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Delayed Gastric Emptying after Billroth I Pylorus-Preserving Pancreatoduodenectomy

Effect of Postoperative Time and Cisapride

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Objective
To study the recovery course of gastric emptying after Billroth I pylorus-preserving pancreatoduodenectomy (PPPD) and therapeutic effects of cisapride.

Methods
To examine gastric emptying, acetaminophen was given, admixed in a pasty liquid meal, to 16 patients undergoing PPPD before surgery and at 1, 3, 6, 9, and 12 months after surgery. Cisapride was given orally to 10 patients before they received the acetaminophen regimen. Electrogastrography was performed at 2 weeks to 1 month after surgery in eight patients and at 6 to 12 months after surgery in seven patients.

Results
Gastric emptying was delayed but returned to the preoperative level by 6 months after surgery. Pretreatment with cisapride accelerated gastric emptying during months 1 to 6 but not during months 6 to 12 after surgery. Electrogastrography frequently showed tachygastria 2 weeks to 1 month after surgery, but seldom 6 to 12 months after surgery.

Conclusions
After Billroth I PPPD, gastric emptying is delayed but recovers by 6 months after surgery. Tachygastria may play a part in the pathogenesis of delayed gastric emptying, but it can be treated with cisapride.

Traverso and Longmire[1] reintroduced pylorus-preserving pancreatoduodenectomy (PPPD) in 1978, hailing its preventive effect on stomal ulceration and early postoperative bleeding, which sometimes arise after standard pancreatoduodenectomy. Moreover, the retained stomach in PPPD improves not only postoperative nutrition but also control of diabetes mellitus, if present. Preservation of the physiologic sequence of the gut that produces intestinal hormones may play a part in improving the postoperative quality of life.[2] Moosa[3] reported that the preserved stomach in PPPD diminishes the risk of dumping syndrome as well. Moreover, a recent study has proved that the antrum regulates pancreatobiliary secretion.[4]

Delayed gastric emptying is a frequent untoward complication after PPPD.[5] However, no previous reports have documented the serial change in gastric emptying after PPPD with end-to-end duodenojejunostomy (Billroth I PPPD) in contrast to PPPD with end-to-side duodenojejunostomy (Billroth II PPPD) preferred in Western countries. We adopted Billroth I PPPD because it has been proposed to be more physiologic with regard to the hormonal milieu and propagation of gastrointestinal motor activity across the anastomosis.

Cisapride, a prokinetic drug, increases the resting release of acetylcholine from the myenteric plexus–longitudinal muscle.[6] Numerous controlled trials have shown that cisapride accelerates gastric emptying in patients with diabetic gastroparesis, chronic idiopathic intestinal pseudoobstruction, and dyspepsia.[7–9] However, no study has yet addressed its efficacy after PPPD. We compared the rate of gastric emptying before and after Billroth I PPPD continually for 1 year, as well as with or without cisapride.

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PATIENTS AND METHODS

Gastric Emptying Studies With or Without Cisapride

Subjects

Eighteen healthy male volunteers without digestive symptoms were recruited as a reference group in the gastric

emptying study (median age 30 years [range 23 to 36], mean weight 63 ± 6 kg).

Sixteen patients (mean age 59 years [range 33 to 81]) were studied before and after PPPD for 1 year. PPPD was performed for benign (n = 9) and malignant (n = 7) disease. The right gastric artery was preserved in half of the patients. Dissection of lymph nodes in the hepatoduodenal ligament was performed in 10 patients. Only one patient had a metastatic lymph node in the retropancreatic head area. Ten of the 16 patients underwent the cisapride study, with a double-blind placebo-controlled design.

Methods

Measurement of Gastric Emptying. Gastric emptying was measured by the acetaminophen method before surgery and 1, 3, 6, 9, and 12 months after surgery according to our modification of the methods previously reported.[10–13] When the gastric emptying rate reached the preoperative value and the patient was asymptomatic, the study was terminated.

