Endoscopic *Botulinum* toxin as a treatment for delayed gastric emptying following oesophagogastrrectomy

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ABSTRACT

INTRODUCTION The incidence of delayed gastric emptying (DGE) following oesophagogastrrectomy with gastric conduit reconstruction is reported to be between 1.7% and 50%. This variation is due to differing practices of intraoperative pylorus drainage procedures, which increase the risk of postoperative biliary reflux and dumping syndrome, resulting in significant morbidity. The aim of our study was to establish rates of DGE in people undergoing oesophagogastrrectomy without routine intraoperative drainage procedures, and to evaluate outcomes of postoperative endoscopically administered *Botulinum* toxin into the pylorus (EBP) for people with DGE resistant to systemic pharmacological treatment.

METHODS All patients undergoing oesophagogastrrectomy between 1 January 2016 and 31 March 2018 at our unit were included. No intraoperative pyloric drainage procedures were performed, and DGE resistant to systemic pharmacotherapy was managed with EBP.

RESULTS Ninety-seven patients were included. Postoperatively, 29 patients (30%) were diagnosed with DGE resistant to pharmacotherapy. Of these, 16 (16.5%) were diagnosed within 30 days of surgery. The median pre-procedure nasogastric tube aspirate was 780ml; following EBP, this fell to 125ml ($p<0.001$). Median delay from surgery to EBP in this cohort was 13 days (IQR 7–16 days). Six patients required a second course of EBP, with 100% successful resolution of DGE before discharge. There were no procedural complications.

CONCLUSIONS This is the largest series of patients without routine intraoperative drainage procedures. Only 30% of patients developed DGE resistant to pharmacotherapy, which was managed safely with EBP in the postoperative period, thus minimising the risk of biliary reflux in people who would otherwise be at risk following prophylactic pylorus drainage procedures.

KEYWORDS

Delayed gastric emptying – Endoscopic *Botulinum* toxin – Oesophagogastrrectomy – Pylorus drainage procedures

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Introduction

The incidence of delayed gastric emptying (DGE) following oesophagogastrrectomy with gastric conduit reconstruction is reported to be between 1.7% and 50%.^{1–6} This variation is due to differing practices with regard to intraoperative pylorus drainage procedures. Pyloroplasty or pyloromyotomy aids the emptying of the denervated gastric conduit following oesophagogastrrectomy; however, they increase the incidence of postoperative biliary reflux and dumping syndrome, which results in significant postoperative morbidity.^{2,5,7,8} Additionally, drainage procedures have been directly attributed to mortality.^{2,9}

In the advent of minimally invasive oesophagogastrrectomy, where pyloroplasty or pyloromyotomy is technically difficult, surgeons have used intrapyloric *Botulinum* toxin (Botox)

as an alternative to surgical drainage procedures. This has reduced the incidence of DGE to 0–10% in the published literature.^{10–12} Some reports, however, have failed to confirm any benefit of intraoperative Botox,¹³ or even suggest that intraoperative Botox may increase complication rates when compared with no drainage procedure.¹⁴

We believe that DGE should be managed expectantly. DGE can be managed with systemic pharmacotherapy in the majority of instances.^{15,16} It is possible that many patients are subject to unnecessary morbidity, and possibly mortality, when prophylactic drainage procedures are performed routinely. The aim of this study was to establish the rate of DGE in people undergoing oesophagogastrrectomy in the absence of routine intraoperative drainage procedures.

We also aimed to evaluate the outcomes of postoperative endoscopically administered Botox into the pylorus (EBP) in people who developed DGE resistant to systemic pharmacological treatment.

