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An Analysis of Possible Risk Factors Contributing to Delayed Gastric Emptying after Distal Gastrectomy for Gastric Cancer

Pradhan Sulav[1], **Shi Xin**[1*], **Hijrat Khalil Ahmad**[1], **Liu Cong Xing**[1] **and Maharjan Pranita**[2]

[1]*Department of General Surgery, Zhong Da Hospital, Southeast University, Nanjing, China*

[2]*Department of Gynecology and Obstetrics, Zhong Da Hospital, Southeast University, Nanjing, China*

[*]**Corresponding author:** Shi Xin, Professor, Department of General Surgery, Zhong Da hospital Southeast University, Southeast University, 210009, Nanjing, China, Tel: 8613851481137; E-mail: shixined@126.com

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Abstract

Gastric cancer is a worldwide epidemic. The standard and definitive treatment for gastric cancer is surgical resection: gastrectomy. Surgery is a common trigger for gastroparesis. DGE is arguably the most common of the post-gastrectomy syndromes, accounting for 5-20% of all cases. A clear etiology still remains unidentified. The purpose of the study is to analyze the possible risk factors contributing to development of DGE after distal gastrectomy for gastric cancer.

A retrospective study of 252 patients, who underwent distal gastrectomy for gastric cancer, was conducted from January 2010 to December 2015. 18 patients developed DGE with an occurrence rate of 7.1%. The incidence of DGE was found to be significantly higher in patients with 1) Gastric outlet obstruction (P=0.031), 2) Roux-en-Y reconstruction surgery (P=0.041), 3) Side to end gastrojejunostomy (P=0.03), 4) Tumor in the lower 1/3rd (P= 0.027) and 5) Ulcerative lesion (P=0.001). DGE continues to affect a considerable number of patients after gastric surgery. Proper preoperative preparation and postoperative management can considerably reduce the incidence of DGE.

Keywords: Gastrectomy; Gastroparesis; DGE; Roux-en-Y

Background

Gastric cancer is a worldwide epidemic. A surgical resection: gastrectomy is the only available standard and definitive treatment [1,2] With recent developments, early diagnosis of the disease has led to a substantial improvement in the survival rate and quality of life.

Prolonged gastric stasis after gastrectomy is not a normal event. Following an uncomplicated surgery, while majority of the patients tolerate oral intakes within 10-14 postoperative days, the normal gastric function maybe delayed in some cases [3,4]. Such a condition is termed post-surgical gastroparesis syndromePGSor delayed gastric emptying (DGE). Accounting for 5-20% [3,4], it is the most common among the post-gastrectomy syndromes.

Surgery is a common trigger for gastroparesis. It is among the three most common etiologies [5], accounting for 13% [6]. Gastric inflammation associated with surgery acutely inhibits its motility. The regulation of the normal gastric motility is mediated by a complex system of neuronal, hormonal and myogenic factors [7-10]. Gastric resection disrupts this regulatory system and thereby predisposing to a number of gastric motility disorders [11]. A current rise in interest in the condition, has led to dramatic escalations in its characterization and diagnosis. However, the condition remains unrecognized [11,12]. A clear etiology has not yet been identified nor has its mechanism been quite clarified [13]. The etiology remains unidentified in 36-49% of the cases [11,14].

Gastric scintigraphy is the gold standard method for diagnosis [5,11,13,15]. DGE may spontaneously resolve overtime [4,16] and its symptoms may be relieved to a degree with medications [5,6,13]. Only a small percentage of the cases require re-surgery [4]. At this point, the management can be particularly challenging. DGE is a debilitating complication afflicting serious nutritional and psychological effects on the patient. It requires hospitalization and prolonged parenteral nutritional support [13].

In the surgical approach for gastric cancer, gastrectomy with D2 lymphadenectomy is justified [17-21], followed by one of three reconstruction techniques for gastric tract continuity *viz.* Billroth I, Billroth II or Roux-en-Y gastrojejunostomy. Over a century after the first gastrectomy, and with countless improvements in the surgical technique, there has been a significant decline of postoperative complications and mortality, DGE however, continues to be a frequent complication.

Therefore, we conducted a study among the patients who underwent distal gastrectomy for gastric cancer to analyze the incidence of DGE and evaluate the possible risk factors contributing to DGE.

