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Gastric motility recovery after Pylorus preserving Pancreaticoduodenectomy

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Gastric motility recovery after Pylorus preserving pancreaticoduodenectomy

Directed by Professor Kyung Sik Kim

Doctoral Dissertation
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Jin Hong Lim

December 2017

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ABSTRACT

Gastric motility recovery after Pylorus Preserving Pancreaticoduodenectomy

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Introduction

Immediate postoperative recovery course of gastric motility after Pylorus Preserving Pancreaticoduodenectomy is not well known. Delayed gastric emptying (DGE) is a frequent complication after pylorus preserving pancreaticoduodenectomy and is thought to be related to gastrointestinal motility recovery. However, it remains incompletely understood despite persistent improvements in perioperative patient management. In this study, we evaluate the gastric motility recovery for finding physiologic features of DGE.

Methods

To examine gastric motility, pre-prandial Electrogastrography was performed at preoperative day, and postoperative days 1,2,3,5,7. Stomach transit time was assessed using Radio-opaque Kolomark (Mi-tech, Gwangyang, Korea) at preoperative day, and postoperative days 3,7. Patients were classified into normal group and DGE group.

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Results

Between 2016.06.01~2017.07.31, 32 patients will be enrolled. DGE was diagnosed in three patients. In the electrogastrography, percentage of normogastria in normal group was decreased from postoperative day(POD)1 to POD3. However, in DGE group, at POD 3, percentage of normogastria and Dominant frequency was higher than those of normal group (P=0.02, 0.03 respectively). in Kolomark study, the number of Kolomark rings in the stomach was higher on POD 3,7 in DGE group (P=0.05,0.05 respectively).

Conclusions

After PPPD, DGE patients showed Increased normal gastric myoelectric activity and delayed stomach transit time at POD3. These observations are expected to play an important role in DGE prediction. Further studies are required to elucidate the pathophysiology of DGE.

Key words : Electrogastrography, PPPD, gastric motility, delayed gastric emptying

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Gastric motility recovery after Pylorus Preserving Pancreaticoduodenectomy

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I. INTRODUCTION

Pylorus preserving pancreaticoduodenectomy(PPPD) is complex procedure with high incidence of postoperative complication. Postoperative pancreatic fistula(POPF) and delayed gastric emptying(DGE) are major complications after PPPD.[1-3] POPF is life threatening complication. However, DGE is self-limiting complication resulting in prolonged hospital stay and increased medical costs.[4,5] The incidence of postoperative DGE after PPPD has been reported from 19 to 44 percent cases.[6-10]

DGE is characterized by Post-operative nausea, vomiting, and belching like as symptom of mechanical obstruction even though there was no mechanical obstruction of the intestine.[11,12] The pathophysiology of DGE after PPPD is not well understood. Universally accepted definition of DGE was proposal of international study group of pancreatic surgery(ISGPS) based on clinical course such as the length of nasogastric tube requirement period and the ability to tolerate a solid food diet.[13]

The pathogenesis has been speculated to include several factors such as damaged nerve supply of stomach,[14,15] ischemia of the pyloric ring and antrum,[16] angulation of duodenojejunostomy,[17] and intra-abdominal abscess.

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Delayed recovery of a gastric phase was also proposed.[18] However, the cause for DGE are still unclear and there is no consensus about pathogenesis of DGE. Several studies were reported about gastric motility recovery after PPPD.[18-20] These studies focused on the long-term treatment of DGE. Erythromycin, cisapride and gum chewing was suggested solution of bowel movement recovery after PPPD. Immediate postoperative physiologic feature of DGE was not reported yet. In this study, we evaluate the gastric motility recovery for finding physiologic features after PPPD to understand pathophysiology lead to DGE.

