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Original Contribution

Effectiveness of glucagon in relieving esophageal foreign body impaction: a multicenter study☆,☆☆

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ABSTRACT

Purpose: Glucagon is thought to decrease lower esophageal sphincter tone and is used as an alternative to invasive endoscopy for esophageal foreign body impaction (EFBI). The purpose of this study was to evaluate efficacy and safety of glucagon and identify characteristics associated with success.
Methods: A multicenter, retrospective study of patients receiving glucagon for EFBI at 2 academic emergency departments was conducted between 2006 and 2010. A control group of patients that did not receive glucagon was evaluated. Data collection included demographics, type of foreign body, glucagon dose, resolution of impaction, incidence of vomiting, additional medication, and endoscopy required. Descriptive and univariate analysis was performed as appropriate.
Results: A total of 133 doses of glucagon were administered in 127 patients. Glucagon-related resolution of EFBI occurred in 18 patients (14.2%) and vomiting in 16 patients (12.6%). No statistical differences between successful and unsuccessful groups were seen with the exception of concomitant medication administration (benzodiazepine or nitroglycerin) being associated with less glucagon success, 33.3% vs 59.6%, respectively ($P = .04$). Eighty-four percent of patients in the unsuccessful group underwent endoscopy. Comparing those that received glucagon ($n = 127$) and the control group ($n = 29$), there was no significant difference in resolution of EFBI, 14.2% vs 10.3%, respectively ($P = .586$).
Conclusions: Glucagon-related resolution occurred in 14.2% of patients and was not significantly different compared with those that did not receive glucagon (10.3%). Concomitant medication administration was associated with lower success. Overall, glucagon had a low success rate, was related to adverse effects, and does not offer advantages for treatment.

1. Introduction

Acute esophageal foreign body impactions (EFBIs) are a relatively rare chief concern in the emergency department (ED); however, the complications to patients can be devastating and costly. An esophageal foreign body can cause abrasions, punctures, and perforations, with resultant injuries and infection to surrounding structures. These can include abscesses, pneumomediastinum, mediastinitis, pneumothorax, pericarditis, cardiac tamponade, fistulas, aspiration pneumonia, and vascular injuries to the aorta or pulmonary vessels. Button battery impaction, in particular, can rapidly cause esophageal necrosis. Therefore, timely treatment is paramount to help mitigate subsequent morbidity and health care costs.

Indications for expectant management include a patent airway and the ability to clear secretions. In many cases, patients may experience significant pain, which heightens the need for early intervention to dislodge the foreign body. Endoscopy with direct visualization and removal of the object or aiding in its distal progression into the stomach is the criterion standard and preferred definitive therapy. This procedure is invasive, expensive, and time consuming because it requires the involvement of a consultant who often may not be on-site, requires procedural sedation, and is not without its own significant risks and complications (eg, esophageal perforation, aspiration, apnea, hypoxia). Therefore, the ideal treatment modality in this clinical scenario would be one that worked rapidly, is noninvasive, and has a low risk of complications.

Many physicians choose to apply one of several less invasive modes of therapy before considering endoscopy. A nonpharmacologic

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treatment option that has been shown to be the most effective nonendoscopic treatment modality is the administration of carbonated beverages which is inexpensive, is safe, and has an average success rate of 79% [1]. Pharmacologic agents that have been described for this purpose include nifedipine, sublingual nitroglycerin, proteolytic enzymes, benzodiazepines, and the most frequently implemented therapy, glucagon [2]. Glucagon, first proposed in 1977, has been shown to decrease lower esophageal sphincter tone by causing smooth muscle relaxation [3,4]. Based on this mechanism of action, glucagon has become one of the most widely accepted, first-line agents for EFBI in the ED despite the fact that the literature supporting its use is controversial and of poor quality [5]. Currently, only 6 studies exist in the medical literature evaluating the efficacy of this therapy despite its widespread use. Of these, only 2 have actually investigated glucagon therapy alone [5]. Glucagon generally has few adverse effects, which may contribute to its popularity, most commonly nausea and vomiting. Consequently, these adverse effects may contribute to the anecdotal success of this agent by causing dislodgement of the foreign body. However, symptom resolution via this mechanism carries with it a significant risk of aspiration. The cost of glucagon is also not inconsequential, as the Average Wholesale Price at the time of publication is approximately $206 for 1 mg. Although this cost is significantly less than that of endoscopy, if it is ineffective or results in aspiration, then this further compounds both the expense and complexity of this clinical scenario.

The purpose of this study was to evaluate the efficacy of glucagon for the resolution of EFBI at 2 large academic EDs. We also hoped to explore the adverse effect profile of this agent in this setting to better clarify the risk-benefit ratio of its use in this scenario. In addition, we sought to evaluate the characteristics associated with the successful use of glucagon for this indication.

2. Materials and methods

2.1. Study design

This was a retrospective, observational study of patients who received glucagon for EFBI in 2 academic EDs (n = 127). A small control group of EFBI that did not receive glucagon was also included for comparison (n = 29). Approval for this study was obtained from the institutional review boards at both institutions.

2.2. Study setting and population

This study was conducted in 2 academic EDs. The University of Rochester Medical Center (URMC) and University of Kentucky Medical Center (UK) are 739-bed and 745-bed university teaching hospitals, respectively at the time of this study. Data were collected from May 2006 through July 2010 at URMC and January 2007 through December 2009 at UK. Patients were captured by retrospective review of automated dispensing cabinet reports and *International Classification of Diseases, Ninth Revision,* codes (ie, 935.1, 938, 530.3, E912, E915) to identify those that received glucagon or presented with EFBI in the EDs. All adult and pediatric patients presenting to the ED that received glucagon for an EFBI were included. Both the administration of glucagon and the indication for its use in EFBI were confirmed by review of medical records. There were no additional exclusion criteria.

