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Research article

Impact of intravenous injection of glucagon on anastomotic leakage in esophagectomy

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ABSTRACT

Background: Anastomotic leakage after esophagectomy affects the early postoperative state and prognosis. However, effective measures to prevent anastomotic leakage in esophagogastric anastomosis have not been established.

Methods: This single-center, retrospective, observational study included 147 patients who underwent esophagectomy for esophageal cancer between 2010 and 2020. Glucagon was administered to extend the gastric tube in patients who underwent esophagectomy from January 2016. The patients were divided into two groups: a glucagon-treated group (2016–2020) and a control group (2010–2015). The incidence of anastomotic leakage was compared between the two groups for evaluation of the preventive effects of glucagon administration on anastomotic leakage.

Results: The length of the gastric tube from the pyloric ring to the final branch of the right gastroepiploic artery was extended by 2.8 cm after glucagon injection. The incidence of anastomotic leakage was significantly lower in the glucagon-treated group (19% vs. 38%; $p = 0.014$). Multivariate analysis showed that glucagon injection was the only independent factor associated with a reduction in anastomotic leakage (odds ratio, 0.26; 95% confidence interval, 0.07–0.87). Esophagogastric anastomosis was performed proximal to the final branch of the right gastroepiploic artery in 37% patients in the glucagon-treated group, and these cases showed a lower incidence of anastomotic leakage than did those with anastomosis distal to the final branch of the right gastroepiploic artery (10% vs. 25%, $p = 0.087$).

Conclusions: Extension of the gastric tube by intravenous glucagon administration during gastric mobilization in esophagectomy for esophageal cancer may be effective in preventing anastomotic leakage.

1. Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide, with the overall 5-year survival rate ranging from 15% to 25% [1]. Although various treatment methods have been developed and the efficacy of chemoradiotherapy for esophageal cancer has been reported, surgical resection of the esophagus with en bloc lymphadenectomy is a fundamental part of treatment for esophageal cancer [2–4]. However, esophagectomy is a highly invasive treatment procedure that can cause serious complications such

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as anastomotic leakage, pneumonia, and recurrent nerve palsy. Despite improvements in surgical techniques and perioperative management, the incidence of anastomotic leakage associated with esophagectomy reportedly ranges from 11% to 34% [5–8]. Anastomotic leakage has a negative impact on not only short-term outcomes but also the nutritional status and long-term prognosis [9–11]. Reconstruction with a gastric tube is a very common procedure in esophageal cancer surgery, and the high frequency of suture failure is attributed to the blood flow in the gastric tube.

Glucagon acts directly on the smooth muscle cells of the gastrointestinal tract, inhibiting gastrointestinal peristalsis [12,13]. It is often administered in endoscopy or fluoroscopy because of its inhibitory effect on gastrointestinal peristalsis, and its usefulness as a pre-treatment for examination has been reported [14,15]. We focused on the inhibitory effects of glucagon on gastric peristalsis and stretching and hypothesized that extension of the gastric tube via administration of glucagon during reconstruction would facilitate anastomosis at a site with better blood flow, thus lowering the incidence of anastomotic leakage. Therefore, in the present study, we investigated whether intravenous glucagon administration could elongate the gastric tube and determined whether the elongated gastric tube could lower the incidence of anastomotic leakage in patients undergoing esophagectomy with cervical esophagogastric anastomosis.

2. Methods

2.1. Patients

This retrospective, single-center, observational study included patients with histopathologically confirmed thoracic esophageal cancer without distant organ metastases who underwent elective esophagectomy with cervical esophagogastric anastomosis at our department between January 2010 and December 2020. The exclusion criteria were as follows: 1) additional requirement of vascular anastomosis, 2) resection and reconstruction in a separate surgery, 3) anastomosis at locations other than the neck, and 4) reconstruction using the jejunum or colon. Glucagon was administered during esophagogastric anastomosis in all patients who underwent esophagectomy from January 2016. Accordingly, the patients were divided into two groups: a control group of patients treated from January 2010 to December 2015 and a glucagon-treated group of patients treated from January 2016 to December 2020. All patients were staged according to the criteria of the 7th edition of the TNM classification proposed by the International Union against Cancer. All patients provided written informed consent to undergo the procedure. This study was approved by the research ethics committee of Kobe City Medical Center General Hospital (No. zn210317). Informed consent for use of the patients' data was waived because of the retrospective study design.