Subjects received no medication known to influence gastrointestinal motility for at least 7 days before the examination. Neither morphine nor epidural local anesthesia was administered. No smoking was permitted for at least 24 hours before the study. The study was started at 9 a.m. after a 12-hour fast. All subjects remained seated upright while being quiescent. The acetaminophen method of gastric emptying was performed during fasting and for 180 minutes after the test meal. Before each study, we confirmed the absence of inflammation and liver or renal dysfunction. In patients receiving intravenous alimentation, the calorie infusion was made free at least 10 hours before the study to keep the patient euglycemic. The venous blood glucose level was checked to ensure that it was <50 mg/dl before the test.

At 9 a.m., the subjects ingested 20 mg/kg of acetaminophen (Kalonal; Showa Yakuhin Co. Ltd., Tokyo, Japan) dissolved in 5 ml/kg of a nutrient pasty liquid test meal (Ensure Liquid; Dainabot Co. Ltd., Osaka, Japan) within 2 minutes. The meal has a caloric value of 1 kcal/ml and contains 3.52% protein, 3.52% fat, and 13.64% carbohydrate. Blood was sampled through an indwelling catheter inserted into an antecubital vein before and 15, 30, 45, 60, 75, 90, 120, 150, and 180 minutes after the administration of the drug. All the plasma samples were stored at −20°C until assayed. The concentrations of unconjugated acetaminophen in the plasma were measured by high-performance liquid chromatography.

The following parameters were calculated from the data: area under the curve of the acetaminophen concentration against time at 60 minutes (AUC60) and 90 minutes (AUC90) after the meal, maximum plasma acetaminophen concentration (C_{max}), and time to reach maximum acetaminophen concentration (T_{max}).

Cisapride Study. Five milligrams of cisapride or placebo was given three times a day for 4 days, with at least 7 washout days and within 2 weeks between each test period.

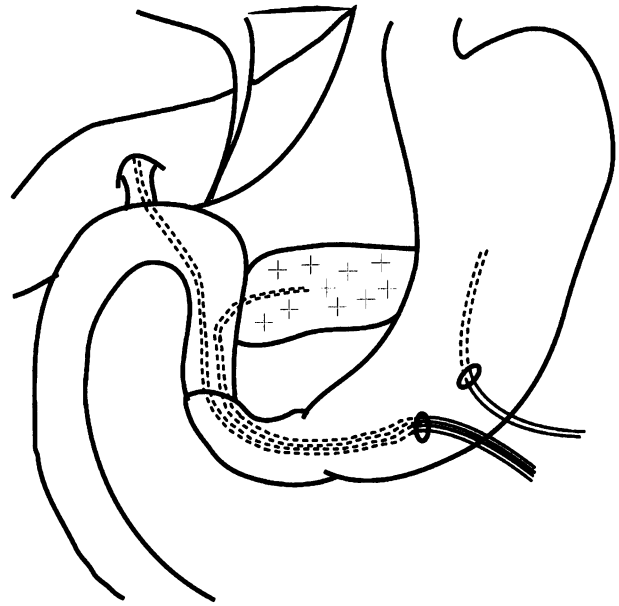

Figure 1. Method of reconstruction used in this study, including an end-to-end anastomosis between the first and fourth portion of the duodenum, pancreatojejunostomy, and hepaticojejunostomy.

Placebo or cisapride was given 30 minutes before breakfast, lunch, and supper. The last tablet of placebo or cisapride was taken 30 minutes before the ingestion of the test meal.