II. MATERIALS AND METHODS

Patients enrollment

This prospective observation study was approved by the institutional review board of the Yonsei university. All patients with suspected pancreatic or periampullary cancer considered resectable with no history of previous abdominal surgery was included before PPPD. During surgery, patients undergone other operation such as total pancreatectomy, resection of pylorus, and segmental resection of bile duct were excluded. Patients who required combined resection of other organ because of tumor invasion or who required additional treatment with Claven-Dindo class 3 or higher complications,[21] such as POPF except ISGPS grade 1, were also excluded.

Surgical procedures and postoperative management

A detailed surgical procedure of PPPD was same with previously published report.[7] Lymph node dissection were carried out including region of the celiac trunk, hepatoduodenal ligament, and tissue around the superior mesenteric artery. After end to side duodenojejunal anastomosis, Naso-jejunal feeding tube was inserted for postoperative nutrient supply instead of tube gastrostomy. Closed drain was placed in posterior side of pancreatojejunostomy and posterior

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side of biliary anastomosis. For postoperative management, an intravenous H2 blocker was administered to all patients. None of all patients was given somatostatin analogues, and prokinetic agents.

Postoperative nutritional support

Nutritional support was initiated at a rate of 25ml/h with commercially available tube feeding (Newcare 300 TF, (Daesang, Seoul, Korea)) from postoperative day 2. Tube feeding was maintained for 12 hours from 8 am to 8 pm. The dosage was increased with 25ml/h every day until postoperative day 6. After no intraabdominal complications were confirmed by computed tomography(CT) on postoperative day 7, naso-jejunal feeding tube was removed and oral feeding was started. When Intraabdominal complication such as pancreatic fistula was identified, Tube feeding was maintained and the patient was excluded from study.

Measurement of Gastric emptying

Electrogastrography (EGG)

EGG was conducted on preoperative day, postoperative days 1,2,3,5,7. EGG was recorded for 20 minutes in the early morning before tube feeding using four electrodes (Physiolab, Seoul, Korea).(Fig 1) The skin was cleaned with water before applying the electrodes. According to the previously reported EGG study protocol,[22] Channel 1, 2, 3, and 4 electrodes were positioned in the left upper abdomen, right upper abdomen, right lower abdomen, and left lower abdomen, respectively, with a 5 cm from the umbilicus. The ground electrode and reference electrode was placed outside the 3,4 channel electrodes, respectively.(Fig 2) Each electrode was connected to Physiolab P400 (Physiolab, Seoul, Korea) via 4 channel cable. 1 cycle per minute(CPM) high-pass filer and 10cpm low-pass filter were applied.

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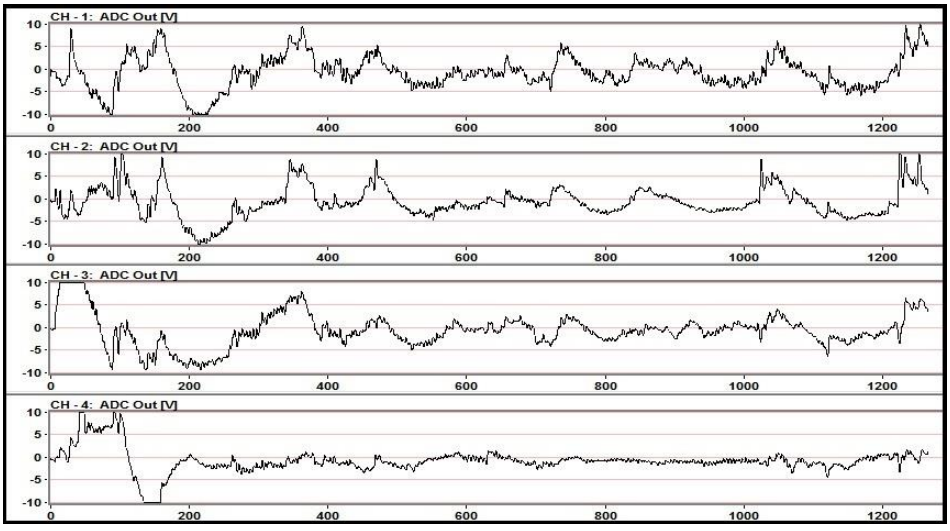

Figure 1. 4 channel electrogastrography tracing.

