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Prophylactic octreotide and delayed gastric emptying after pancreaticoduodenectomy: Results of a prospective randomized double-blinded placebo-controlled trial

O. Kollmar [a], M.R. Moussavian [a], S. Richter [a], P. de Roi [a], C.A. Maurer [b], M.K. Schilling [a,*]

[a] Department of General, Visceral, Vascular and Pediatric Surgery, Kirrbergerstr, University of Saarland, D-66421 Homburg/Saar, Germany
[b] Department of Surgery, Hospital of Liestal, CH-4410 Liestal, Switzerland

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Abstract

Aims: To evaluate the impact of prophylactic octreotide on gastric emptying in patients undergoing pancreaticoduodenectomy. Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) are common complications after pancreaticoduodenectomy. Whereas several prospective randomized trials propose the prophylactic use of octreotide to prevent pancreatic fistula formation, somatostatin has, however, been associated with delayed gastric emptying after partial duodenopancreatectomy.

Methods: In this prospective, randomized, double-blinded, placebo-controlled trial we analyzed the influence of prophylactic octreotide on delayed gastric empting after pancreaticoduodenectomy. Patients were randomized to the placebo group ($n = 32$) and the octreotide group ($n = 35$). Primary endpoint was the incidence of delayed gastric emptying, secondary endpoints included perioperative morbidity other than DGE. DGE was measured by clinical signs, gastric scintigraphy and the hydrogen breath test. Risk factors for DGE other than octreotide were analyzed by univariate and multivariate analyses.

Results: DGE measured by clinical signs was similar between both groups studied (~20% of the patients). Gastric scintigraphy ($T_{1/2}$) was 76.3 ± 15.2 min in the octreotide group and 86.7 ± 18.0 min in controls at day 7, respectively. The H_2 breath test was 65.0 ± 6.5 min in octreotide treatment group and 67.0 ± 5.7 min in controls at day 8. POPF grade C occurred in ~3% of the patients, although prophylactic treatment of octreotide did not reduce the incidence of POPF. Multivariate analysis showed that postoperative intraabdominal bleeding and infection were independent risk factors for DGE. Furthermore preoperative biliary stenting reduced postoperative DGE after partial duodenopancreatectomy.

Conclusion: Prophylactic octreotide has no influence on gastric emptying and does not decrease the incidence of postoperative pancreatic fistula after pancreaticoduodenectomy.

Keywords: Prophylactic octreotide; Delayed gastric emptying; Pancreaticoduodenectomy; Postoperative pancreatic fistula

Introduction

Partial duodenopancreatectomy has become a safe treatment modality for various benign and malignant pancreatic diseases with mortality rates below 5% in most high volume centers.[1] Research has therefore focused on prevention and treatment of complications such as postoperative pancreatic fistula (POPF) formation and delayed gastric emptying.[2,3] While POPF might become life threatening in the case of vascular erosions, DGE after pancreaticoduodenectomy is usually self-limiting, but significantly contributes to patient discomfort and prolongs hospital stay.[4–7] Morbidity secondary to DGE, such as aspiration of gastric contents, depletion of caloric reserves or infection of feeding catheters, however, might further aggravate the postoperative course.[8–10]

The etiology of DGE after pancreaticoduodenectomy is discussed controversially, with diabetes mellitus, malnutrition and pancreatic fibrosis[3,11] being associated with

* Corresponding author. Tel.: +49 6841 163 1000; fax: +49 6841 163 1003.
E-mail address: martin.schilling@uniklinikum-saarland.de (M.K. Schilling).

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postoperative DGE. Other studies focus on surgical factors like trauma of the pylorus,[5,12] resection of duodenal pacemakers with decreased motilin production,[13,14] as well as different types of gastrointestinal reconstruction contributing to DGE.[10,15,16] Furthermore, postoperative intraabdominal complications,[10] treatment with dopamine[17] and early jejunal feeding might influence gastric emptying.[18]

Somatostatin inhibits gastroenteropancreatic exocrine secretion. Octreotide, its long-acting analogue, has been studied in multiple randomized controlled trials and is thought to prevent POPF formation after pancreatic surgery, however, results are controversial. While some European studies found a significant reduction of POPF after pancreas resection in octreotide treated patients,[19,20] several international studies failed to demonstrate a beneficial effect.[2,21–23]

Besides the secretory effects, octreotide decreases gastric motility and prolongates orocaecal transit time in healthy humans[2,24,25] and has therefore been used in the treatment of dumping syndrome after gastric surgery.[26] We therefore studied the effect of octreotide prophylaxis on delayed gastric empting after pancreaticoduodenectomy.

