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ORIGINAL ARTICLE

Primary versus secondary delayed gastric emptying (DGE) grades B and C of the International Study Group of Pancreatic Surgery after pancreatoduodenectomy: a retrospective analysis on a group of 132 patients

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Abstract Delayed gastric emptying (DGE) is a common complication after pancreaticoduodenectomy (PDD) significantly contributing to post-operative morbidity. Clinical risk factors for DGE occurrence after PDD remain controversial. From January 2004 to December 2011, a total of 132 patients underwent PDD for either malignancies (73.5 %) or benign diseases (26.5 %) in one single universitary center. Post-operative mortality and morbidity were, respectively, 3 and 44.7 %. DGE has been defined in accordance with the International Study Group of Pancreatic Surgery (ISGPS) classification. DGE was distinguished in primary or secondary. Factors associated with grades B and C of DGE, based on severity and clinical impact, were assessed by means of univariate and multivariate analysis. Thirty-eight patients (28.8 %) had clinical DGE grade B or C. Post-operative complications (pancreatic fistula and/or hemorrhage or anastomotic leak) were reported in 25 out of the 38 patients (65.8 %, secondary DGE), while in 13 patients it was not associated to any other complication (34.2 %, primary DGE). Post-operative complications (pancreatic fistula and hemorrhage) appeared to be the most important predictive factor for Grade B or C DGE.

Keywords Pancreatic surgery · Delayed gastric emptying · Secondary delayed gastric emptying

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Introduction

Delayed gastric emptying (DGE) is a frequent complication following pancreaticoduodenectomy (PDD) [1]. DGE is not a life-threatening event; nevertheless it significantly prolongs hospital stays and increases surgical overall costs [2]. The International Study Group of Pancreatic Surgery (ISGPS) has classified into 3 grades DGE according to its severity (Table 1) [3]. Only grades B and C correspond to a DGE with clinical impact prolonging the overall hospital stay [2, 3]. Etiological factors for DGE involve: surgical technique, surgical setup and post-operative (po) cares [2]. In literature there are different studies which have shown that DGE is often associated with severe post-operative complications such as fistulas or hemorrhages [4, 5]. Thus, it is possible to differentiate DGE into primary (only related to surgical procedure) and secondary (due to post-operative complications). The objective of this paper is to evaluate the overall incidence of DGE in patient undergoing PDD and look over the possible risk factors for primary or secondary DGE.

Materials and methods

From January 2004 until December 2011, 132 patients underwent PDD in a single universitary center (CHU Poitiers, France). Patient's data were retrospectively collected and analyzed.

Surgical technique

The pancreaticoduodenectomy (PDD) was carried out in en bloc fashion, without preservation of the pylorus. Bile duct section was performed at the distal third; resection of the

Table 1 Definition of delayed gastric emptying (DGE) after pancreatic surgery according to the ISGPS classification

DGE grade	Nasogastric (NG) tube necessary	Orally ingested solid food not tolerated at post-operative day
A	From 4th to 7th day or NG reset >3 po days	7
B	From 8th to 14th day or NG reset >7 po days	14
C	>14 days or NG reset >14 po days	21

retroportal lamina with regional node dissection carried out to the right edge of the superior mesenteric artery and along the hepatic artery, up until the celiac tripod. Pancreato-gastric anastomosis was performed in 56 patients (42.4 %) and pancreato-jejunal anastomosis was carried out in 76 patients (57.6 %). Gastro-entero anastomosis was made antecolic in 98.5 % patients. Major vascular resection (i.e., splenic vein) was carried out in 18 patients (13 %).

Post-operative cares

All of the patients received a proton-pump inhibitor and pancreatic fistula prophylaxis with a somatostatin analog. A nasogastric tube remained in place until po day 4th. Amylase level in the drains was systematically assayed at po days 3 and 5.

Definition of delayed gastric emptying with clinical repercussions

The definition of the International Study Group of Pancreatic Surgery (ISGPS) is used to classify gastro paresis (DGE) according to its grade (3) (Table 1) [3].