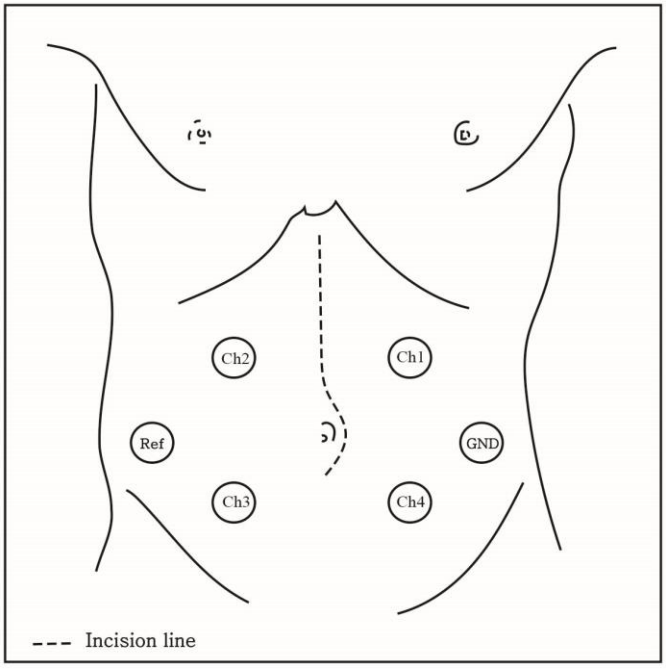

Figure 2. Location of electrodes on abdomen.

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Analysis of EGG

Bradygastria, normogastria, and tachygastria were defined as cycle frequency ranges of 1.0~2.0cpm, 2.0~4.0cpm, and 4.0~9.0cpm, respectively. Frequencies outside these ranges were considered as arrhythmia. The relative times of each during the recording period are reported as %normogastria, %Bradygastria, %Tachygastria, and the %arrhythmia respectively. The %normogastria, %bradygastria, and %tachgastria values analyzed from Channel 1 to channel 4. Among them, channel recorded the highest %normogastria was selected to the best channel for analysis. %normogastria, %bradygastria and %tachgastria of the best channel was analyzed. Dominant Frequency and dominant power was derived from the power spectral density and also analyzed.

Stomach transit time analysis

Stomach transit time was obtained using Kolomark (Mi-tech, Gwangyang, Korea). In Kolomark capsule, there are twenty radiopaque rings and it can be easily counted in simple abdominal X-ray. Kolomark study was performed on preoperative day, postoperative days 3,7. Patients took one Kolomark capsule at 5pm on study day. Abdominal X-ray films taken at 9pm same day. We counted the number of Kolomark ring on stomach.

Postoperative symptoms

After surgery, postoperative gastrointestinal symptoms were assessed carefully. Nausea, vomiting, and abdominal distension was checked. DGE was diagnosed according to ISGPS guideline. DGE grade A was excluded in this study Because Patients did not have oral intake until postoperative day 6. After nasojejunal tube removal, patients started oral intake. When patients were unable to tolerate a solid diet or nasogastric tube was inserted due to nausea and vomiting, DGE was diagnosed.

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Data collection

Data were collected prospectively for all patients and included history, operation time, interoperative blood loss, transfusion requirements, pathologic result, postoperative clinical information, and complication. Perioperative risk was classified according to the American Society of Anesthesiologist(ASA) physical status classification system.[23] Complications were documented according to the Claven-Dindo classification.[21]

Study endpoints

The first endpoints were observation of physiologic features about gastric motility recovery after PPPD. Detailed postoperative bowel symptoms were recorded. EGG analysis and Kolomark study was conducted and recorded by research team member. The second endpoints were prediction of DGE before oral intake. Delayed gastric emptying grade B,C was recorded according to ISGPS guideline.

