



# Management of delayed gastric conduit emptying after esophagectomy

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**Abstract:** Delayed gastric conduit emptying (DGE) is a common complication after esophagectomy. Currently, pyloric interventions are the major prevention and treatment for DGE. In this review, we attempt to evaluate the clinical effect and safety of different pyloric interventions in esophagectomy patients. Moreover, other important management of DGE, including size of esophageal substitute, erythromycin and nasogastric tube (NGT) will also be discussed.

**Keywords:** Esophagectomy; delayed gastric emptying (DGE); pyloric intervention; nasogastric tube (NGT)

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## Introduction

Esophagectomy is undoubtedly the mainstay curative therapy for resectable esophageal cancer. However, the morbidity and mortality rates of esophagectomy are relatively high compared to other gastrointestinal surgeries. Delayed gastric emptying (DGE) is one of the major complications occurring in 15–39% patients after esophagectomy despite recent progress in anesthesia and surgical techniques (1-3). It is widely believed that bilateral vagotomy and increased pyloric resistance are the major culprits of DGE after esophagectomy. Patients suffering from DGE mainly complain of nausea, vomiting, anorexia, early satiety, bloating and abdominal pain, but without any evidence of mechanical obstruction from CT/MR enterography. DGE can be further confirmed by scintigraphy in clinically suspected patients (4). More importantly, DGE increases the risk of aspiration pneumonia and anastomosis leak.

## Pyloric interventions to manage DGE

As increased pyloric resistance is a major DGE pathogenesis mechanism, multiple pyloric interventions with varying effect and safety have been proposed to manage DGE. The following discussion will include pyloroplasty, pyloromyotomy, pyloric finger fracture, intrapyloric botulinum toxin injection (IBTJ) and endoscopic pyloric balloon dilatation (EPBD). Proponents believe that these pyloric interventions manage to prevent or cure DGE with tolerable adverse events. Conversely, opponents argue that these interventions fail to prevent DGE while increasing the risks of bile reflux and dumping syndrome.

Actually, a systemic review claimed that pyloric interventions showed a non-significant trend toward lower risk of DGE (5). However, during the meta-analysis of DGE, all different pyloric interventions were combined into one entity. We believe that this manipulation was inappropriate as considerable heterogeneity existed among

different pyloric interventions (Cochran's  $Q = 19.18$ ;  $P = 0.002$ ;  $I^2 = 73.9\%$ ).

Therefore, in this review, we attempt to evaluate the clinical effect and safety of different pyloric interventions individually to better determine their feasibility in esophagectomy patients.

### **Pyloroplasty**

Pyloroplasty is a surgical procedure that widens the gastric outlet to facilitate the gastric contents passage. It may be performed as an adjunct procedure to esophagectomy. Heineke-Mikulicz pyloroplasty, which is the most commonly used technique, incises the pylorus longitudinally then closes the incision transversely. Theoretically, this procedure may effectively obviate the pyloric obstruction immediately after the esophagectomy. However, opponents have raised concerns on long-term complications including bile reflux and dumping syndrome, emphasizing the benefits of an intact pylorus.

Multiple studies have investigated the clinical effect and safety of pyloroplasty. The majority of evidence opposes pyloroplasty as no difference can be found on DGE compared with no intervention (2,6-8). Therefore, pyloroplasty in esophagectomy patients is unnecessary due to its accompanying risks. On the contrary, a meta-analysis in 2002 did suggest that pyloroplasty could reduce the incidence of DGE (9). However, 2 randomized controlled trials, which constituted a major part of the meta-analysis, performed whole stomach esophagogastric anastomosis (10,11). Unfortunately, it has been shown that whole stomach esophagogastric anastomosis significantly increased the risk of DGE (12). To our best knowledge, no RCT has been conducted to investigate the necessity of pyloroplasty in the recent 10 years, during which minimally invasive esophagectomy and other surgical techniques have been developed rapidly. Further RCT is needed to confirm the safety and clinical effect of pyloroplasty. Until then, routine pyloroplasty in esophagectomy patients may be unwarranted.

### **Pyloromyotomy**

Pyloromyotomy is another common pyloric intervention during the surgery of esophagectomy. Similar to pyloroplasty, pyloromyotomy also serves to widen the pyloric passage, but with slight difference. Pyloromyotomy

incises the pyloric muscle but keeps the pyloric mucosa intact, thus considered a less invasive pyloric drainage. In fact, a RCT including 92 patients in 1992 compared pyloromyotomy with pyloroplasty and found that both groups have low incidence rate of DGE and other complications (13). However, all patients received pyloroplasty or pyloromyotomy in the trial; thus the DGE incidence rate of none-intervention group was not compared or evaluated.

Conversely, more recent studies have demonstrated that pyloromyotomy failed to reduce the risk of DGE while increasing the risk of reflux and dumping syndrome (6,7,14). However, no RCT has been conducted to investigate the clinical effect and safety of pyloromyotomy in the recent 10 years. Based on the current evidence, universal unselective pyloromyotomy in esophagectomy patients should be avoided until proven otherwise.

