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Effectiveness of intraoperative botulinum toxin injection on gastric emptying during Oesophagectomy: A systematic review

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Abstract

Introduction: Oesophagectomy is the standard of care for resectable oesophageal carcinoma and remains pivotal for curative treatment. Pull-up with gastric conduit remains the most common reconstruction. Delayed gastric emptying (DGE) is a recognised complication and may lead to delayed postoperative recovery and prolonged hospital stay. Botulinum Toxin BTA has been used to relax the hypertonic pylorus intraoperatively and improve DGE. The aim of this review was to assess the efficacy of intraoperative BTA on gastric emptying and the need for postoperative endoscopic pyloric intervention (EPI).

Methods: Systematic review of literature was conducted using electronic database searched up to October 2020 including Cochrane Library, Medline, Embase and Goggle Scholars to identify relevant studies. Data was extracted and critically appraised by two independent authors.

Results: Eleven studies were included for systematic review with 1800 patients assigned to BTA, pyloroplasty, pyloromyotomy, or no-intervention. Ten were observational studies and one was a randomised experimental study. Two studies reported a statistically significant benefit of BTA on early DGE (Day 4, 59%, P< 0.001). Three studies reported higher rates of postoperative EPI when chemical pyloroplasty was used. Length of Hospital stay was higher for patients who had BTA compared to other techniques in three studies.

Conclusion: This systematic review did not demonstrate any significant benefit of intraoperative BTA on gastric emptying on the long term. The rate of endoscopic pyloric intervention was higher in these patients as reported by some studies. Further studies are required to investigate the outcome of chemical pyloroplasty during oesophagectomy.

Keywords: Mesh Terms used for database search:

- Botulinum toxin and esophagectomy/oesophagectomy
- Botox and esophagectomy/oesophagectomy
- Esophagectomy/oesophagectomy and gastroparesis

Introduction

Oesophageal cancer is among the most common gastrointestinal cancers [1]. Oesophagectomy is the standard of care for resectable oesophageal carcinoma and remains pivotal for curative treatment [2]. While several technical approaches exist for performing oesophagectomy, all are associated with significant

morbidity and mortality, in the ranges of 50-60% and 5-11%, respectively [3,4]. Regardless of the surgical approach, pull-up with gastric conduit remains the most common reconstruction [5]. Problems associated with this include a stomach emptying disorders due to bilateral vagotomies. Delayed gastric emptying (DGE) symptoms such as nausea, dysphagia and/or early satiety can be seen in as many as 15%–30% of postoperative oesophagectomy patients [6.7]. These symptoms have been associated with aspiration, prolonged hospital stay and decrease satisfaction in patients post oesophagectomy [8.9].

Several techniques have been described to prophylactically treat the hypertonic pylorus intraoperatively and avoid protracted DGE. These interventions can include pyloroplasty (PP), pyloromyotomy (PM), and pyloric injections with botulinum toxin type-A (BI). Additionally, pyloric instrument dilation or dilation by finger fracture (DL) may be performed. Pyloromyotomy and pyloroplasty are generally considered simple procedures; however, they may be complicated by stricture, leak, and even death. Because of these complications, and the limited demonstrated benefit, some advocate not performing an emptying procedure during oesophagectomy [10].

Botox injection has so far been used in the treatment of achalasia and diabetic gastroparesis [11,12]. Botulinum toxin (BTA) works by blocking presynaptic neuromuscular receptors, capable of creating muscular weakness within moments of its intramuscular injection[12]. Botox injection is also used as an alternative method for the treatment of gastric emptying disorder [9,13]. However, it also has been reported to cause increased incidence of post-operative bile reflux and dumping syndrome[18.23].

The aim of this review was to assess the safety and efficacy of intraoperative Botulinum toxin Type-A (BTA) therapy during oesophagectomy and the rates of postoperative endoscopic pyloric intervention needed following surgery.

Materials and Methods

This review was conducted according to the Preferred Reporting Items for Systematic

Reviews and meta-Analysis (PRISMA) guidelines for systematic review (figure 1) reporting and quality assessment of each trial using Cochrane collaboration tool for assessing risk bias ROBINS-I[23] and RoB2[24].

This review included Observational studies evaluating the effect of pyloric intraoperative **botulinum toxin** A (BTA) injection during oesophagectomy on gastric emptying. Inclusion criteria were RCTs, Observational studies investigating BTA injection during oesophagectomy in adults 18 years of age or older. Exclusion criteria were studies not published in English, conference articles and abstracts. Non-English studies were excluded to maintain uniformity in demographic distribution of the cohorts included.