2.2. Surgical procedures

The basic surgical procedures comprised thoracoscopic subtotal esophagectomy with mediastinal and abdominal lymphadenectomy, reconstruction using a gastric tube, and anastomosis at the cervical incision. Cervical lymph node resection was performed at the discretion of the surgeon, whose decision was based on the tumor location and clinical stage. The gastric mobilization and reconstruction procedure is illustrated in Fig. 1. After the gastric tube created by the abdominal procedures was constructed ex vivo, the distance from the pyloric ring to the final branch of the right gastroepiploic artery (RGEA) was measured as the length of the gastric

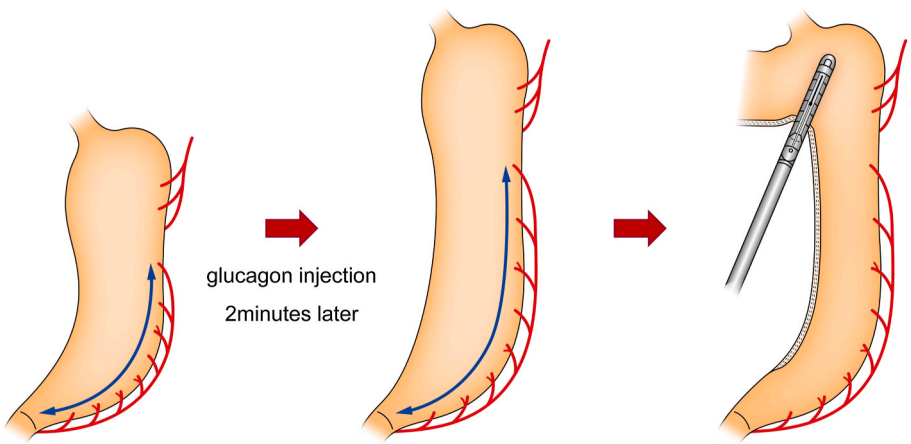

Fig. 1. Gastric mobilization and reconstruction with a gastric tube in esophagectomy for esophageal cancer. After the gastric tube created by abdominal procedures was constructed ex vivo, the distance from the pyloric ring to the final branch of the right gastroepiploic artery (RGEA) was measured as the length of the gastric tube before glucagon injection. Two minutes after intravenous administration of 1 mg of glucagon, the length from the pyloric ring to the final branch of the RGEA was measured again. Then, while the stomach was stretched and extended, a narrow gastric tube with a width of 4 cm was created using a linear stapler along the greater curvature of the stomach. After the stomach was pulled up to the neck, esophagogastric anastomosis was performed.

tube before glucagon injection. Two minutes after intravenous administration of 1 mg of glucagon, the length from the pyloric ring to the final branch of RGEA was measured again. Then, while the stomach was stretched and extended, a narrow gastric tube with a width of 4 cm was created using a linear stapler along the greater curvature of the stomach. After the stomach was pulled up to the neck, esophagogastric anastomosis was performed.

2.3. Outcomes

Information on perioperative data was retrieved from our medical records. Postoperative complications were defined using the Clavien–Dindo classification [16]. The short-term perioperative results, particularly the incidence of anastomotic leakage, were compared between the control group and glucagon-treated group. Independent factors related to the occurrence of anastomotic leakage were identified using multivariate analysis. In a secondary analysis for the glucagon-treated group, we assessed the site of the final anastomosis in the gastric tube and compared the incidence of anastomotic leakage according to the identified sites. To investigate the effectiveness of anastomosis at a site with better blood flow, we classified the patients in the glucagon-treated group into two groups: a group with anastomosis proximal to the final branch of RGEA and a group with anastomosis distal to the final branch of RGEA.

2.4. Statistical analysis

The baseline characteristics of the control and glucagon-treated groups were compared using the Mann-Whitney *U* test, the chi-square test, and Student's *t-test*. A Cox proportional hazards regression model was used to identify variables that were significantly associated with the prevention of anastomotic leakage. Continuous variables are expressed as means and standard deviations. All statistical analyses were performed using JMP version 12 (SAS Institute Inc., Cary, NC, USA). A *P*-value of <0.05 was considered statistically significant.