### **IBTJ**

Initially as the culprit of botulism disease, botulinum toxin has been one of the most requested therapies to remove facial wrinkles in cosmetics. The toxin blocks the release of the acetylcholine into the neuromuscular junction, thus inhibiting muscle contraction. IBTJ has been a tempting pyloric intervention for esophagectomy patients as a simple and effective way to prevent DGE. Theoretically, as the depletion of injected toxin and recovery of pyloric function, IBTJ has lower risk of reflux and dumping syndrome than conventional pyloric drainages.

Preliminary case series showed that IBTJ could be safely performed in esophagectomy patients (15,16) and a comparative study recommended IBTJ over pyloroplasty based on similar effect with simpler technique and less pyloric damage (17). However, further study found that although IBTJ might significantly decrease operative time, patients receiving IBTJ experienced more DGE and reflux compared to the ones receiving pyloroplasty or pyloromyotomy (18). Furthermore, a study doubted the necessity of IBTJ in minimally invasive esophagectomy patients as both IBTJ and no-intervention controlled group had low incidence of DGE (IBTJ: 8.6%, 3/35 *vs.* Controlled: 5.6%, 2/36) (19). Fortunately, a phase II RCT (NCT02965976) is recruiting patients to answer this unsolved problem and hopefully we will know whether we should perform IBTJ in esophagectomy patients before long.

### **Pyloric finger fracture**

Pyloric finger fracture is a unique pyloric intervention that the surgeon uses his fingers to pinch the contracted pyloric sphincter after anastomosis until chالاس during the esophagectomy surgery. It is believed to be a less aggressive technique than pyloroplasty as the fractured muscle fiber may recover gradually along with the pyloric function. Therefore, long-term complications including reflux and dumping syndrome can be avoided. However, current evidence on pyloric finger fracture has been scarce. A comparative study demonstrated that pyloric finger fracture could effectively decrease the pyloric pressure as well as the risk of early DGE (20). The study included 48 patients receiving the pyloric finger fracture and 30 patients without any intervention. All patients included received cervical anastomosis, and it is not a randomized trial, thus limiting the strength of its conclusion. Further randomized, controlled trial is needed to determine the clinical effect and safety of pyloric finger fracture on esophagectomy patients.

### **EPBD**

Postoperative EPBD has been widely accepted as a feasible therapy for postoperative DGE in esophagectomy patients. Via endoscope, EPBD inflates the balloon in the constricted pylorus to a designated diameter for a designated length of time to widen the pyloric passage. Multiple studies found that EPBD for postoperative DGE was safe and effective, regardless of previous pyloric drainage (14,21-23). These studies have demonstrated that no major complications including stricture or perforation occurred during or after the procedure. Although mild mucosal bleeding did happen sometimes, extra hemostatic clipping was not required and the bleeding generally stopped spontaneously. Moreover, the procedure had more than 95% success rate to achieve the immediate relief of related symptoms. However, quite a few patients (10–35%) required a second or third procedure to maintain the effect. To address this problem, one study proposed 30 mm diameter balloon to replace the 20 mm balloon in EPBD (21). This study found that 30 mm balloon was not only safe for esophagectomy patients, but could also significantly reduce the need of re-dilatation.

EPBD has predominantly remained to be a post hoc management of DGE. However, we believe that proactive measures to prevent DGE are more preferable. Because DGE is a common complication after esophagectomy; patients may suffer from DGE before postoperative

EPBD, which will significantly lower the quality of life. Furthermore, patients may consider the surgery a failure and lose faith in their doctors and further treatment. Interestingly, a case series including 25 patients demonstrated that preoperative EPBD was safe (24). Nevertheless, the DGE incidence of those who receive preoperative EPBD (16%, 4/25) was similar to previous study, which made its effect on DGE prevention remain doubtful.

Based on current available evidence, EPBD is a safe and effective management for DGE after esophagectomy. However, it should be noted that the majority of the current evidence comes from retrospective studies with small sample size. Besides, the optimal balloon size and dilatation time have not been clarified yet.

### **Other management for DGE**

Besides pyloric interventions, other management to prevent and treat DGE is also important. Theoretically, many factors may influence the occurrence of DGE, including gender, age, BMI, diabetes mellitus, smoking, histology type of esophageal cancer, cancer stage, surgical approach, anastomotic site, etc. In the following text, we will discuss the size of esophageal substitute, erythromycin and nasogastric tube (NGT), as we believe that these factors have significant impact on DGE.