The primary outcome measure was the presence of post-operative delayed gastric emptying symptoms post assessed both clinically and radiologically. Secondary outcomes included the rates of endoscopic intervention for DGE symptoms post-surgery and length of hospital stay following surgery.

Search methods

Electronic database searched up to Oct 2020 included Cochrane Central Register of

Controlled trials in the Cochrane library, Medline, Embase, and Google Scholar.

Key words were mapped to Medline medical subject Heading (MESH) terms and searched for as text items by two independent authors. Hand searches of references of cited journal conducted to identify potential eligible articles for this review. Each title was further screened by

review of the abstract and full text to identify matching primary and secondary outcome measures for our study.

The included studies were reviewed independently by two authors for data extraction as well as bias determination and results were collaborated accordingly. Any discrepancies at any stage of the study from inclusion to bias determination were resolved by focussing on the primary outcome of our review and exclusion of any study not meeting that criteria as well as independent presentation of results to the third author.

Results

The literature search identified 263 studies, including 218 in Medline, 31 in Embase and 16 in the Cochrane Central Register of Controlled Trial. Internet-based registry search yielded 14. No randomised clinical trials evaluating BTA on gastric emptying following oesophagectomy were found.

After further screening by the investigative team 165 out of these studies were duplicate and 70 out of 98 studies were excluded because they did not meet the search criteria (achalasia studies, dysmotility studies). The remaining 28 articles were extracted for full text review. Another 13 articles were excluded because they failed to meet the search criteria (abstracts, pilot studies, and registered trials).

Eleven studies were finally included for systematic review Table 1. Ten were observational studies with one randomised experimental study evaluating the effect of intraoperative botulinum toxin therapy during oesophagectomy on gastric emptying. There were 1800 patients in total assigned to either botulinum toxin (BTA), Pyloroplasty (PP), pyloromyotomy (PM) or no intervention (NI) groups.

Study Characteristics

Extensive database search identified 11 studies with 1941 patients assigned to either BTA with or without DL, PP, PM or NI. Seven studies reported data on delayed gastric emptying (DGE) clinically and/ or radiologically as a primary outcome [1,2,9,15,17,18, 22]. The need for Endoscopic pyloric intervention (EPI) after surgery was studied in 4 articles [2, 16, 17, 18]. Only 4 studies evaluated the length of hospital stay following surgery [5,17,19,22] (Table 2).

Assessment of risks of bias

The assessment of risk of bias was done on the observational studies using the seven main components of Cochrane tool ROBINS-I (figure 2).

The randomised experimental study was assessed using the six main component Cochrane tool RoB2. Details of the methodological assessments (can be seen in figures 3 and 4). All the observational studies had serious risk of bias except for one study (Antonoff et al) which had critical risk. Most of this resulted from confounding factors, selection of participants and measurement of outcomes. The experimental study[1] demonstrated some concerns mostly from their randomisation process and deviation from the intended intervention.

Discussion

The most suitable method of digestive tract reconstruction after oesophagectomy for oesophageal cancer is the anastomosis of the oesophageal remnant with the stomach[25]. Truncal vagotomy while preparing the gastric conduit for anastomosis is necessary and this in turn leads to diminished function[26]. Other factors may affect the gastric conduit motility include angulation of the conduit at the hiatus and redundancy of the conduit resulting in pyloric dysfunction and delayed gastric emptying. This would manifest as nausea, vomiting and could potentially lead to significant morbidity such as aspiration[8,9].

Several intraoperative pyloric drainage procedures have been advocated to prevent pyloric dysfunction postoperatively. These include surgical procedures such

as pyloroplasty, pyloromyotomy or injection of Botulinum toxin. Chemical pyloroplasty using BTA is a simple and fast method for treatment of the pylorus[14,15]. This literature review identified 11 studies evaluating the effect of intraoperative BTA injection during oesophagectomy.

Primary outcome: delayed gastric emptying

Seven out of these 11 studies reported DGE as a primary outcome [1,2,4,9,15,16,17]. These studies compared BTA versus other surgical pyloric procedures or no intervention. Only two studies demonstrated statistically significant difference in term of developing DGE after oesophagectomy between groups.