Methods

All patients in our supraregional specialist unit who underwent oesophagogastrectomy for cancer between 1 January 2016 and 31 March 2018 were included in a prospectively maintained database. Patients underwent either an open two-stage Ivor-Lewis left thoracoabdominal oesophagogastrectomy or a three-stage McKeown oesophagogastrectomy. No intraoperative pyloric drainage procedures were performed during this time period. All patients received a high thoracic epidural catheter, nasogastric tube and urinary catheter as part of the perioperative bundle. Postoperative pain was managed with an epidural catheter and augmented with transdermal lignocaine patches as part of an established Enhanced Recovery After Surgery pathway. DGE was defined as having persistent nasogastric tube aspirates over 400ml in a 24-hour period from the third postoperative day. Plain erect chest radiograph was used to confirm the location of the nasogastric tube and to assess dilatation of the gastric conduit. First-line management of DGE was a subcutaneous infusion of metoclopramide (150mg/24 hours), provided there were no contraindications. If there was no resolution of DGE within 72 hours after commencing metoclopramide, then *Botulinum* toxin (100iu in 4ml) was administered in a quadrantic fashion around the pylorus via endoscopy. Nasogastric output was monitored postoperatively to confirm resolution of DGE.

Results

During the study period, 97 patients underwent oesophagogastrectomy (Fig 1). A total of 56 patients (58%) developed DGE requiring pharmacotherapy; nearly half of these (27/56) settled with subcutaneous metoclopramide infusion alone. There was no significant difference in patients who went on to develop DGE and those who did not, in terms of age, gender, histology type, anatomical location of tumour, operation performed or resection margin (Table 1).

Of the 29 patients diagnosed with DGE resistant to pharmacotherapy, 16 (16.5%) developed it within 30 days of surgery (which we categorised as “early”) and underwent EBP. In this group, the median pre-procedure nasogastric tube aspirate was 780ml; following EBP, this fell to 125ml ($p<0.001$). The median delay from operation to EBP in the early cohort was 13 days (IQR 7–16 days).

A total of 13 patients (13%) went on to develop DGE more than 30 days after surgery. This was diagnosed during outpatient follow-up, with complaints of postprandial chest pain, vomiting and weight loss. Chest radiograph was undertaken to assess the gastric conduit dilatation, and patients went on to receive EBP directly. All patients reported symptom improvement in this cohort following the intervention.

In total, six patients required a second course of EBP, with 100% successful resolution of DGE before discharge. There were no procedural complications. One patient developed aspiration pneumonia while awaiting EBP.

The median length of stay of the whole cohort during the study period was 14.5 days. Subgroup analysis showed the median stay of the EBP cohort was 18 days, and that of the non-EBP group was 12 days. This was found to be statistically significant ($p=0.0005$).

Discussion

The use of a gastric conduit to restore continuity of the gastrointestinal tract following oesophagogastrectomy results in significant anatomical and physiological changes.¹ There is a reduction in blood supply due to ligation of the left gastric and left gastroepiploic arteries; parietal cell mass is restricted due to resection of the gastric fundus; and innervation is reduced due to inherent vagotomy.¹ In light of this, some centres perform intraoperative drainage procedures to aid gastric emptying,^{4,21} because DGE is associated with increased length of hospital stay, aspiration and morbidity.¹⁷

Trials comparing the use of surgical drainage procedures during oesophagogastrectomy have at best demonstrated a marginal benefit when compared with no drainage procedures.^{9,18,19} A number of meta-analyses have demonstrated no difference with regard to respiratory complications,^{4,20,21} failure to thrive,^{4,20} anastomotic leak,⁴ dumping syndrome,²¹ mortality,²⁰ length of hospital stay,²¹ overall morbidity,²¹ or long-term gastric emptying.⁴ A number of studies have concluded that operative drainage procedures result in increased rates of complications when compared with no drainage procedures, including bile reflux or reflux oesophagitis,^{5,7,21} dumping syndrome,⁷ aspiration pneumonia,⁷ gastric ulceration,⁷ and gastric outlet obstruction.¹⁹ In a series of 197 people who underwent oesophagogastrectomy with pyloroplasty or pyloromyotomy, 2 patients had complications, including 1 mortality, directly attributable to the drainage procedure.²

Considering the results mentioned above and the results of our current study, whereby only 30% of patients developed pharmacotherapy-resistant DGE, we cannot advocate prophylactic drainage procedures. We would therefore argue that DGE can be managed with medical and endoscopic measures if these symptoms occur. Interestingly, Nakabayashi and colleagues demonstrated that the denervated intrathoracic stomach begins to recover 12 months after oesophagectomy,²² again suggesting that long-term drainage procedures may not be indicated.