- Grade A: No modification of post-operative treatment is required. Vomiting is infrequent and no nutritional support is necessary. Grade A was not taken into account for our review, given the fact that in principle, the gastric tube remains in place until D4.
- Grades B and C: They often necessitate administration of prokinetic drugs. Hospital stay is prolonged and parenteral or enteral nutrition (by naso-jejunal or jejunostomy tube) is often necessary.

Statistics

Descriptive analysis

Regarding qualitative data population and percentages are calculated as well as means and standard deviations are also calculated for quantitative data. In case of major variation of the mean value (standard deviation greater than half of the mean value), calculation of the median value was preferred.

Patient's data (age, sex, ASA score, tobacco usage, BMI, preoperative nutritional status, presence of diabetes, previous surgery, preoperative symptoms, preoperative liver function and need of preoperative bile drainage) as well as technical data (duration of surgery, need of vascular resections, type of reconstruction, blood loss) were analyzed as possible predictive factors of DGE.

Univariate analysis

Univariate analysis was carried out by means of the Fisher's exact test and the non-parametric Mann–Whitney test, respectively, for qualitative and quantitative variables. A value of $p < 0.05$ was considered statistically significant. Various parameters were taken into account: demographics and anamnestic data (sex, age, ASA score, tobacco usage, weight loss, BMI, nutritional status, diabetes, previous abdominal surgery), preoperative data (jaundice, previous pancreatitis, abdominal pain, sign of bowel occlusion, presence of cholangitis, worsening of pre-existing diabetes, bilirubin level, ALT values, need for biliary drainage), surgical indication for PDD (malignancy, benign condition), intraoperative findings and data (vascular invasion, need of vascular resection and reconstruction, extended resection, operative time), surgical anastomosis [type of pancreatic anastomosis, type of gastro-jejunal anastomosis, pancreas consistency(fibrous or normal)], hemorrhage (intraoperative bleeding, need of transfusion, post-operative bleeding, number of blood units transfused), pancreatic fistula (amylase levels >3 × N on post-operative day 3 and 5, pancreatic fistula grade B or C), post-operative course (antalgic treatment, presence of naso-jejunal feeding tube, need of surgical or radiological intervention, hospital stay).

Multivariate analysis

Factors liable to influence occurrence of grade B or grade C DGE in univariate analysis were analyzed. A logistic regression method was used; it involved an ascending stepwise procedure selecting factors with a threshold $p < 0.05$.

Results

There were 79 male and 53 female patients (59.8 and 40.2 %, respectively). Mean age at surgery was 64.1 years (range 23–82). ASA score was 1 or 2 in 86 patients, 3 in 42 patients and 4 in 4 patients. Surgical indication was related to malignancy in 97 patients (73.5 %) and a benign pathology in 35 patients (26.5 %) (Table 2).

Table 2 Patient's data: surgical indications

Surgical indications	$N = 132$	%
Malignant pathologies	$N = 97$	73.5
Pancreatic adenocarcinoma	44	33.3
Adenocarcinoma of the ampulla of Vater	32	24.2
Adenocarcinoma of the common bile duct	8	6.1
Neuroendocrine tumor	5	3.8
Degenerative IPMN	3	2.3
Duodenal adenocarcinoma	2	1.5
Metastases (1 kidney, 1 melanoma)	2	1.5
Degenerative duodenal GIST	1	0.8
Benign pathologies	$N = 35$	26.5
Benign ampulloma	9	6.8
Non-degenerative IPMN	9	6.8
Benign pancreatic lesion (1 serous cystadenoma, 1 mucinous cystadenoma, 2 cysts, 1 neuronal hyperplasia, 1 adenoma)	6	4.5
Pancreatitis	5	3.8
Adenoma of the duodenum	3	2.3
Adenoma of the common bile duct	1	0.8
Inflammatory pseudotumor	1	0.8
No lesion	1	0.8

The most frequent symptom was jaundice (66.7 %), followed by abdominal pain (32.6 %), cholangitis (11.4 %) and pancreatitis (7.6 %). Preoperative biliary drainage (endoscopic biliary stenting) was performed in 21 out of the 34 patients presenting with a bilirubin level higher than 250 μmol/l (14.6 mg/dl) at the time of diagnosis. Median length of hospital stay was 13 days, and mean length was 18 days.