Patients and Methods

After approval, a retrospective study was conducted in Zhong Da Hospital, affiliated to Southeast University. Clinical data of patients who underwent gastrectomy for gastric cancer, in Department of General Surgery, Zhong Da Hospital, from January 2010-December 2015 was collected from the electronic record database of the institute. The study endpoint was the analysis of the incidence of DGE and evaluating the possible risk factors.

Consulting previous researches on the subject, basic criteria for the condition was formulated.

Cases were diagnosed according to the following criteria

1) Patients unable to tolerate oral intakes after 10th postoperative days

2) Nasogastric drainage >800 ml/day lasting for more than 10 postoperative days

3) No evidence of obvious obstruction.

The inclusion criteria include

1) Patients who underwent distal gastrectomy for gastric cancer;

2) Any operative and reconstruction method;

3) Cases without mechanical obstruction;

Among the 252 patients who underwent distal gastrectomy, 18 patients (7.14%) were diagnosed with DGE. Clinico-pathologic feature such as age, gender, blood type, comorbidity (such as diabetes mellitus, hypertension, cardiac or cerebrovascular ischemic disease), operative conditions, tumor site, TNM stage, anastomosis type, reconstruction method, resection extent were reviewed. DGE was diagnosis as per the above criteria and confirmed by upper gastroeneterography with 30% meglumine diatrizoate.

Treatment module

In Zhong Da Hospital, patients undergo standardized treatment. Gastrectomy with D2 lymphadenectomy is performed, following proper preoperative preparations. Under general anesthesia, patients undergo distal gastrectomy followed by gastrojejunostomy. Linear and circular surgical staplers are used for intestinal resection and anastomosis. A drainage tube is placed as long as required. A Ryle's nasogastric tube and a nasojejunal feeding tube are inserted intraoperative. Postoperative management includes IV fluids, enteral nutrition, proton pump inhibitors, analgesics, albumin and electrolyte supplements and other supportive medications as required. Nasogastric drainage is continued as long as required. On the 8th postoperative day, oral liquids is initiated and continued as tolerated by the patient.

Statistical analysis

SPSS v.20 was used for statistical analysis. Clinical characteristics of patients were summarized as whole as well as described specifically for subgroups by descriptive studies. All values are expressed as their mean ± standard deviation (SD) (Table 1). After descriptive studies, either a t-test or chi square test was used to compare variables between groups. Multiple logistic regression was used to analyze the risk factors for DGE (Table 2).

Variables	NON-DGE (N=234)	DGE (N=18)	P-value
Age	62.19 ± 12.425	65 (median)	0.499
Gender			
Male	162	15	0.207
Female	72	3	
Comorbidity	94	9	0.549
DM*	34	2	0.805
HTN*	84	8	0.468
Ischemia*	34	3	0.805
Prev. Surgery	38	2	0.566
GI bleeding	38	3	0.962
GOO*	25	5	0.031
Surgical setting			
Elective	173	11	0.238
Emergency	61	7	
Surgery			
BILLROTH-I	74	1	0.041(R)
BILLROTH-II	74	6	
ROUX-EN-Y	86	11	
Resection			
Partial	23	0	0.243
Hemi	27	1	
Subtotal	184	17	
G-J* anastamosis			
E-E*	48	0	0.003(S-E)
E-S*	57	6	
S-S*	31	0	
S-E*	98	12	
Curative	209	18	0.144
Palliative	25	0	
Surgical bleeding	229.06 ± 192.48	183.33 ± 61.835	0.317
Surgery time	189.53 ± 54.38	185 ± 49.294	0.732
PRE-OP albumin	38.17 ± 6.63	37.42 ± 6.003	0.643
Pre-OP Hypoalb	124	13	0.114
Post-OP ALB	30.838 ± 6.25	29.61 ± 5.11	0.418
Post-OP Hypoalb	212	17	0.585
Haemoglobin	118.5 ± 26.362	126.11 ± 21.497	0.234
Anemia	85	2	0.092
Electrolyte	46	4	0.793
WBC	21	3	0.284
Ulcer	77	13	0.001
Tumor stage			
I	87	6	0.579
II	61	7	

III	76	5	
IV	10	0	
Differentiation*			
H	12	2	
H-M	9	0	0.679
M	81	5	
M-L	62	5	
L	71	6	
Tumor position			
Lower	183	18	0.027(L)
Middle	51	0	

*DM: Diabetes Mellitus; HTN: Hypertension; Ischemic disease-cardiac or cerebrovascular; GOO: gastric outlet obstruction; GJ: gastro-jejunal; S side, E end (E-S end to side); H: highly differentiated; M: moderately differentiated; L: poorly differentiated (H-M: high to moderate differentiation).