3. Results

In total, 168 patients underwent transthoracic esophagectomy with lymph node dissection at our hospital between 2010 and 2020. From these, 147 patients who underwent thoracoscopic esophagectomy with gastric reconstruction and met the inclusion criteria were enrolled in our study. The control and glucagon-treated groups included 64 and 83 patients, respectively. The characteristics of patients in the two groups are shown in Table 1. Triangulating anastomosis through the posterior mediastinal route was more common in

Table 1
Characteristics of patients who underwent esophagectomy for esophageal cancer.

Variable		Control group	Glucagon group	*P*-value
n		64	83	
Age (years)		65.6 ± 7.0	66.3 ± 8.6	0.585
Sex	Male	50	62	0.629
	Female	14	21	
Body mass index (kg/m^2)		21.8 ± 3.1	21.4 ± 3.1	0.481
Histology	SCC	59	71	0.256
	AC	5	12	
Clinical stage	Stage 0	0	4	0.198
	Stage I	33	36	
	Stage II	14	12	
	Stage III	11	20	
	Stage IVA	6	11	
Neoadjuvant therapy	Performed	33	39	0.582
	Not performed	31	44	
CCI	0	37	47	0.821
	1–2	20	29	
	≥3	7	7	
GPS	0	52	74	0.266
	1	11	7	
	2	1	2	
PNI		47.3 ± 4.9	48.8 ± 5.4	0.152
Anastomosis method	Modified Collard	29	12	<0.001
	Circular stapler	30	7	
	Triangulating	5	64	
Reconstruction route	Retrosternal	37	80	<0.001
	Posterior mediastinal	27	3	

Glucagon was administered to extend the gastric tube in patients who underwent esophagectomy from January 2016. The patients were divided into two groups: a glucagon-treated group (2016–2020) and a control group (2010–2015).
SCC: squamous cell carcinoma, AC: adenocarcinoma, CCI: Charlson Comorbidity Index, GPS: Glasgow Prognostic Score, PNI: Prognostic Nutritional Index.

the glucagon-treated group. There were no significant between-group differences in the clinical background, including age; sex; body mass index; histology; clinical stage; neoadjuvant therapy; and past medical history of hypertension, hyperlipidaemia, and diabetes mellitus.

After glucagon administration, the length of the gastric tube did not decrease in any case, and it increased in 95% cases. The mean length of the gastric tube from the pyloric ring to the final branch of RGEA was 25.0 (±3.3) and 27.8 (±3.5) cm before and after glucagon administration, respectively (Fig. 2). Thus, glucagon administration prolonged the gastric tube by 2.8 (±1.4) cm. With regard to the outcomes during the perioperative period, the operation time was significantly longer in the glucagon-treated group than in the control group (572 min vs. 530 min, $p = 0.006$), whereas the incidence of anastomotic leakage was significantly lower in the former than in the latter group (19% vs. 38%, $p = 0.014$, Table 2).

In multivariate analysis to adjust for differences in patient backgrounds between the two groups, glucagon administration was identified as the only independent factor associated with the prevention of anastomotic leakage ($p = 0.042$, Table 3). The preoperative status, anastomotic method, and reconstruction route were not associated with the incidence of anastomotic leakage.

Esophagogastric anastomosis was achieved proximal to the final branch of RGEA in 31 of the 83 (37%) patients in the glucagon-treated group; these patients tended to show a lower frequency of anastomotic leakage than did patients with anastomosis distal to the final branch of RGEA (10% vs. 25%, $p = 0.087$, Table 4).