Statistical analysis

The study design to predict the number of patients necessary for statistical validity was based on the incidence of DGE rate from 10% to 30% with the α set at 0.05 and the β set at 0.2, yielding a power of 80%. We calculated that 106 patients were required. Statistical evaluation was carried out by use of Mann-Whitney U test. For comparison of gastric motility change gradient, we used the multilevel approach in linear mixed model. All continuous data are expressed as the mean value ± Standard deviation. The Fisher's exact test was used to compare categorical variables where appropriate. Statistical analyses were performed using SPSS 23 for Microsoft windows (IBM, Chicago, IL USA). Statistical significance was set at $P<0.05$.

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III. RESULTS

Between 2016.06.01 to 2017.07.31, PPPD was planned in 73 patients. 12 patients did not meet the inclusion criteria and two patients declined to participate before surgery. seven patients withdrew from study after surgery. Three patients were excluded because of advanced cancer. Postoperative complication (acute myocadiac infarction, postoperative bleeding) was occurred in two patients and these patients was excluded. Only 32 patients were enrolled except patients underwent modified surgery. (Fig 3) The mean age of all patients was 67.06 years and The mean Body Mass Index(BMI) of all patients was 23.62 kg/m^2. Among them, three patients were diagnosed DGE finally. The patients were divided into two groups according to bowel recovery pattern: patients diagnosed with DGE (DGE group) and patient with normal bowel recovery (normal group).

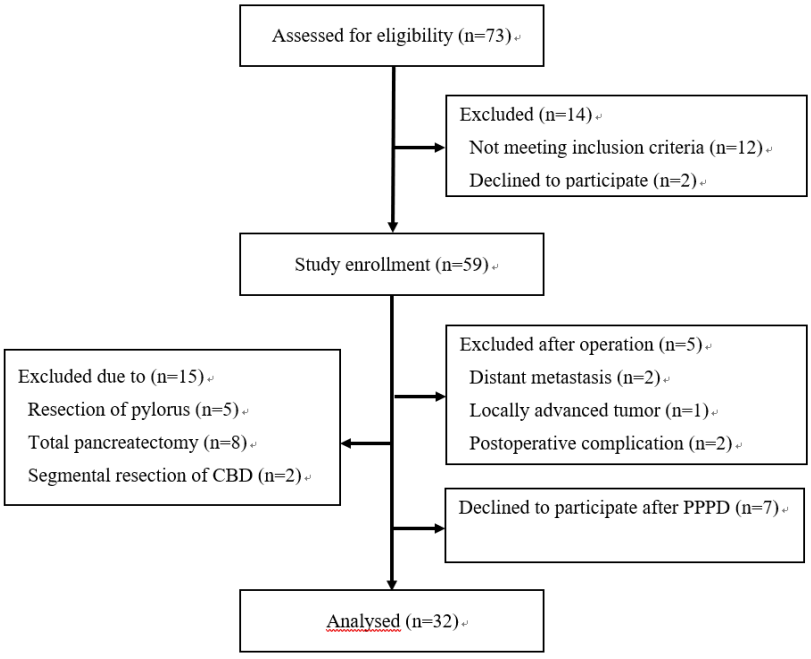

Figure 3. Patient enrollment flowchart.

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Table 1 presents patient clinicopathologic characteristics between the two groups. there were no differences in age, gender, BMI and American Society of Anesthesiologists (ASA) score between the two groups. Intraoperative blood loss and transfusion requirement did not differ. There was no significant difference in the number of lymph node dissection.

Table 1. Comparison of clinicopathologic characteristics between the two groups.