Table 1: Summary of Clinico-pathologic features according to presence of DGE.

Relevant factors	Chi-square	P-value
Roux-en-Y reconstruction	6.702	0.035
GJ anastomosis (S-E)	11.826	0.008
Pre-op* hypoalbuminemia	7.353	0.007
Pre-op* low haemoglobin	5.846	0.016
Ulcerative lesion	24.645	<0.001

*pre-op: pre-operative

Table 2: Results of multiple logistic regression analysis.

Results

Among the 252 patients who had undergone distal gastrectomy for gastric cancer, 18 patients developed DGE with an occurrence rate of 7.14%. Clinic pathological features of all patients are shown in Table 1, with regard to presence of DGE. Among the patients who developed DGE (Table 3), 15 were male and 3 were female with a median age of 65.

We conducted a correlation analysis between incidence of DGE and different risk factors such as age, gender, blood group, hypoalbuminemia before and after operation, blood parameters, electrolyte status before surgery, presence of gastric bleeding and outlet obstruction, surgical setting, surgery type, reconstruction type, anastomosis type, extent of surgical resection, surgery time and blood loss, tumor position, type and staging, and presence of ulcerative lesion.

S. No	Age/sex	GI* Bleed	GOO**	Reconstruction	G-J***	Ulcer
1	59/M	NO	N0	Billroth II	E-S	YES
2	54/M	NO	YES	Roux-en-Y	E-S	NO
3	49/M	NO	N0	Billroth II	E-S	YES
4	64/M	NO	N0	Roux-en-Y	S-E	NO
5	51/M	NO	N0	Roux-en-Y	S-E	YES
6	54/M	NO	YES	Roux-en-Y	S-E	YES
7	60/M	NO	YES	Roux-en-Y	S-E	YES
8	55/M	NO	NO	Roux-en-Y	S-E	NO
9	66/M	NO	NO	Roux-en-Y	S-E	NO
10	80/F	NO	NO	Billroth II	S-E	YES
11	73/M	NO	NO	Billroth II	E-S	YES
12	79/M	NO	YES	Billroth II	E-S	YES
13	78/M	NO	NO	Billroth II	E-S	YES
14	72/F	NO	NO	Roux-en-Y	S-E	YES
15	70/F	NO	NO	Roux-en-Y	S-E	NO
16	68/M	YES	YES	Roux-en-Y	S-E	YES
17	54/M	YES	NO	Roux-en-Y	S-E	YES
18	70/M	YES	NO	Billroth I	S-E	YES

*Gastrointestinal; ** Gastric outlet obstruction; ***Gastrojejunal anastomosis

Table 3: Summary of patients with DGE.

The incidence of DGE was found to be significantly higher in patients with gastric outlet obstruction (P=0.031). The incidence of DGE in patients who underwent Roux-en-Y reconstruction was found to be significantly higher than those who had Billroth I or II. (P=0.041). The incidence of DGE was significantly high in patients who had a side to end gastrojejunostomy (P=0.03). Furthermore, the occurrence rate was significantly higher in patients with tumor in the lower 1/3rd (P=0.027) of the stomach and in patients with ulcerative lesion (P= 0.001). No significant association was found with age, gender, blood type, GI bleeding, hypoalbuminemia before and after operation, tumor differentiation and extent of gastric resection.

The incidence of DGE was relatively less in patients who underwent Billroth I reconstruction than those who underwent Billroth II (P=0.06) and Roux-en-Y (P=0.011) reconstructions. The choice between Billroth II and Roux-en-Y is rather hard (P=0.388). The study found no significant relation to conclude a better one.

All DGE patients were provided with continuous gastrointestinal decompression, fluid infusion with electrolyte supplements and enteral nutrition. Patients with hypoalbuminemia were given albumin transfusion, and those who had low hemoglobin levels (<7 g/L) were given blood transfusions. Patients received no further drugs specific for DGE but, were symptomatically treated. All patients with DGE recovered within 6 weeks and justified with repeat upper gastroenterography. Reoperation specific for DGE was not performed.