Surgical Method

The duodenal bulb was transected 2 to 5 cm (mean 3 cm) aborad to the pylorus, preserving (in eight patients) or dividing (in eight patients) the right gastric artery. The gut was reconstructed using the Imanaga procedure[14] (Fig. 1): an end-to-end anastomosis was made between the first and fourth portion of the duodenum or jejunum. One patient (case 16) underwent pancreatogastrostomy according to the method of Flautner et al.[15]

Symptom Evaluation

A variety of symptoms, including abdominal pain, nausea and vomiting, early satiety, loss of appetite, and postprandial bloating, were quantified using a scoring system on each test day. The severity of the symptoms was graded as 0 (absent), 1 (mild), 2 (moderate), and 3 (severe). These scores were added to obtain the symptom score (maximum 15).

Electrogastrographic Study

Subjects

Nine male healthy volunteers with no digestive symptoms constituted a reference group in an electrogastrographic (EGG) study (mean age 31 years [range 28 to 34], mean weight 65 ± 4 kg).

Eight patients who had undergone PPPD 2 weeks to 1 month previously and seven patients who had undergone

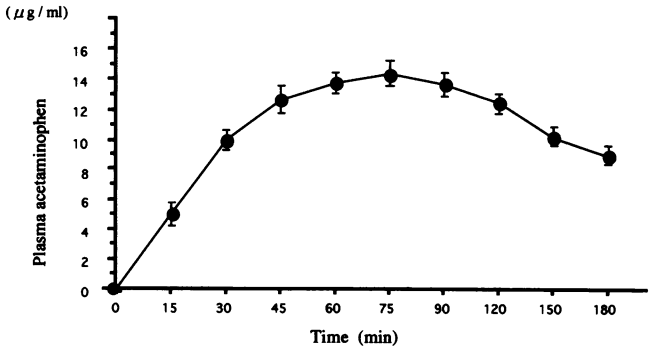

Figure 2. Time course of the plasma acetaminophen concentration in healthy volunteers, showing the peak concentration at 75 minutes after ingestion.

PPPD 6 to 12 months also underwent EGG. The former group was defined as the 2W–1M group, the latter as the 6–12M group. The EGG study was performed for 60 minutes during fasting. Two surface electrodes and one reference electrode were placed on the skin according to the method of Pfaffenbach et al.[16]

Methods

Electrogastrography was performed using a 96-kb ambulatory EGG recorder (Digitrapper EGG, Synetics Medical Inc., Irving, TX). All the recordings were made at sampling frequencies of 4 Hz. The high- and low-pass filters were set at 0.01 and 0.5 Hz, respectively. Digital data were downloaded to a personal computer using the accompanying software package (Electrogastrogram, Gastrosoft Inc., Irving, TX).

To represent the gastric electrical activity, several parameters were selected: (1) the dominant frequency (DF) and percentages of DF in the normal frequency range (2–4 cpm), the bradygastric range (<2 cpm), and the tachygastric range (4 to 10 cpm) and (2) the instability of the electrical frequency, or the dominant frequency instability coefficient (DFIC). DF is calculated as the highest peak of the mean fast-Fourier transform line for a given period. The DFIC is a measure of how much (in percent) the DF changes over the course of the period—in other words, the coefficient of variation (%) (standard deviation/mean DF) of DF. In the spectrum analysis that uses a fast-Fourier transform algorithm of a 256-second window of the raw data, power spectra of overlapping stretches of the electrical signal yielded frequency and amplitude information over the course of time.[17]

Statistical Analysis

Results were expressed as mean ± standard error of the mean. Differences between groups were tested for statistical significance using the Mann–Whitney test. Paired data within each group were compared using the Wilcoxon signed-rank test. Probability values < 0.05 were considered statistically significant.

RESULTS

Gastric Emptying With or Without Cisapride

Study Without Cisapride

The course of the plasma acetaminophen concentration in healthy volunteers is shown in Figure 2. The mean time of T_{max} in healthy volunteers was 68.3 ± 4.3 minutes.

Figure 3 shows the clinical details of the 16 patients on each baseline test day after the operation. The score was highest 1 month after surgery.