4. Discussion

Anastomotic leakage in esophagogastric anastomosis is a frequent and important problem after esophageal resection. Prevention of postoperative complications such as anastomotic leakage and strictures is important to decrease associated morbidities and mortality [17–20]. Previous studies have reported several predictors of anastomotic leakage, such as the size of the narrow thoracic inlet and the length from the suprasternal notch to the trachea [21,22]. Although diabetes mellitus, cardiovascular disease, active smoking, and obesity are also considered risk factors for anastomotic leakage, these preoperative factors are difficult to manage or modify. Various anastomotic methods to reduce anastomotic leakage have been developed and tested for their effectiveness [23–25]. A systematic review and meta-analysis found that gastric ischemic conditioning before esophagectomy plays an important role in reducing the risk of anastomotic leakage and stricture [26]. However, to our knowledge, no widely accepted method has been developed for enhancing blood flow in the gastric tube during esophagectomy. We found that intravenous administration of glucagon extended the gastric tube and lowered the incidence of anastomotic leakage in patients with esophagogastric anastomosis after esophagectomy.

Only two studies by Michael et al. and Francis et al. respectively, have reported the effectiveness of glucagon administration during anastomosis [27,28]. These studies involved anastomosis of the rectum and showed that administration of glucagon was useful in overcoming the spasm of the rectal stump, which disrupted transanal end-to-end anastomosis using a stapler. To our knowledge, there have been no reports of the use of glucagon in gastrointestinal anastomosis other than rectal anastomosis, and this is the first study to demonstrate the effectiveness of intravenous glucagon administration in the prevention of anastomotic leakage in esophagogastric anastomosis.

Glucagon and anticholinergics are the key drugs that are usually necessary for endoscopy to facilitate endoscopic intubation. However, anticholinergic medications should be cautiously used in patients with heart disease, hypertension, glaucoma, and urinary difficulties. In contrast, diabetes mellitus is a risk factor for glucagon administration because of the hyperglycemic effects of glucagon. Glucagon as well as anticholinergic agents act directly on the smooth muscles of the gastrointestinal tract and inhibit peristaltic activity [12]. In terms of adverse effects, the effect of glucagon on hemodynamic parameters such as blood pressure and heart rate is negligible when compared with the effect of anticholinergic agents [29]. In this study, we intravenously administered glucagon to prolong the

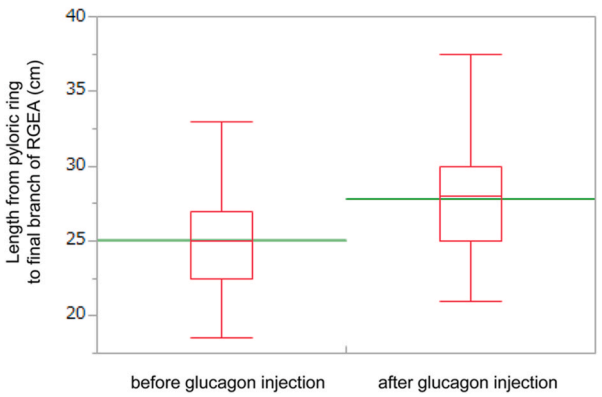

Fig. 2. Length from the pyloric ring to the final branch of the right gastroepiploic artery (RGEA) before and after intravenous glucagon administration to extend the gastric tube in patients subjected to esophagectomy. The boxplots represent median, first and third quarter, and minimum and maximum values. Each horizontal line indicates the value.
The mean length of the gastric tube from the pyloric ring to the final branch of RGEA was 25.0 (±3.3) and 27.8 (±3.5) cm before and after glucagon administration, respectively. Thus, glucagon administration prolonged the gastric tube by 2.8 cm (±1.4 cm).

Table 2
Outcomes during the perioperative period for patients who underwent esophagectomy for esophageal cancer.

Variable	Control group	Glucagon group	*P*-value
Operation time	530 ± 11	572 ± 10	0.006
Blood loss (ml)	292 ± 30	215 ± 26	0.056
Pulmonary complication (%)	12 (19)	11 (13)	0.363
Recurrent nerve palsy (%)	17 (26)	15 (18)	0.216
Anastomotic leakage (%)	24 (38)	16 (19)	0.014
Anastomotic leakage > Grade III (%)	16 (25)	8 (10)	0.013

Glucagon was administered to extend the gastric tube in patients who underwent esophagectomy from January 2016. The patients were divided into two groups: a glucagon-treated group (2016–2020) and a control group (2010–2015).