	Normal group (n=29)	DGE group (n=3)	*P* value
Age (years)	66.9 ± 12.47	69.0 ± 1.00	0.77
Gender (male : female)	3:0	16:13	0.25
BMI[1] (kg/m^2)	23.7 ± 2.66	23.8 ± 0.70	0.93
ASA score[2]	2.6 ± 0.63	3.0 ± 0.58	<0.01
Operation time (min)	438.7 ± 84.20	472.3 ± 28.71	0.50
Blood loss (ml)	1135.9 ± 518.39	1100.0 ± 550.00	0.91
Transfusion r(ml)	262.6 ± 291.96	326.7 ± 283.08	0.72
The number of lymph node	13.3 ± 9.00	16.3 ± 7.37	0.58
Diagnosis			0.53
Pancreatic cancer	14	0	
Ampulla of vater cancer	7	2	
Distal CBD cancer	7	1	
Borderline disease	1	0	

1. BMI : body mass index; 2. ASA : American Society of Anesthesiologists.

The comparison of the percentage of recording time between normal group and DGE group are shown in table 2. Most EGG result did not show difference between the two groups. however, at postoperative day(POD) 3, %normogastria of DGE group was significantly higher than that of normal groups. (P=0.02)

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Table 2. Comparison of the gastric myoelectric activity between the two groups

		Preop[6]	POD[7]1	POD[7]2	POD[7]3	POD[7]5	POD[7]7
%B[1]	Normal[4]	29.4 ± 12.26	25.0 ± 13.11	31.3 ± 10.17	30.9 ± 10.58	34.9 ± 13.69	30.5 ± 11.81
	DGE[5]	23.6 ± 4.77	25.2 ± 11.71	33.2 ± 7.38	22.9 ± 7.67	33.2 ± 7.96	33.3 ± 13.35
	P value	0.43	0.98	0.76	0.22	0.83	0.70
%N[2]	Normal	41.2 ± 12.81	47.0 ± 16.02	38.4 ± 11.09	37.3 ± 9.84	38.9 ± 11.26	39.9 ± 12.80
	DGE	45.6 ± 10.59	35.5 ± 10.41	40.3 ± 2.39	52.1 ± 9.18	39.1 ± 6.66	39.5 ± 9.02
	P value	0.57	0.24	0.76	0.02	0.97	0.96
%T[3]	Normal	18.6 ± 6.16	16.4 ± 8.60	17.8 ± 7.19	19.2 ± 7.31	15.9 ± 8.13	17.7 ± 5.66
	DGE	20.9 ± 6.31	26.5 ± 20.76	17.7 ± 8.63	17.1 ± 0.47	17.4 ± 3.70	15.8 ± 7.54
	P value	0.54	0.49	0.99	0.17	0.76	0.54

1. %B: %bradygastria; 2. %N:normogastria; 3. %T:Tachygastria; 4. Normal: normal group; 5. DGE: DGE group; 6. Preop: preoperative day; 7. POD: postoperative day.

In %normogastria gradient trend, the estimated slope of normogastria from POD1 to POD3 showed a difference between the two groups (P=0.03). However, those from POD3 to POD7 did not show significant difference between the two group. In normal group, the estimated slope of %normogastria from POD1 to POD3 of normal group decreased significantly. (P=0.02). (Table 3), (Fig 4).