### **Size of esophageal substitute**

After the resection of affected esophagus, the esophageal substitute may be created by whole stomach or gastric tube method. The whole stomach procedure directly reconnects the gastric fundus and proximal stump of the esophagus via anastomosis. As for the gastric tube procedure, a gastric tube is created by a resection 4–6 cm below the esophagogastric junction via serial application of linear stapler device parallel to the greater curvature. The remaining anastomosis is similar to the whole stomach method. It seems logical that whole stomach method, which preserves more stomach and gastric vasculature, may facilitate recovery and reduce the risk of DGE. However, the evidence to recommend gastric tube over whole stomach method has been overwhelming. A systemic review has confirmed that gastric tube substitute significantly lowered the risk of DGE compared to whole stomach substitute (25). This seemingly illogical phenomenon, in fact, is rather straightforward in flow mechanics and has been excellently explained by

a flow model to mimic the gastric substitute (26). The study presumed that the key force of gastric emptying was gravitation, which was reasonable as the gastric contraction force and viscous force in the early postoperative period were negligible. As it turns out, the gastric emptying time decreased as the diameter of the gastric tube decreased according to the Bernoulli equation as follows:

$$t = \sqrt{\frac{8V_0}{\pi g D^2} \left[ \left(\frac{D}{d}\right)^4 - 1 \right]}$$

t: gastric emptying time,

$V_0$ : initial volume of gastric content,

D: diameter of gastric tube, d: diameter of gastric opening (pylorus),

g: gravitational acceleration.

Therefore, gastric tube is highly recommended over whole stomach in esophageal substitute reconstruction for esophagectomy patients.

### Erythromycin

Erythromycin is a motilin agonist that stimulates gastric propulsive contraction, thus increasing gastric emptying. Oral erythromycin has been widely adopted as the initial treatment for gastroparesis while intravenous erythromycin is reserved for acute exacerbation of the situation. Both oral and intravenous erythromycins have been found to be effective in accelerating gastric emptying for esophagectomy patients (27,28). However, the effect and safety of long-term erythromycin usage in esophagectomy patients has not been evaluated yet. It should be noted that long-term usage may experience gradual decrease in drug action due to tachyphylaxis. Furthermore, potential side effects including ototoxicity, alteration of intestinal flora, gastrointestinal disorder and arrhythmia may occur. The evidence of other prokinetics on esophagectomy patients is insufficient for evaluation, further research is needed. Based on the current evidence, we recommend erythromycin as initial pharmacological management of DGE after esophagectomy, but EPBD should be considered if persistent pyloric constriction occurs.

### Necessity of NGT

Conventionally, NGT was routinely placed preoperatively for postoperative decompression in gastrointestinal surgery. It was widely believed that such decompression served to decrease anastomotic and respiratory complications in case

of DGE. However, in the era of evidence-based medicine, overwhelming evidence has proved routine NGT placement failed to achieve the benefits describe above (29,30). And nowadays, most gastrointestinal surgeries do not require prophylactic placement of NGT (31). However, issue on routine NGT placement in esophagectomy patients still remains controversial. A 2006 RCT with 34 patients demonstrated that NGT could significantly decrease pulmonary aspiration, hence respiratory complications in esophagectomy patients (32). The patient's tracheal pH was monitored for 48 hours after the surgery via a pH probe placed in the trachea. The result showed that patients with NGT had less gastric acid aspiration compared to the ones without. However, we find several limitations in the RCT as following: (I) the authors stated that neither enteral nor parenteral nutritional support was given and all patients received only crystalloid solution during the study. We find it deeply contradictory to modern clinical practice as the presumed fasting or peroral feeding immediately after surgery was detrimental to esophagectomy patients; (II) no pyloric intervention or other management of DGE was administered besides NGT intubation or reintubation. We believe erythromycin or other available prokinetics was indicated in DGE patients postoperatively as described above; (III) the authors emphasized the tracheal pH differences among groups but seem to neglect the measure of patients' actual feeling, as NGT may cause significant discomfort.

On the other hand, multiple studies opposed unselective prophylactic placement of NGT in esophagectomy patients. A 2017 meta-analysis showed that early or perioperative removal of NGT did not result in increased respiratory complications, anastomosis leak or mortality; but instead significantly shortened hospital length of stay (33). Moreover, a RCT found that early removal of NGT significantly reduced patients' discomfort caused by the NGT (34). Furthermore, several studies demonstrated that the complete omission of NGT in esophagectomy patients did not increase respiratory or anastomotic complications necessarily but with sooner recovery (35-38). They argued that retention of NGT prevented effective coughing and expectoration, which compromised pulmonary hygiene and led to pulmonary infection. As most NGT is placed preoperatively, a study has raised concern that retention of NGT postoperatively may lead to seeding of intraluminal tumor cell into the anastomosis site, thus increasing the risk of anastomotic recurrence (39). However, this study didn't compare the contamination rate between

NGT group and no-NGT group as the seeding might also occur in no-NGT group.

Based on the current evidence, we don't recommend routine NGT intubation in esophagectomy patients as it may cause discomfort and hinder recovery without decreasing anastomotic or respiratory complications.

## Conclusions

In this literature review, we have discussed different pyloric interventions and other important management for the management of DGE in esophagectomy patients. We have found that routine prophylactic pyloroplasty, pyloromyotomy or NGT placement is unwarranted. Also, IBTJ, pyloric finger fracture and preoperative EPBD need further randomized, controlled trial to determine their clinical effect and safety. Moreover, we should use gastric tube instead of whole stomach as esophageal substitute to prevent DGE. As for postoperative DGE treatment in esophagectomy patients, erythromycin and EPBD are relatively safe and effective.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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