Cerfolio and his colleagues were able to demonstrate benefit of BTA on DGE ($p<0.001$) along with improved LOS and operative time ($p<0.015$ & $p< 0.037$) compared to NI, PM, PP groups. . This study eliminated some confounding effects by analysing the results of one technique performed by single operator. Fuchs et al. retrospectively reviewed 41 patients underwent robotic assisted trans-hiatal oesophagectomy and found that patients who had intraoperative BTA (14) had no pyloric dysfunction postoperatively, while eight patients in the no-BTA group (30%) required endoscopic therapy ($P < .05$). This study is limited by the small sample size.

Bagheri et al. studied 60 patients for the presence of DGE on radiological tests after surgery. He found no significant difference between the two groups and therefore, concluded that BTA is simple less invasive and complication free in preventing delayed gastric emptying. Similarly, Martin et al. reviewed 45 patients that underwent BTA injection during oesophagectomy. Only 2 patients developed clinically significant DGE requiring further intervention. He concluded that BTA is safe, simple and effective means of avoiding DGE.

On the other hand, Stewart et al retrospectively compared 71 patients undergoing minimally invasive oesophagectomy. They found that chemical pyloroplasty did not reduce DGE or other post-operative complications, although he noted that the BTA group had longer median hospital stay (13 vs 11) P 0.009.

Secondary outcome: Rate of endoscopic intervention (EPI)

In terms of requirement for endoscopic pyloric intervention (EPI), we identified four studies [2,17,16,18] that reported EPI in their outcomes. Only one study was a multi-centre study (Marchese et al) and all studies compared BTA to no intervention alone (Stuart et al) or to other pyloric drainage procedures (Pyloroplasty -PP, Pyloromyotomy- PM). Two studies reported statistically significant rate of postoperative endoscopic intervention when chemical pyloroplasty was used [2,18].

Marchese et al. retrospectively reviewed 90 patients and found that patients who had BTA required more EPI both during inpatient and outpatient settings (P: 0.032 and P: 0.003 respectively). A further sub-group pairwise analysis again demonstrated the same statistical significance for both in-patient and out-patient, between BTA and PP ($p= 0.038$ and 0.011) as well as BTA and NI groups ($p=0.038$ and 0.010). He concluded that there is no evidence of superiority of pyloric intervention compared to no treatment on gastric emptying. Similarly, Eldaif et al. retrospectively evaluated 322 patients. He concluded that patients in BTA group required more subsequent endoscopic interventions $P< 0.001$ and developed more reflux symptoms P 0.001. However, the operative time was much less compared to other groups $P<0.001$. Moreover, In Guiglano et al. study, of the 146 included patients, 26% required EPI, of which BTA group had the highest proportion (31.7%). However, this was not statistically significant. The BTA group also had

the highest odd ratios of EPI when compared to both PM (OR 3.84, p=0.03) and the PP group (OR 2.57, p=0.09).

Length of hospital stay

The length of stay following oesophagectomy as an outcome appeared in 4 studies [4,17,19,22]. One of these studies, Stewart et al. showed that patients who had BTA at time of oesophagectomy had a longer hospital stay compared to no pyloric intervention (median 13 vs 11 day, P 0.009). However, the reasons for these findings were unclear and it seem unlikely related to BTA intervention. Similar result was also suggested by Fuchs et al ($p<0.05$) and Cerfolio et al ($p<0.015$).

A number of confounding factors were identified such as: the brand of BTA, the dosage used, the exact type of operation (minimally invasive, 2-stage, 3-stage oesophagectomy) the precise administration of BTA, the presence or absence of gastric dysmotility prior to surgery and the use of prokinetic drugs. Coleski et al. reported that response to botulinum toxin injection in gastroparesis is dose dependent and more likely to occur in specific subgroups of patients. Thus, it is unclear whether the dosage of botulinum toxin used has any effect on the results of these studies. Five studies [1,2,4,19] used 200 units of BTA while two other studies injected half of this amount [16,18]. Stewart et al, used only 10 unit for chemical pyloroplasty.

The limitations of this study include the type of articles included. The majority was single institutional retrospective observational studies and no randomised controlled trials were identified; hence a pooled analysis of the results was not possible.

Given that the included studies are retrospective in nature and the selection of participants was made after the start of interventions, there are some concerns regarding selection bias compared to well conducted prospective randomised clinical trials. Moreover, the lack of standard definition for DGE results in difficulty in comparing outcomes from different studies.