Methods

Inclusion criteria, randomization and study drugs

Sample size was calculated based on the incidence of delayed gastric emptying for 40% of the patients with somatostatin and for 12% without somatostatin treatment.[27] This ratio reflects our experience in >400 patients undergoing partial pancreaticoduodenectomy. The level of statistical significance was set to 0.05 and a power of 0.80, using a post hoc 2-sample *t* test with Bonferroni correction.

After approval by the local ethical committee, patients 18 years or older undergoing partial duodenopancreatectomy were evaluated for the study before surgery on an intention to treat basis. Informed consent was obtained preoperatively for all patients. Data from all patients were entered in a database on an ISH-Med SAP platform (SAP, St. Leon, Germany). Data included all biographic and perioperative data as well as postoperative outcome.

Between April 1, 2002, and January 31, 2005, 67 patients were enrolled and randomized to either the octreotide or the control group by means of a randomly generated number pattern. Octreotide (100 μg Sandostatin®, Novartis Pharma GmbH, Nürnberg, Germany) and control saline placebo were prepared in the local investigational drug pharmacy and were identical in appearance, volume and labelling (consecutive numbers), masking the nursing staff, physicians and patients to their contents. Patients received the study drug in a volume of 1 ml subcutaneously once randomization took place and every 8 h at the same dose (300 μg per day) for 7 days.

Surgical technique and postoperative care

All patients received antibiotic prophylaxis prior to surgery. Antibiotic therapy was repeated every 4 h during the operative procedure. In all patients pancreaticoduodenal resection was performed as a partial pancreatectomy with either pylorus preservation (pylorus-preserving) or distal gastrectomy (classic). Orthotope reconstruction of the pancreaticojejunostomy was performed as end-to-side anastomosis in duct to mucosa technique with PDS. Also the hepaticojejunostomie was performed 10–20 cm distal to the pancreatojejunostomy and the gastrojejunostomie 20–30 cm distal to the hepaticojejunostomie on the same jejunal loop. Radical extended lymphadenectomy was routinely performed in patients with malignant disease.[28,29]

The structural quality of the pancreatic parenchyma and the diameter of the pancreatic duct were assessed with a pancreas anastomosis score (PAS; range 0–4 points) by the following classification: pancreas parenchyma (soft = 2 points, intermediate = 1 point, hard = 0 points) summed with the size of the pancreatic duct (<2 mm = 2 points, 2–5 mm = 1 point, >5 mm = 0 points).

One closed suction drain was placed behind both the pancreaticojejunal and hepaticojejunal anastomoses and was kept in place for 7 days in patients that did not develop fistulas. In patients developing fistulas, drains were kept until spontaneous closure of the fistula. Pancreatic fistula was classified as described by the ISGPF.[4]

All patients had a nasogastric feeding tube for decompression. Oral diet was initiated at the 4th or 5th postoperative day (POD). DGE was defined as the need for nasogastric decompression more than 10 days and/or intolerance of normal diet beyond the 14th POD.

Postoperative follow-up

Gastric scintigraphy, a non-invasive technique for the assessment of post-prandial gastric contractions, has been used to demonstrate gastric emptying. At the 7th POD, after an overnight fasting period, patients received a standardized semi-solid test meal consisting of 25 g of oatmeal dissolved in 400 ml of water labelled with 50 MBq ^{99m}Tc-Sn colloid according to standards.[30] A whole body acquisition from anterior and posterior view (Siemens MSII-Camera, 1024 × 256 Matrix, whole body acquisition, 5 cm/min) and a SPECT-acquisition of the stomach region was performed. The quantitative analysis of the images was performed with ROI-techniques.

To analyse the orocaecal transit time a hydrogen (H_2) breath test (HBT) was performed at the 8th POD as published previously.[31] After overnight fasting for 8 h, patients received 25 g lactulose in 300 ml water. Mouth-to-caecum-transit time was analyzed by H_2-measurements before and 10, 20, 30, 40, 50, 60, 80, 100, as well as, 120 min after intake of the lactulose drink (single-breath technique).