The change in body weight is shown in Figure 4. Six months after the operation, the body weight returned to the ideal body weight in each individual. Compared with the healthy volunteers, the patients' AUC60 and AUC90 tended to be lower ($p = 0.05$ to 0.1) (Table 1). Compared with the patients' own preoperative levels, AUC60 was lower 1 month ($p = 0.0128$) and 3 months ($p = 0.0609$) after surgery; AUC90 was significantly lower at 1 and 3 months (Fig. 5). C_{max} tended to be lower at 1 month ($p = 0.0754$) and 3 months ($p = 0.0995$) compared with the preoperative C_{max} (see Fig. 5). T_{max} at 3 months was significantly prolonged compared with the preoperative T_{max} (see Fig. 5). However, none of the parameters were significantly different between the preoperative and 9-month levels, or between the preoperative and 12-month levels.

At 3 months after PPPD, no significant difference was seen in any parameters between benign and malignant groups (AUC60, 346.3 ± 37.1 and 283.4 ± 52.3 μg/min/ml; AUC90, 681.8 ± 63.9 and 507.9 ± 85.8 μg/min/ml; C_{max}, 13.1 ± 1 and 13.0 ± 1 μg/ml; T_{max}, 144 ± 11.2 and 101.6 ± 12.9 minutes). Nor was there any difference in the parameters between the groups with the right gastric artery divided and preserved (AUC60, 337.4 ± 34.5 and 305.3 ±

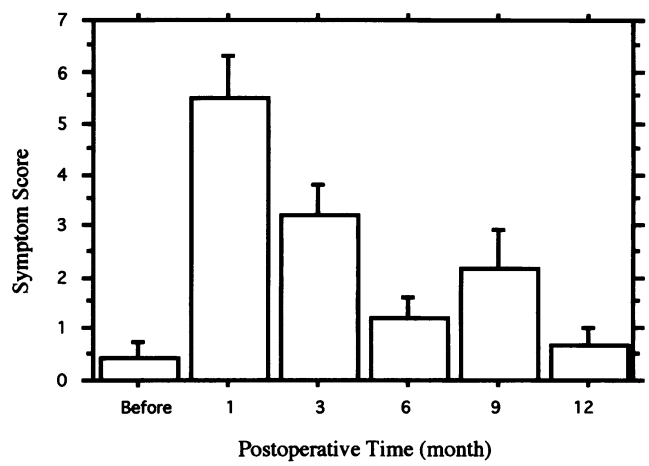

Figure 3. Change in the symptom score in patients for the first year after surgery.

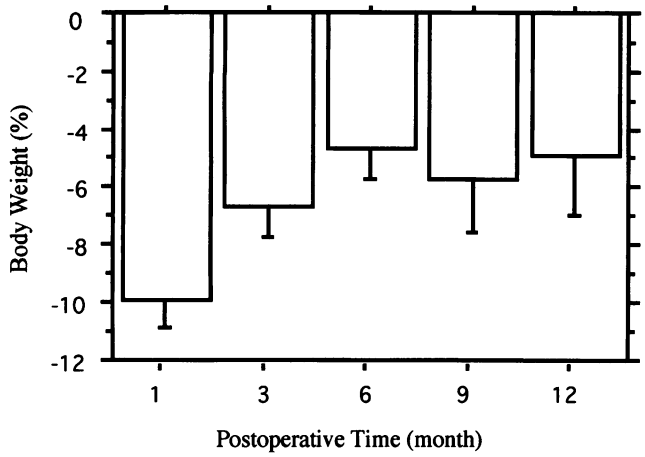

Figure 4. Postoperative change in body weight (%) at 3-month intervals. One year after the operation, body weight returned to the ideal value.