Bagheri and colleagues found that the success rate of intraoperative Botox for the prevention of DGE was 90%.¹⁰ Cerfolio and colleagues demonstrated that intraoperative Botox reduced the rates of DGE when compared with both a group of patients who had surgical drainage procedures and a group of patients who had no drainage procedures; they also demonstrated that rates of postoperative biliary reflux were lowest in their intraoperative Botox group.²³ A further study compared intraoperative endoscopic

pyloric Botox with no Botox in minimally invasive oesophagogastrectomy, noting no pyloric dysfunction in 14/14 patients in the Botox group compared with 8/27 in the no Botox group; the Botox group also had a statistically significant reduced length of stay.¹² Martin and colleagues reviewed the rates of DGE in 45 patients who had intraoperative Botox: only 2 patients (4%) had immediate postoperative DGE, and 1 was managed successfully with endoscopic balloon dilatation; however, 3 patients went on to develop late DGE requiring endoscopic intervention, all of whom had resolution of symptoms.¹¹

Despite these promising results, whereby 70% of patients were treated without invasive intervention for DGE, we would argue that intraoperative Botox as a blanket strategy is not required. Marchese and colleagues demonstrated that intraoperative Botox increased the length of time required for postoperative nasogastric tube and resulted in higher rates of requirement for endoscopic pyloric treatment when compared with surgical drainage procedures and no surgical drainage procedures.¹⁴ Stewart and colleagues demonstrated that intraoperative Botox was not superior in terms of DGE, aspiration pneumonia or need for

Table 1 Comparison of people who developed and those who did not develop delayed gastric emptying (DGE)

Variable		DGE (<i>n</i> = 29)	No DGE (<i>n</i> = 68)	<i>p</i> -value
Gender (M/F)		19/10	49/19	NS (Student's <i>t</i> -test)
Mean age		68.3 years	67.8 years	NS (Mann–Whitney U test)
Tumour type	Adenocarcinoma	21	42	NS (Fisher's exact test)
	Squamous cell carcinoma	7	18	
	Other	1	8	
Location of tumour	Proximal oesophagus	0	2	NS (Fisher's exact test)
	Mid-oesophagus	5	10	
	Distal oesophagus	9	19	
	Gastro-oesophageal junction	15	37	
Operation type (IL/LTA/McK)		26/2/1	47/18/3	NS
Margin	R1	6	16	NS
IL = Ivor–Lewis; LTA = left thoracoabdominal; McK = McKeown; NS = not statistically significant				

Table 2 Median inpatient stay of EBP and non-EBP group

	EBP group	Non-EBP group	p-value
Median inpatient stay (days)	18	12	0.0005 (Kruskal–Wallis test)
EBP = endoscopically administered Botox into the pylorus			

further pyloric intervention.¹⁵ Eldaif and colleagues demonstrated that intraoperative Botox results in increased postoperative reflux symptoms without decreasing the need for pro-motility agents when compared with surgical draining procedures, suggesting that intraoperative Botox may increase rates of complications without confirming the same benefit of surgical drainage procedures.²⁴

In the present study, we have demonstrated that 70% of patients undergoing oesophagogastrrectomy either do not experience significant DGE or can be managed by systemic pharmacotherapy alone. We have also demonstrated that the remaining 30% of patients can be managed safely with EBP. There are, however, other endoscopic methods of managing DGE. Lanuti and colleagues successfully treated 95% of patients with endoscopic balloon dilatation.¹⁹ Kim and colleagues stated that following endoscopic balloon dilatation in 21 patients with DGE, all had improvement in symptoms, although all patients had surgical drainage procedures performed during their resection.²⁵ More data are required before conclusions can be made regarding which endoscopic measure is superior.

Conclusions

This is the largest series of patients who have not had routine intraoperative drainage procedures. We have demonstrated that pharmacotherapy-resistant DGE following oesophagogastrrectomy arose in only 30% of patients. In light of this, DGE can be expectantly managed with either metoclopramide or endoscopic Botox delivered to the pylorus in the postoperative period. Only one patient in the present cohort developed a complication while awaiting EBP, and there were no mortalities or procedural complications.

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