Mean operation time was 374 min (range 240–540 min). It has been reduced progressively with the increasing experience of our surgical equipe. Mean intraoperative blood loss was 547 ml (range 0–3500 ml). It also has progressively lowered since the beginning of our study. Mean time of hospitalization was 18 days (range 8–75 days), with a median value of 13 days.

Post-operative mortality was 3 % (4 out of 132 patients). Post-operative morbidity was 44.7 % (59/132 patients). DGE grade B/C overall occurred in 38 out of 132 patients (28.8 %). There were respectively 23 of type B and 15 type C.

Pancreatic fistula was observed in 44/132 patients (33.3 %). In 18 of these 44 patients (40.9 %) it was associated with DGE grade B or C, while in 26/44 (56.1 %) was diagnosed biologically on a drain sample (amylase >3 N serum at po day 3 and 5), without any further consequences.

A post-operative hemorrhage was reported in 11 out of 132 patients (8.3 %) and all of them had grade B or C DGE.

Table 3 DGE and post-operative complications (pancreatic fistula and hemorrhage) on univariate analysis

Risk factor	DGE grade B or C	*P* value
Amylase >3 N to D3	8/44	0.82
Amylase >3 N to D5	3/44	0.08
Pancreatic fistula with DGE B or C	15/44	**<0.0001**
Post-operative hemorrhage	19/44	**0.005**
Need of transfusion (Blood units) on po course	3.71 (±6.15)	**<0.0001**
Further surgery or interventional radiology	15 (75.0 %)	**<0.0001**

Statistically significant *p* values are in bold ($p < 0.05$)

Table 4 Risk factors for DGE on multivariate analysis

	P	Odds ratio	Confidence interval at 95 %
Further surgery or interventional radiology	**<0.0001**	28.03	6.61–118.90
Intraoperative transfusion	**0.02**	3.97	1.25–12.60

Statistically significant *p* values are in bold ($p < 0.05$)

Cases of delayed gastric emptying

Grade B or C DGE was present in 38 out of 132 patients who underwent PDD (28.8 %). primary (without post-operative complications) and secondary DGE accounted respectively for 13/38 patients (34.2 %) and 25/38 patients (65.8 %).

Causes of secondary DGE were: pancreatic fistula alone (13/38), hemorrhage alone (6/38), fistula + hemorrhage (5/38), anastomotic leak (1/38).

Surgical treatment was necessary in all 11 patients with hemorrhage and the patient with anastomotic leak, overall in 12 out of 25 patients with DGE Grade B or C (48.0 %). In the 13 patients with fistula alone a percutaneous radioguided drainage was performed in 4 cases, while the other nine patients underwent medical treatment with somatostatin or its analogs. Underlying treatment of complications allowed the resolution of all secondary DGE.

Patients with primary DGE Grade B/C exhibited anyway a spontaneous recovery of gastric emptying with a mean time before complete re-alimentation was achieved of 16.1 days (range 10–28).

On univariate analysis (performed on all variables listed on "Methods") a significant correlation with grade B or C secondary DGE was found regarding the presence of pancreatic fistula ($p < 0.0001$), post-operative hemorrhage (0.005), need for blood transfusion after surgery ($p < 0.0001$), further surgical or radiological treatment ($p < 0.0001$) (Table 3). Simple biological findings of pancreatic fistula on drain samples did not show statistical

significance with secondary DGE ($p = 0.82$ and $p = 0.08$, on sample on p.o. days 3 and 5, respectively). Surgical technique (i.e., type of pancreaticojejunostomy) did not influence DGE occurrence.

On multivariate analysis, two risk factors were identified as predictive for grade B or C secondary DGE (Table 4). The model used shows good overall predictive performance (c-statistic = 0.826). The risk factors were: need for further surgery or interventional radiology ($p < 0.0001$, OR 28.03) and need of post-operative transfusions ($p = 0.02$, OR 3.97).