50.6 μg/min/ml; AUC90, 648.5 ± 66.9 and 531.8 ± 78.4 μg/min/ml; C_{max}, 14.4 ± 0.72 and 11.7 ± 1.1 μg/ml; T_{max}, 122.1 ± 9.5 and 111.4 ± 19.6 minutes). However, there was a significant difference in AUC60, AUC90, and T_{max} between the patients with lymph node dissection along the hepatoduodenal ligament and the patients without (Table 2). Eight of the 16 patients (50%) had diabetes mellitus before surgery without neuropathy; the Mann-Whitney test showed no difference in the parameters of gastric emptying between the groups with and without diabetes mellitus.

Study With Cisapride

The symptom score was not significantly different before (2.2 ± 0.57) and after (1.9 ± 0.43) cisapride administration. In the patients studied 1, 3, and 6 months after surgery, gastric emptying was significantly accelerated in terms of AUC60 and AUC90; T_{max} tended to be accelerated (Table 3). In none of the patients studied 9 or 12 months after surgery did cisapride significantly accelerate gastric emptying (AUC60, 473.3 ± 43.5 and 454.1 ± 46.0 μg/min/ml; AUC90, 797.6 ± 55.9 and 782.8 ± 67.8 μg/min/ml; C_{max}, 13.1 ± 0.7 and 13.0 ± 0.7 μg/ml; T_{max}, 87.3 ± 13.2 and 80.5 ± 14.6 minutes) (placebo *vs.* cisapride).

Electrogastrographic Study

The normal range of the percentage of DF demonstrated in the healthy volunteers was 86.4 ± 4.1%. The DF was 2.61 ± 0.19 cpm and DFIC 21.5 ± 3.5%. The only notable finding was tachygastria in the 2W–1M group (Table 4).

DISCUSSION

Methodologic Considerations

The diagnosis of delayed gastric emptying is frequently entertained by the radionuclide test. A number of technical problems, however, need to be resolved, such as correction for attenuation, septal penetration, and down-scatter.[18] Moreover, it requires specialized, expensive instruments, and radionuclide-labeled test meals are radioactive. Thus, the repetitive use of radioactive materials is prohibitively expensive and impractical in an outpatient unit.

The rationale of using acetaminophen for the gastric emptying test is that it is absorbed only from the small intestine. Some authors[10,19,20] have reported its correlation with other methods to study gastric emptying that have been previously validated (*i.e.*, a scintigraphic method and an ultrasonographic method). The acetaminophen absorption method has been used in several studies of gastric emptying of liquids.[11–13,21,22] Thus, we could use this method safely.

Factors That Influence Gastric Emptying

Diabetes mellitus may impair gastric emptying; in our study, however, no difference was seen between those with and without diabetes. Barkin et al[23] reported that patients with pancreatic cancer can have delayed gastric emptying even before the tumor invades the duodenum, possibly because of autovagotomy due to nodal metastasis or inhibitory hormones secreted from the tumor. In our study group, however, no patients had lymph node metastasis such as to delay gastric emptying.

Delayed gastric emptying in the early post-PPPD course occurs in 25% to 51% of patients.[24–27] Warshaw and Torchiana[24] reported that the number of days before the resumption of a solid diet was 16.1 in the group with bulb-preserving pancreatoduodenectomy and 9.8 days in the group with pancreatoduodenectomy plus pylorectomy. In 1986, Itani et al[5] reported that the mean period of an indwelling intragastric tube was 11 days. Braasch et al[25] reported that 45 of 87 patients (51.7%) developed delayed gastric emptying as an early complication.

Our study may be the first to clarify the recovery course of delayed gastric emptying in the late post-PPPD period.

Table 1. PARAMETERS OF GASTRIC EMPTYING IN HEALTHY VOLUNTEERS AND PREOPERATIVE PATIENTS (MEAN ± SEM)

Parameters of Gastric Emptying	Healthy Volunteers (n = 18)	Patients (n = 16)
AUC60* (μg · min · ml^{-1})	484.2 ± 31.7	391.3 ± 35.6
AUC90† (μg · min · ml^{-1})	920.3 ± 51.9	750.6 ± 54.3
Cmax‡ (μg · ml^{-1})	15.6 ± 0.85	13.8 ± 0.87
Tmax§ (min)	68.3 ± 4.3	88.1 ± 9.8

* AUC60 = area under the curve of the AA concentration against time until 60 min.
† AUC90 = area under the curve of the AA concentration against time until 90 min.
‡ Cmax = maximum plasma AA concentration.
§ Tmax = time to reach maximum AA.