Table 3
Multivariate analysis of factors associated with anastomotic leakage in esophagectomy for esophageal cancer.

Variable		Odds Ratio	95% CI	*P*-value
Body mass index		1.10	0.96–1.27	0.162
Operation time		0.99	0.99–1.00	0.327
Blood loss		1.00	0.99–1.00	0.147
Neoadjuvant chemotherapy	Performed	0.46	0.19–1.09	0.077
PNI		1.30	0.14–12.06	0.817
CCI	0	1 (reference)		
	1–2	0.477	0.11–0.18	0.109
	≥3	1.41	0.36–5.22	0.613
Anastomotic method	Modified Collard	1 (reference)		
	Circular stapler	0.79	0.22–2.72	0.71
	Triangulating	1.14	0.32–4.59	0.85
Reconstruction route	Retrosternal	2.65	0.70–11.52	0.155
Glucagon administration	Performed	0.26	0.07–0.87	0.028

CI: confidence interval, CCI: Charlson Comorbidity Index, GPS: Glasgow Prognostic Score, PNI: Prognostic Nutritional Index.

Table 4
Frequency of anastomotic leakage according to the location of the anastomosis relative to the RGEA in the glucagon-treated group.

Variable	Proximal to the final branch of RGEA	Distal to the final branch of RGEA	*P*-value
Anastomotic site	31	52	
Anastomotic leakage (%)	3 (10)	13 (25)	0.087
Anastomotic leakage > Grade III (%)	1 (3)	7 (13)	0.126

Glucagon was administered to extend the gastric tube in patients who underwent esophagectomy from January 2016.
RGEA: right gastroepiploic artery.

gastric tube. Glucagon-induced hyperglycemia is considered transient, and there were no cases with difficult anaesthetic management in the glucagon-treated group.

Ischemia can be a risk factor for anastomotic leakage [30–33]. Ikeda et al. examined the tissue blood flow in the gastric tube and reported an association between decreased blood flow and anastomotic leakage [29]. Libermann-Meffert et al. reported that RGEA is the main feeder for the greater curvature gastric tube, while the contribution of the right gastric vessels is negligible [34]. Glucagon administration increased the control area of RGEA by elongating the gastric tube, and this increased the possibility of anastomosis at a site with better blood flow and, consequently, reduced anastomotic leakage. This was confirmed by our finding of less frequent anastomotic leakage in cases with anastomosis proximal to the final branch of RGEA than in cases with anastomosis distal to the final branch of RGEA. One concern related to our method is the reshortening of the gastric tube due to gastric peristalsis, attributed to loss of the effect of glucagon. However, we believe that the gastric tube will not shrink even after cessation of the effect of glucagon because there is no change in the stapler length, which defines the length of the gastric tube.

The perioperative results of the present study showed that the operation time was significantly longer in the glucagon-treated group than in the control group. This was probably related to the introduction of robotic esophagectomy from April 2018, which tends to take longer than does thoracoscopic esophagectomy. Glucagon administration does not prolong the operation time because the drug is intravenously injected, and the time for onset of action is estimated at approximately 45 s [35]. A wait time of 2 min after glucagon administration is considered sufficient to achieve gastric tube elongation.

This study has several limitations. First, it was a single-center, retrospective study with a relatively small sample size. Second, the anastomotic technique and reconstruction route differed between the two groups. Our surgical techniques for anastomosis and reconstruction have changed greatly in the past decade. Although we conducted a multivariate analysis including factors believed to be related to anastomotic leakage to determine if the administration of glucagon plays a role in decreasing the incidence of anastomotic leakage, factors such as the experience and maturity of the surgeon and team over time could not be adjusted. Further prospective

studies, including randomised studies with standardised anastomotic methods and reconstruction routes, are warranted to confirm the effectiveness of glucagon administration in esophagogastric anastomosis.

In conclusion, the findings of this study suggest that intravenous glucagon administration is an easy, safe, and effective technique to prolong the gastric tube and prevent anastomotic leakage in patients undergoing esophagectomy with cervical esophagogastric anastomosis.

Author contribution statement

Ryosuke KITA: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hiroyuki Kobayashi: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Msato Kondo: Satoshi Kaihara: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Sources of funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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