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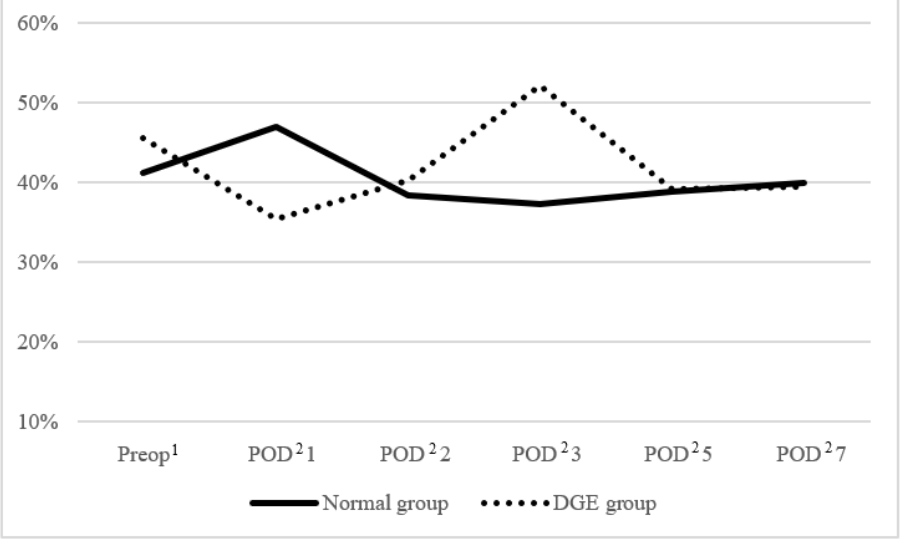
Table 3. Comparison of %normogastria gradient between the two groups

	%N[3](Preop[4] – POD[5]3)		%N[3](POD[5]1 – POD[5]3)		%N[3](POD[5]3 – POD[5]7)	
	Estimated slope (SE)	P value	Estimated slope (SE)	P value	Estimated slope (SE)	P value
Normal[1]	-1.59(0.98)	0.11	-4.56(1.84)	0.02	1.37(1.48)	0.36
DGE[2]	2.92(2.77)	0.30	8.31(5.32)	0.13	-7.07(4.11)	0.10
Normal[1] vs DGE[2]	4.51(2.94)	0.14	12.87(5.63)	0.03	8.43(4.37)	0.06

1. Normal: normal group; 2. DGE: DGE group; 3. %N; %normogastria; 4. Preop: preoperative day; 5. POD: postoperative day.



1. Preop: preoperative day; 2. POD: postoperative day.

Figure 4. Normogastria change of EGG for one week after PPPD

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In dominant frequency analysis, DGE group had significantly higher dominant frequency at POD3 than normal group. (P=0.03) Dominant frequency of DGE group at POD1 tended to be lower than that of normal group. however, there was no significant statistical difference. (P=0.06)(Table 4)

Table 4. Comparision of dominant frequency between the two groups

		Preop[4]	POD[5]1	POD[5]2	POD[5]3	POD[5]5	POD[5]7
DF[1]	Normal[2]	2.2 ± 0.94	2.4 ± 0.98	2.4 ± 0.93	2.1 ± 0.93	2.0 ± 0.75	2.1 ± 0.90
	DGE[3]	2.7 ± 1.18	1.2 ± 0.23	2.7 ± 0.56	3.2 ± 0.06	1.5 ± 0.17	1.8 ± 0.43
	P value	0.26	0.06	0.76	0.03	0.62	0.96

1. DF: dominant frequency; 2. Normal: normal group; 3. DGE: DGE group; 4. Preop: preoperative day; 5. POD: postoperative day.

In Kolomark study, the number of Kolomark ring in stomach was highest on postoperative day 3 in both groups. However, in DGE group, there are significant higher number of ring in stomach than that in normal group on postoperative days 3,7. (Table 5)

Table 5. Comparison of the number of Kolomark ring in the stomach between the two groups

	Preop[1]	POD[2]3	POD[2]7
Normal group	5.3 ± 7.71	9.2 ± 6.41	5.4 ± 6.75
DGE group	5.0 ± 8.66	17.0 ± 5.20	13.7 ± 4.16
P value	0.25	0.05	0.05

1.Preop: preoperative day; 2. POD: postoperative day.