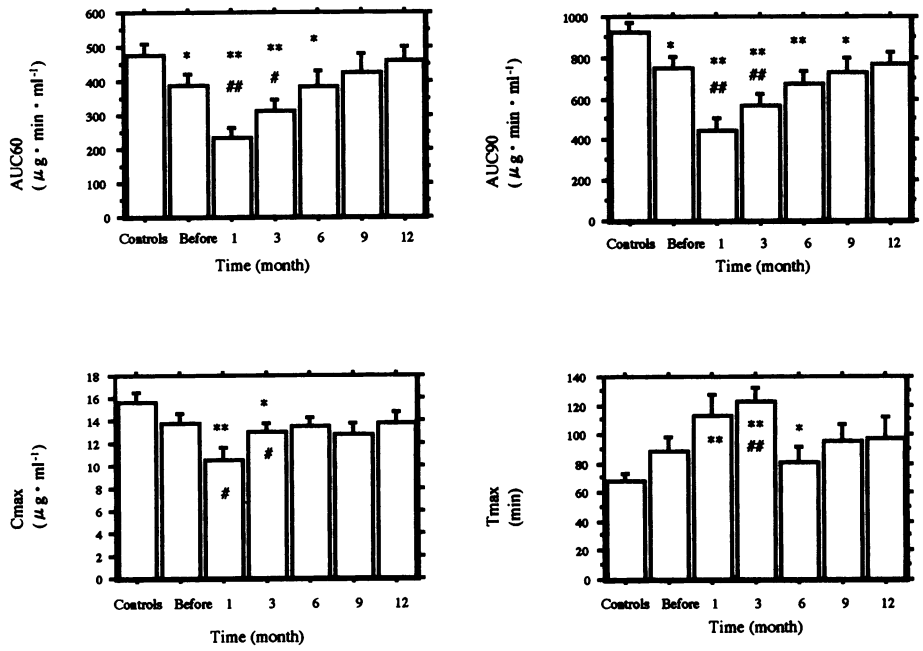

Figure 5. Gastric emptying in healthy volunteers (controls) and patients before and after surgery. Preoperative AUC60 and AUC90 tended to be lower than in the healthy volunteers. Compared to the patients' own preoperative levels, AUC60 was lower 1 and 3 months after surgery; AUC90 was significantly lower at 1 and 3 months. C_{max} tended to be lower at 1 and 3 months after surgery than before the operation. T_{max} at 3 months was significantly longer than the preoperative value. **, $p < 0.05$, *, $p < 0.1$ *vs.* controls, Mann–Whitney test. ##, $p < 0.05$, # $p < 0.1$ *vs.* preoperative values, Wilcoxon signed rank test.

Delayed gastric emptying has been defined as the need for postoperative nasogastric decompression for >10 days.[28] All of our patients after PPPD met this criterion. Our results showed that the AUC90 level at 1 month after surgery averaged 48.1% of the preoperative level and returned to the baseline level at 6 months. This recovery of gastric emptying coincided with that of symptoms, and was followed by recovery of body weight.

Etiology of Delayed Gastric Emptying

Blood Supply

We did not always preserve the right gastric artery for the purpose of dissecting lymph nodes. Williamson et al[29] reported that the right gastric artery is often impossible to preserve because it tethers the stomach, hampering creation of the duodenojejunostomy. Grace et al,[30] however, stressed the importance of preserving the right gastric artery to maintain the blood supply to the pylorus. In our study, no statistical difference in gastric emptying was seen between the group with the right gastric artery preserved and the group without. Further studies are needed to settle this issue.