Conclusion

Although chemical pyloroplasty intraoperatively with botulinum toxin is simple and safe, this literature review did not demonstrate any statistically significant benefit on gastric emptying following oesophagectomy. The rate of endoscopic pyloric intervention was higher in these patients as reported by some studies. Further studies in the form of multi-institutional randomised clinical trials will be necessary to investigate the outcome of chemical pyloroplasty during oesophagectomy.

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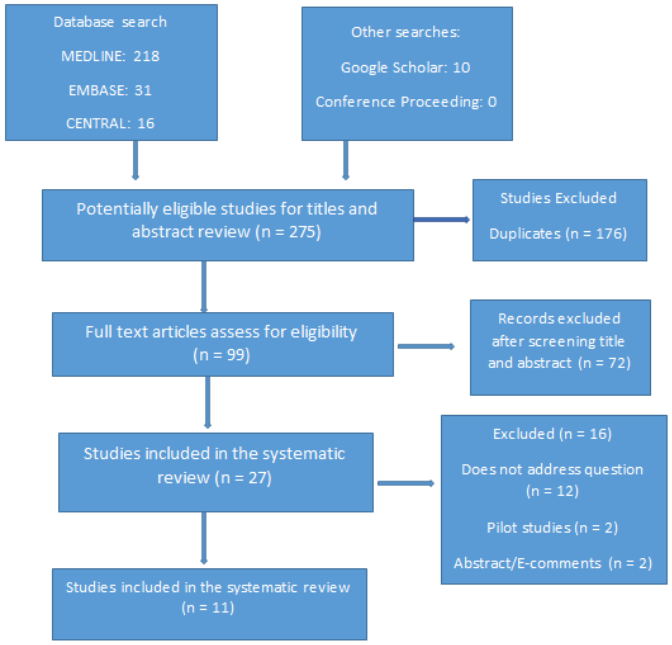
Legend Figures

Figure 1: Flow Diagram of Study Search



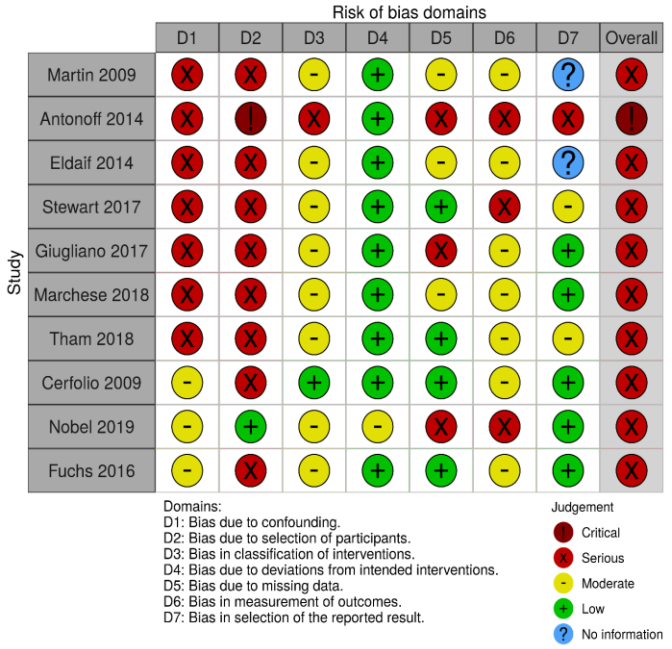


Figure 2: Assessment of risk of bias of the observational studies.

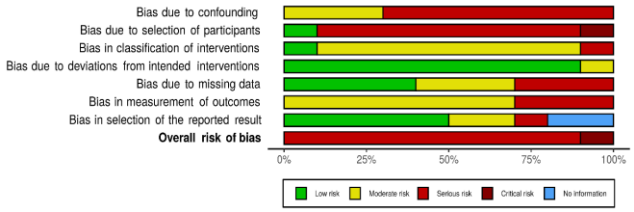


Figure 3: Risk of Bias graph (Observational studies).