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IV. DISCUSSION

After Traverso and Longmire reintroduced PPPD,[24] PPPD become standardized procedure in patients with periampullary cancer.[25,26] PPPD was thought to improve nutritional status compared with classical whipple operation.[24] the theoretical advantage is the stomach function preservation as a result of preserved vagal nerve and antrum, resulting in normal secretion of gastrin and normal gastric digestion. Nutritional Improvement after PPPD with the conservation of normal secretion of gastric hormones such as gastrin, secretin, and cholecystokinin was reported by many authors.[27-29] However, this technique of antrum preservation may increase delayed gastric emptying and marginal ulcer.[8,30]

Many studies have been reported to elucidate pathogenesis of DGE after PPPD. However, most studies retrospectively compared DGE patients with no DGE patients[12,31] or prospectively analyzed divided patients group according to interested factor.[32-36] Some studies reported prospective observation of gastric motility recovery after surgery.[18,19,37] However, all of them was conducted at least two weeks after surgery.

This study is prospective observation study for analysis of immediate postoperative stomach motility recovery after PPPD. Like as other studies for bowel movement recovery after Gastrointestinal surgery,[38-40] this study showed minimized decreased stomach motility of normal group at POD3. In analysis of EGG gradient trend, normal group showed significantly decreased trend from POD1 to POD3. On Kolomark study in normal group, stomach movement seem to be recovered slightly after POD3. However, on DGE group, unexpected result was reported that normal stomach movement was increased and many Kolomark ring in stomach was remained at POD3. Increased normal gastric myoelectric activity and delayed stomach transit time means that DGE patients have difference postoperative gastric motility recovery pattern. It has been not reported previously. Our results showed possibility of DGE prediction although

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we could not propose normal range of Kolomark and electrogastrography in immediate postoperative period because of small case number.

Increased normal gastric myoelectric activity and delayed stomach transit time can be observed at gastric outlet obstruction patients. Ronald et al reported gastric myoelectric activity in patients with gastric outlet obstruction and idiopathic gastroparesis.[41] In their report, patients with pyloric stenosis secondary to peptic ulcer disease had high-amplitude, more increased normal gastric myoelectric activity than healthy control. These patients also have 75% to 100% retained meal in stomach. however, idiopathic gastroparesis patients had dominant 1-2CPM signal of stomach and 42% to 90% retained stomach content. These results mean that delayed gastric emptying after PPPD was not caused by stomach motility change. Mechanical disturbances should also be excluded before diagnosing delayed gastric emptying after PPPD. The cause of DGE may be a small intestine motility disorder.

EGG evaluation of the gastric motility is old method. however, EGG has not been widely applied because the signal produced by the stomach muscles is very weak. In our study, we used four channel EGG system according to the method developed by Kim DW et al.[22] This system has higher accuracy than one channel EGG system because of the considerably variable position of postoperative individual's stomach. We used the highest channel of 3cpm percentage of the four channels for analysis. There is a previous report that best channel selection increases statistical significance in EGG analysis.[22]

Kolomark was developed for evaluation of bowel transit time.[38,42] There are 20 radio-opaque rings in Kolomark capsule and the capsule dissolve rapidly in the stomach. This method can be performed more easily than barium study.[43] However, there are no report using Kolomark in patients who underwent PPPD. In normal patients, stomach transit time is 1.2 hours and small bowel transit time 4.0 hours.[44] According this previous report, patients had abdominal X-ray films taken on 4 hours after Kolomark oral administration. Our result of

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Kolomark study reflected delayed stomach transit time in DGE patients.

In this study, we did not analyze gastrointestinal hormone. Gastric motility is regulated by Gastrointestinal hormone such as motilin, 5-hydroxytryptamine 3(5-HT_3), and Ghrelin.[45] Motilin plays an important role to stimulates gastric phase III.[46] Intestinal phase seem to be regulated by 5-HT_3.[47] For comprehension of gastric motility recovery in immediate postoperative period, Further study are required to clarify the relationship between gastrointestinal hormone and bowel movement recovery in immediate postoperative period.