Damage to the Vagal Nerve

Braasch et al[25] stated that damage to the nerves of Laterjet would cause transient gastroparesis after PPPD. Evidence exists for decreased antral motility and gastric dysrhythmia after PPPD.[25] This gastric dysmotility after PPPD may be attributable to the damage to the pyloric branches of the vagus. In our study, the delay in gastric emptying in the group with hepatoduodenal lymph node dissection was significantly greater than in the group without at 3 months after surgery. This may suggest that the damage to the branch of the vagal nerve delayed gastric emptying.

Stoddard et al[31] observed tachyarrhythmia and tachygastria in all patients after highly selective vagotomy. Geldof et al[17] also reported that highly selective vagotomy was associated with abnormal myoelectric activity in the stomach. They reported that increased frequency of electrical control activity was the only abnormality persisting for 6 months after the highly selective vagotomy. Hocking et al[32] reported on a patient with gastric dysrhythmia and delayed gastric emptying after PPPD. They postulated that gastric dysrhythmia might be one of the mechanisms for gastric dysfunction in the early postoperative period. In our study, EGG in the 2W–1M group was significantly abnormal com-

Table 2. PARAMETERS OF GASTRIC EMPTYING WITH (DISSECTION+) OR WITHOUT (DISSECTION−) HEPATODUODENAL LYMPHNODAL DISSECTION IN 3POM (MEAN ± SEM)

Parameters of Gastric Emptying	Dissection+ (n = 9)	Dissection− (n = 6)
AUC60 (μg · min · ml^{-1})*	270.0 ± 34.2	‖415.8 ± 32.6
AUC90 (μg · min · ml^{-1})†	532.4 ± 57.2	‖758.0 ± 61.6
Cmax (μg · ml^{-1})‡	12.4 ± 1.13	14.0 ± 0.76
Tmax (min)§	138.7 ± 7.9	‖87.5 ± 16.2

* AUC60 = area under the curve of the AA concentration against time until 60 min.
† AUC90 = area under the curve of the AA concentration against time until 90 min.
‡ Cmax = maximum plasma AA concentration.
§ Tmax = time to reach maximum AA.
‖ $p < 0.05$ *vs.* dissection+.

Table 3. PARAMETERS OF GASTRIC EMPTYING AFTER PLACEBO OR CISAPRIDE IN 1 POM, 3 POM, AND 6 POM (MEAN ± SEM)

Parameters of Gastric Emptying	Placebo (n = 9)	Cisapride (n = 9)
AUC60 ($\mu g \cdot min \cdot ml^{-1}$)*	288.0 ± 55.9	‖372.3 ± 67.3
AUC90 ($\mu g \cdot min \cdot ml^{-1}$)†	495.0 ± 75.0	‖646.1 ± 98.5
Cmax ($\mu g \cdot ml^{-1}$)	10.6 ± 1.48	12.5 ± 1.93
Tmax (min)§	115.0 ± 15.8	101.2 ± 17.6

* AUC60 = area under the curve of the AA concentration against time until 60 min.
† AUC90 = area under the curve of the AA concentration against time until 90 min.
‡ Cmax = maximum plasma AA concentration.
§ Tmax = time to reach maximum AA.
‖ $p < 0.05$ *vs.* placebo.

pared with the 6–12M group. This may support the idea that damage to the branch of the vagus is one of the reasons for delayed gastric emptying in PPPD.

Transection of Neural Continuity

The degree of antroduodenal coordination is currently considered important in determining the rate of gastric emptying, in addition to the motor indices.[33] In other words, poor gastric emptying results from a disturbed propagation of neural continuity across the gastroduodenostomy or duodenojejunostomy. The propagation of phase III activity fronts is interrupted by complete transection of the small intestine.[34] Arnold et al[35] reported that in dogs, only 1 of 36 activity fronts propagated across the end-to-end anastomosis within 45 days after partial resection of the jejunum, but that 45 to 60 days after transection, phase III activity fronts began to propagate across the anastomosis. Thus, reconnection of the neural continuity may play a role in the restoration of post-PPPD gastric emptying. However, other factors seem to be important in view of the longer time required for recovery, as shown in this study.