Discussion

DGE is a chronic heterogeneous disorder of gastric motility and is defined as delayed emptying of a solid meal in the absence of mechanical obstruction [5,6,22]. It is a complex disorder characterized by postprandial nausea, vomiting and gastric atony without evidence of mechanical gastric outlet obstruction [7,13].

In our study, the incidence of DGE was found to be 7.14%, which no less than 5-20% as described by other investigators [3,4]. With regard to the delayed return period, different authors have defined DGE with different postoperative days [3,4,10,11]. Bar-Natan defined DGE as the inability to eat a regular diet after 7-10 postoperative days [4] while Cohen et al. [3] and Meng et al. [11] defined DGE as the inability to tolerate oral intakes after 10 postoperative days. For this study, we have chosen 10 postoperative days.

The incidence of DGE was slightly higher in male patients than female and in patients with age >60 years and with a co-morbid condition, but the variables were found not to be statistically significant. On the other hand, patients with preoperative gastric outlet obstruction has significantly higher rate of DGE. The finding is consistent with other previous reports [4,11]. Hermann and Johnson stated a 2.5 times increase of DGE in patients with gastric outlet obstruction [23].

Preoperative albumin status, electrolyte imbalance, decreased hemoglobin level and also postoperative albumin status were found to be statistically insignificant variables. This finding is similar to previous reports [10,11]. Theoretically, this may be attributed to proper preoperative conditioning and postoperative management. Enteral feeding, adequate fluid infusion with electrolyte supplements and albumins transfusions postoperatively could potentially eliminate malnutrition as a causative factor for DGE.

Surgical setting (elective or emergency), surgical resection, operative time and blood loss, history of previous abdominal surgery were found to be statistically insignificant. Previous studies however show operative time and previous abdominal surgery to have effect on the incidence of DGE. Previous abdominal surgery can cause serious intraperitoneal adhesions and prolong operative time. The development of surgical instrument such as staplers for anastomosis and resection, electrical cauterization devices have significantly reduced the operative time and made it less troublesome for surgeons.

The ideal gastrointestinal reconstruction procedure should diminish postoperative morbidity and improve quality of life. Although Roux-en-Y has been associated with significant reduction in the complications rate [2] and DGE as well, our study finds it as a significant risk factor. This finding does conflict with some previous investigations [2,11]. Dong et al. and Kung et al. [10] did cite Roux-en-Y reconstruction as a risk factor [13]. Hirao M et al. also found a strong association between DGE and Roux-en-Y reconstruction [24]. The Roux-en-Y is however, the ideal choice of reconstruction after total gastrectomy [2]. Completion or subtotal gastrectomy with Roux-en-Y gastrojejunostomy has been recommended for treatment of persisting or unresolved DGE [5, 6, 25].

Furthermore, a side to end gastrojejunostomy emerged as a risk factor for DGE. The exact etiology is not clear and a further evaluation is in progress. A hypothesis states that the formation of rugae of mucosal and sub-mucosal folds associated with the use of staplers for anastomosis does create a somehow significant luminal narrowing and disruption in normal mucosal and sub-mucosal continuity resulting in motility dysfunction.

With regards to tumor factors, no significant relation was found with tumor staging and differentiation. Total gastrectomy was preferred with majority of the cases with low differentiation. Tumors in the lower 1/3rd of the stomach and presence of ulcerative lesion were however, found significant to incidence of DGE.

Apart from DGE, other surgical complications were also observed in the patients (7/252) such as afferent loop syndrome, anastomosis leakage and stricture, bleeding etc. but a further analysis was not done.

Conclusion

DGE is still a frequent complication of gastric cancer surgery and is further psychological and financial burden for patients. In majority of the cases, DGE spontaneously resolves within 6 weeks and re-operation is seldom required thus, the eagerness for reoperation should be avoided. The resolution of symptoms may also be accompanied by improvement in gastric emptying suggesting that either the enteric nervous system may be able to adapt the loss of vagal input or that vagal innervation or regeneration of nerve fiber may occur.

The study revealed several risk factors for DGE including Roux-en-Y reconstruction, gastric outlet obstruction, tumor of the lower 1/3rd stomach, side to end gastrojejunostomy and presence of ulcerative lesion. Proper preoperative preparation and postoperative management can considerably reduce the incidence of DGE.

This report does have some limitations and hence, the results should be interpreted with a degree of caution. The study has a relatively small sample size. Although DGE is normally not a very serious complication, it is better to avoid it.

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