Discussion

Even though mortality decreased and is now equal to or lower than 3 %, morbidity remained high for PDD [4]. Addeo et al. [4] reported in a multicenter study morbidity and relaparotomy rates, respectively, of 54.4 and 11.7 %. Pancreatic fistulas and hemorrhages may be life-threatening complications, while simple DGE, which occur in between 20 and 50 % of patients, usually results in a lengthening of hospital stay and increases overall surgical costs [2, 4]. Factors possibly associated to DGE have been widely reported in literature: patient characteristics, surgical technique of pancreatic resection and/or reconstruction and post-operative cares [2, 5–16]. In our retrospective analysis grade B or C DGE was mainly associated to pancreatic fistula development or hemorrhage. Thus, 25 out of 38 patients (65.8 %) suffered from secondary DGE, while in the remaining 13 cases a primary DGE was found. It is worthwhile to differentiate the two types of DGE [17]. In fact, in primary DGE the cause resides into the major anatomo-physiological derangement following PDD [18–20]. The normal digestive cycle of secretion and motricity is characterized by the appearance of waves of activity known as migrating motor (or myoelectric) complexes (MMC) that evolve over four phases during the fasting period [18–20]. During phase I, basal gastric, biliary and pancreatic secretions lead to increased duodenal pressure and release of serotonin (5-HT) in the intestinal lumen [20]. During phase II, released 5-HT promotes MMC at the duodenal level by means of the intrinsic nervous system of the duodenal wall [20]. Phase III is characterized by 5-HT release and duodenal production of motilin by endocrine cells along with quantitative and qualitative MMC growth [21]. Stimulation of the intrinsic nervous system is associated with stimulation of the sensitive endings of the vagus nerve into the duodenum. Consequently by "reflex" gastric motricity originates in the vagus nerve [21]. Phase IV corresponds to a return to the basal state with disappearance of the MMCs [19]. So PDD entails major pathophysiological modifications. Duodenal resection eliminates motilin secretion, thereby counteracting MMC induction and impairing not only gastric emptying, but also the motricity of the efferent loop of the gastro-entero anastomosis [22]. Total resection of the retroportal lamina up until the hemi-circumference of the superior mesenteric artery allows for ablation of the cellular-node tissue of the recommended « regional » lymph node dissection, but it concomitantly damages autonomic innervation as well as the motricity of the efferent loop of the gastro-entero anastomosis [23]. Lastly, gastric and intestinal sectioning brings about sectioning of the longitudinal muscle layers and the intrinsic nerve fibers and this is responsible for disruption of the MCCs [19, 24]. On the contrary in secondary DGE, the driving cause is a major post-operative complication [4, 17, 25, 26]. Thus, when grade B or C DGE is encountered following PDD, a thorough clinical evaluation might be carried out, to discriminate the presence of post-operative complication. By our retrospective analysis, a post-operative complication stands for about two-thirds of grade B or C DGE. In these cases prompt recognition and removal of the underlying cause is the mainstay of treatment, which aim to decrease morbidity and mortality in PDD's patients. Our paper has anyway some limitations we would like to discuss. It is a retrospective analysis which reports a surgical experience in a quite wide period (8 years). Some of the surgical and medical management has been changed over time. To make an example, on the beginning of our experience NG tube was placed to every patient after PDD and removed on po day 4th. After 2011 we did not place systematically the NG tube, but its usage change within patient's characteristics and also refeeding starts early on po day 3rd (data not yet available). A second limitation is represented by the possible bias in collecting data. Although incomplete patient's charts were not used in this study, retrospective analysis always carries risks of misevaluation or underestimation of surgical complications. Finally technical data did not show risk factors predictive of DGE even if surgical time was quite high. This may be taken in count when statistical analysis did not find predictive factors for DGE within variables like duration of surgery, intraoperative blood loss or patient's BMI. We believe that to achieve the best and most clear results we should conduct, in the future, a retrospective study on prospectively collected data, lowering the possible bias and deeply analyzing all risks linked to PDD.

Conclusion

Primary DGE appears as a multifactorial phenomenon that is linked to the patient's characteristics, surgical resection/reconstruction and post-operative cares. It should always

be carefully evaluated to find out if an underlying surgical complication (thus causing secondary DGE) may be responsible, to properly treat the patient, avoiding an increase in morbidity and/or mortality.

Conflict of interest None.

Ethical Standard All procedures performed in the study involving human participants were in accordance with the ethical standards and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants or animals Data reported in this study does not contain experimentation on humans participants nor animals. Data were collected within standards medical procedures and after regular informed consent demanded to all patients enrolled.

Informed consent Informed consent and anonymity maintained.

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