is no duodenal resection, no ischemia or denervation of the stomach and no alimentary reconstruction. Other contributing factors such as pancreatic fistula and intraabdominal abscess formation, which have been shown to cause DGE [3, 5], also occur in DPR. In our analysis, infectious complications, such as wound infections and intraabdominal collections, showed no significant correlation with DGE, although they are twice as common in DGE than in patients without DGE. Possibly, this is due to the relatively small sample size of our study. A significant correlation could be shown with pancreatic fistula: 36 % of the patients who did not suffer from DGE developed PF while 58 % of the patients who did,

Table 5 Risk factors for DGE

	Odds ratio	95 % CI	*P* value
Univariate			
Age >75 years	5.85	1.65–20.69	*0.007*
Pancreatic fistula	2.54	1–6.49	*0.048*
Malign diagnosis	2.47	0.94–6.46	0.061
Major complications (Dindo-Clavien °3–5)	2.54	0.98–6.6	0.052
Multivariate			
Pancreatic fistula	3.38	1.23–9.29	*0.018*
Malign diagnosis	3.31	1.18–9.33	*0.024*

CI confidence interval. Statistical significance indicated by italics developed PF ($P = 0.048$). This is in line with previous studies, showing PF as a risk factor for DGE [3, 5, 8, 12].

PF is the most frequent major surgical complication after DPR [25, 30] and many efforts have been made to lower its incidence. Especially the closure technique of the pancreatic remnant was believed to influence the PF rate, but a randomized multicenter trial showed no difference between stapler and hand-suture [31]. Somatostatin-analogues have been tested to assess whether they can reduce the incidence of pancreatic fistula. Two systematic reviews reached partially different conclusion. In the therapy of already existing fistula [32], no effect was noted, while a prophylactic use after pancreatic surgery reduced complications and PF, with the authors opting for routine use of somatostatin-analogues [33]. We do not routinely use somatostatin-analogues and in the present study, it had no effect on PF formation and DGE. If PF B/C develops, it can be managed with interventional procedures (e.g., CT guided drain) in most instances. Only a minority of patients has to undergo redo-laparotomy for this indication [34]. Apart from PF, DGE is associated with complications in general: 25 % of patients without and 46 % of patients with DGE encountered major complications (grade 3–5 according to the Clavien-classification). Although this finding did not achieve statistical significance ($P = 0.052$)—possibly due to the small patient cohort—it is in line with previous studies [35, 36]. In the multivariate regression analysis, pancreatic fistula and a malign diagnosis significantly contributed to DGE formation. For DPR, no relationship between DGE frequency and pathology has been reported to date. Following PD, the description is inconsistent. In one older examination, DGE is more frequent in patients with chronic pancreatitis [8], while two recent studies found no correlation [11, 27]. A possible explanation was given by the extent of lymphadenectomy (and associated resection of vegetative nerve fibers?). As the amount of lymphadenectomy must not be reduced in oncological distal pancreatectomy, we should concentrate on the prophylaxis of pancreatic fistula to reduce the incidence of DGE.

Conclusion

DGE occurs frequently following DPR, its incidence correlates with PF formation. Lowering the frequency of PF therefore seems to be of outstanding importance.

Compliance with ethical standards All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Author's contributions Study conception and design: Tim R. Glowka, Jens Standop, Nico Schäfer. Acquisition of data: Tim R. Glowka, Dimitrios Pantelis, Steffen Manekeller, Nico Schäfer. Analysis and interpretation of data: Tim R. Glowka, Martin von Websky, Dimitrios Pantelis, Steffen Manekeller, Nico Schäfer. Drafting of manuscript: Tim R. Glowka and Nico Schäfer. Critical revision of manuscript: Tim R. Glowka, Martin von Websky, Dimitrios Pantelis, Steffen Manekeller, Jens Standop, Jörg C. Kalff, Nico Schäfer.

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

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