There are two limitations in our study. One is laborious patients' enrollment. During EGG, patients were kept in a supine position and maintained for at least 20 minutes. This situation was unbearable in immediate postoperative period although patients could move their arm and talk with researcher. For this reason, seven patients were withdrawn from the study after surgery. Operation plan was sometimes changed during surgery because of advanced lesion in which preoperative evaluation was not identified. 15 patient's operation procedure was changed and excluded in this study. Postoperative complications were frequently occurred in PPPD. Patients with major complications were also excluded. another limitation is EGG. EGG has not become a standard testing method to measure gastric motility. The location of EGG leads and the number of electrodes on abdominal wall is not standardized.[12,39,48] It is difficult to obtain a good quality of recording because of very low frequency and extremely low amplitude signal.[48] However, EGG will be widely accepted and standardized after improvement because it is simple, noninvasive, repeatable method.

V. CONCLUSION

After PPPD, fasting stomach motility in DGE group increased maximum on postoperative day 3. However, stomach transit time on Kolomark study was decreased minimum on postoperative day 3. Further studies are required to explain this phenomenon. Relationship between gastrointestinal hormone and

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stomach motility must play a key role in gastric motility recovery after PPPD. These observations will be turning point in elucidating the pathophysiology of DGE.

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ABSTRACT(IN KOREAN)

췌두십이지장 절제술후 위운동의 회복

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임진홍

췌두십이지장 절제술(pancreaticoduodenectomy) 직후 위운동의 회복 과정에 대해서는 잘 알려진 바가 없다. 특히 췌두십이지장 절제술후 나타나는 빈번한 합병증인 위배출지연장애(delayed gastric emptying,k DGE)는 수술 후 위 운동 회복 과정과 밀접한 관련이 있는 것으로 알려져 있다. 최근 수술 전 후 환자 관리에 많은 연구 및 진전이 있었으나, 위 배출 지연 장애에 대한 이해는 부족한 것이 현실이다. 본 연구에서 췌두십이지장 절제술 대상 환자에서 수술 전 및 수술 후 1,2,3,5,7일째 식전 위전도(electrogastrography)를 이용하여 위전도를 측정하였으며, 방사선 사진에서 불투명하게 나타나는 콜로마크(Kolomark (엠아이텍, 광양, 대한민국)를 이용하여 수술 전 및 수술 후 3,7일째 식전 위통과 시간을 측정하였다. 환자들은 수술 후 위 배출 지연 장애 합병증이 발생한 군과 정상 회복군으로 분류하여 결과를 비교 분석 하였다.

2016년 6월 1일부터 2017년 7월 31일 까지 최종 32명의 환자가 연구에 등록되었으며 이중 세명에서 위 배출 지연 장애가 발생하였다. 정상 회복군에서는 위전도상 수술 후 3일째 위 운동이 감소하는 양상을 보였으며 위 배출 지연 장애가 발생한 군에서는 수술 후 3일째 정상적인 위운동(P=0.02)과 주요주파수(P=0.03)가 정상 회복군보다 높게 나타나는 양상을 나타내었다. 콜로마크를 이용한 위통과 시간 검사에서는 위내

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콜로마크의 개수가 위 배출 지연 장애가 발생한 군에서 수술 후 3,7일째 정상 회복군보다 많은 것으로 관찰되었다. (P=0.05,0.05) 이번 연구 결과 췌두십이지장 절제술 후 위 배출 지연 장애가 발생한 군에서는 수술 후 3일째 위 근육 전기 활동은 증가하나 위 통과 시간은 더 오래걸리는 것으로 관찰되었다. 이러한 결과는 췌두십이지장 절제술 후 위 배출 지연 장애의 예측에 중요한 역할을 할 것으로 기대된다. 추가 연구를 통해 위 배출 지연 장애의 병리생리학적 특징을 밝힐 수 있을 것이다.

핵심되는 말 : 위전도, 췌두십이지장절제술, 위운동, 위배출지연