Angulation

Ueno et al[36] speculated that the anatomic position—namely a transient torsion or angulation of the reconstructed alimentary tract—might be the main cause of delayed gastric emptying after PPPD. They demonstrated a delay in gastric emptying after Billroth I PPPD but not after Billroth II. Our patients, having undergone Billroth I PPPD, may have suffered from this effect.

Motilin

Yeo et al[28] speculated that delayed gastric emptying after PPPD results from reduced circulating levels of motilin, a hormone primarily localized in enterochromaffin cells of the duodenum and proximal small intestine. They reported the successful use of erythromycin to improve gastric emptying after PPPD on the basis of this hypothesis. We previously showed that poor recovery of an activity front or phase III activity of the migrating motor complex was associated with lower levels of the plasma concentration of motilin after PPPD than after duodenum-preserving pancreatic head resection.[37] Further, intravenous administration of exogenous motilin induces premature phase III-like activity in the stomach and reduces gastric juice output.[38] Motilin seems to play a pivotal role in the mechanism of gastric stasis in the early postoperative period after PPPD; however, its role in delayed gastric emptying in the intermediate period (<6 months) remains to be elucidated.

Efficacy of Cisapride

Cisapride, a gastrointestinal prokinetic drug, increases the resting release of acetylcholine from the myenteric plexus–longitudinal muscle.[6] Numerous controlled trials have shown that the drug accelerates gastric emptying in patients with diabetic or idiopathic gastroparesis, chronic idiopathic intestinal pseudoobstruction, and dyspepsia.[7–9,39] However, studies on the effect of cisapride on gastric emptying in healthy subjects are conflicting. Edwards et al[40] could demonstrate no effect in a group of normal subjects. Wulschke et al[41] observed that under physiologic conditions, the control mechanisms for gastric emptying provide an optimal emptying rate that cannot be markedly accelerated by cisapride.

In our study, the administration of cisapride 15 mg/day and 5 mg on the test day accelerated gastric emptying 1 to 6 months after surgery but not 9 to 12 months after surgery. One of the reasons for the poor effect during the late postoperative period may be that gastric emptying returns to normal by 9 months. Conversely, our results have shown that cisapride administration may be justified 1 to 6 months after PPPD. Further studies are needed to clarify the discrepancy between gastric stasis and the symptoms.

CONCLUSIONS

We conclude that (1) delayed gastric emptying after PPPD needs 6 months to recover, (2) lymph node dissection

Table 4. ELECTROGASTROGRAPHIC PARAMETERS (MEAN ± SEM)

Electrogastrographic Parameters	Healthy Volunteers (n = 9)	2 wks–1 mo Group (n = 8)	6–12 mo Group (n = 7)
DF in normal range (%)	86.4 ± 4.1	73.1 ± 6.1	74.9 ± 7.1
Bradygastria (%)	7.3 ± 3.4	14.2 ± 4.0	20.1 ± 7.4
Tachygastria (%)	6.4 ± 2.5	*12.7 ± 2.6	4.9 ± 2.1
DF (cpm)	2.61 ± 0.19	2.75 ± 0.13	2.81 ± 0.26
DFIC (%)	21.5 ± 3.5	33.1 ± 4.9	27.0 ± 4.6

* $p < 0.05$ *vs.* healthy volunteers.
DF = dominant frequency; DFIC = dominant frequency instability coefficient.

in the hepatoduodenal ligament causes a greater delay in gastric emptying until the third month, and (3) orally administered cisapride accelerates gastric emptying during the intermediate postoperative period (<6 months) when delayed.

Acknowledgment

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