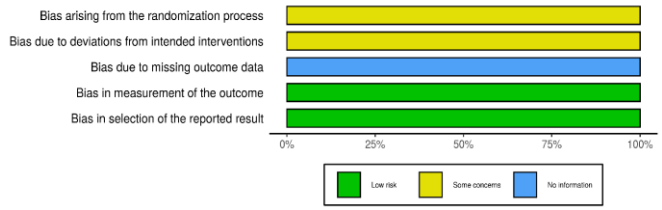


Figure 4: Risk of bias graph (Experimental study)

Table 1: Study characteristics

Year of study	Study design	Intervention	Number of patients	BTA dose	Outcomes
Bagheri 2012	Experimental randomised	BTA vs PP	30 vs 30 Total: 60	Botox 200 ml at upper and lower parts.	DGE evidenced by barium and isotope scans.
Stewart 2017	Observational study	BTA vs NI	35 vs 36 Total: 71 (MIE)	10 units injected at anterior pylorus at two sites.	DGE: clinical and radiological by barium study, EPI, median hospital stays.
Marchese 2018	Observational study	BTA vs PP vs NI	30 vs 30 vs 30 Total: 90	Pyloric digital dilatation and 200 U of BTA injected into 4 quadrants	NGT duration, NGT re-siting, EPI (IP&OP), DGE symptoms.
Giugliano 2017	Observational study	BTA vs PM vs PP vs NI	41 vs 38 vs 59 vs 8 Total: 146	100 units of BTA in 10 ml of solution to pyloric ring	EPI within 6 months due to conduit dysfunction.
Martin 2009	Observational study	BTA	Total: 45	200 U in 5 ml of 0.9% saline injected into pylorus at 4 points.	DGE: clinical, radiological (barium and isotope), self-assessment dysphagia
Antonoff 2014	Retrospective observational study	DL&BTA vs DL vs PP/PM vs NI	44 vs 8 vs 197 vs 44 Total: 293	200 mg in 8 ml delivered circumferentially into the pylorus.	Aspiration, anastomotic leak, gastric outlet obstruction, LOS, PP/PM complications.
Eldaif 2014	Observational study	BTA vs PP vs PM	78 vs 199 vs 45 Total: 322	Extraluminal pyloric injection using 100 U of BTA in 2 mL of NS (into 4 separate quadrants)	LOP, DGE by radiology, anastomotic dilation, EPI, postop promotility agents, reflux and/or dumping symptoms
Tham 2019	Retrospective observational study.	NI vs BTA	163 vs 65 Total 228	OGD 200 units in 4 separate quadrants or by lap open approach	DGE (NG output, radiological), leak rate, pneumonia risk, LOS
Fuchs 2016	Retrospective	BTA vs NI	14 vs 27	Robotic, intraluminal	Post-op pyloric stenosis,

	observational		Total: 41	injection of 200 U in 10ml of 0.9% saline	LOS, M&M
Nobel 2019	Retrospective observational	NI vs BTA vs PP/PM	157 vs 53 vs 73 Total: 283	Transabdominal, dose not specified	Any complication within 90 days
Cerfolio 2009	Retrospective Single centre	NI vs PP vs PM vs BTA	54 vs 28 vs 71 vs 68 Total 221	100 U in four quadrants	DGE, LOS, operative time

BTA: botulinum toxin A, PP: pyloroplasty, PM: pyloromyotomy, NI: no intervention, DL: digital dilatation, EPI: endoscopic pyloric intervention, LOS: length of stay, LOP: length of procedure, M&M: morbidity and mortality

Table 2: Summary of statistically significant results.

Year of study	Statistically significant outcome	P value	In favour of
Bagheri 2012	-	-	
Stewart 2017	LOS Operative time	0.009 0.001	Not in favour of BTA
Marchese 2018	NGT duration IP EPI OP EPI	0.001 0.032 0.003	Not in favour of BTA
Giugliano 2017	EPI (BTA vs PM)	0.03	No superiority of any intervention
Martin 2009	-	-	
Antonoff 2014	Aspiration	0.03	In favour of any pyloric drainage
Eldaif 2014	30 days mortality Dilation of oesophagus Dilation of pylorus Reflux Promotility agent LOP	0.009 0.001 0.001 0.001 0.04 0.001	Not in favour of BTA Not in favour of BTA Not in favour of BTA Not in favour of BTA Not in favour of BTA In favour of BTA
Fuchs 2016	No pyloric dysfunction, LOS	<0.05	In favour of BTA
Nobal 2019	More morbidity with Botox	<0.0001	Not in favour of BTA
Tham 2019	-	-	
Cerfolio 2009	DGE improved LOS Operative time	<0.001 <0.015 <0.037	In favour of BTA

EPI: endoscopic pyloric intervention, BTA: botulinum toxin, IP/OP: inpatient/outpatient, LOS: length of stay, LOP: length of procedure.