2.3. Study protocol

A complete medical record review was conducted by 1 abstractor at each institution using a standardized abstraction form and code book to gather demographics including age, sex, type of foreign body ingested, glucagon dose administered, incidence of resolution of the EFBI, time to resolution, incidence of vomiting, time from glucagon administration to vomiting, and known patient esophageal abnormalities. Additional medications given for EFBI (ie, benzodiazepines, nitroglycerin), the need for endoscopy, and endoscopy-related adverse effects were collected. *Glucagon efficacy* was defined as documented resolution of symptoms within 60 minutes from administration. Sixty minutes was chosen based on the peak effect of glucagon, the published duration of glucagon-induced lower esophageal sphincter relaxation, and use of this time frame in the only available randomized controlled trial [3,6,7]. Patients that were administered glucagon and vomited within 60 minutes were not deemed successful because this is not the proposed mechanism of glucagon for relief of EFBI. After patients were determined to have had successful or unsuccessful resolution of symptoms with glucagon, these 2 groups were further analyzed to attempt to describe characteristics associated with glucagon success. Also, success of EFBI relief with glucagon was compared with a small group of EFBI patients that did not receive glucagon. *Spontaneous resolution* in the patients that did not receive glucagon or any pharmacologic therapy was defined as self-reported resolution of symptoms at any point during the ED visit.

2.4. Data analysis

Descriptive analyses were performed for all variables collected. Associations between continuous and categorical variable were assessed using Wilcoxon rank sum and Fisher exact analysis, respectively. Statistical significance was defined as a 2-tailed P value ≤ .05.

3. Results

A total of 127 patients that received intravenous or intramuscular glucagon for the indication of EFBI between May 2006 and July 2010 at URMC and January 2007 and December 2009 at UK were included in this review. There were 85 males (66.9%), and the median age of the patients was 35.5 years (range, 2-89 years). The most common types of foreign body impaction were food (89%) and coins (8%). Esophageal abnormalities were present in 22 patients (17.3%).

There were 133 doses of glucagon administered, and the median glucagon dose was 1 mg (interquartile range, 1-1 mg). Glucagon was successful in the resolution of EFBI symptoms in 18 patients (14.2%). Four patients received 2 sequential doses of glucagon and 1 patient received 3 sequential doses of glucagon without success. Overall, vomiting occurred in 16 patients (12.6%). A total of 73 patients (57.5%) received an additional medication for EFBI (ie, benzodiazepines, nitroglycerin). Five patients received more than 1 concomitant medication in addition to glucagon. Timing of benzodiazepine and nitroglycerin administration compared with glucagon varied greatly, with 46.2%, 34.6%, and 19.2% of doses occurring before, after, or simultaneously with glucagon, respectively. However, only 6 patients that received glucagon and another medication had glucagon-related EFBI symptom resolution. Endoscopy was required in 92 patients (84.4%) that did not have glucagon-related success. A superficial esophageal laceration was reported during the procedure in 1 patient. No major adverse events were noted with the endoscopy procedure.

Analysis was performed to assess the characteristics associated with glucagon-related success (Table 1). Comparisons between the successful and unsuccessful groups did not reveal any statistical differences with the exception of concomitant medication administration.

Table 1
Comparisons between glucagon-related successful and unsuccessful groups

Characteristics	Successful (n = 18)	Unsuccessful (n = 109)	P value
Median age, y (range)	45 (12-67)	34.5 (2.1-89)	.30[a]
Sex, no. male (%)	12 (66.7)	73 (67.0)	.98[b]
Type of foreign body, no. food (%)	18 (100)	95 (87.2)	.11[b]
Esophageal abnormality, no. (%)	1 (5.6)	21 (11.0)	.15[b]
Concomitant medications, no. (%)	6 (33.3)	65 (59.6)	.04[b]

[a] Wilcoxon rank sum.
[b] Fisher exact test.

Table 2
Comparisons between glucagon administration and control groups

Characteristics	Glucagon administered (n = 127)	Control (n = 29)	*P* value
Median age, y. (range)	35.5 (2.1-89)	55 (20-82)	<.0001[a]
Sex, no. male (%)	85 (66.9)	17 (58.6)	.40[b]
Type of foreign body, no. food (%)	113 (89.0)	27 (93.1)	.74[b]
Esophageal abnormality, no. (%)	22 (17.3)	6 (20.7)	.79[b]
Concomitant medications, no. (%)	71 (55.9)	2 (6.9)	<.0001[b]
Successful resolution, no. (%)	18 (14.2)	3 (10.3)	.59[b]

[a] Wilcoxon rank sum.
[b] Fisher exact test.

Concomitant medication administration occurred more often in the unsuccessful group compared with the successful group, 59.6% vs 33.3%, respectively ($P = .04$).

A small group of control patients with EFBI that did not receive glucagon was included (n = 29). There were no differences in sex, type of foreign body, or esophageal abnormality, but a significant difference in age and use of concomitant medication between those that received glucagon and those that did not was identified (Table 2). Only 3 patients (10.3%) had spontaneous resolution, and the other 26 patients (89.7%) required endoscopy. There was no significant difference in resolution of EFBI between those that received glucagon (14.2%) compared with those that did not (10.3%), $P = .586$.

4. Discussion

Treatment of EFBI can include expectant management for stable patients, carbonated beverage administration, pharmacological intervention, and endoscopic evaluation. Glucagon is one of the more commonly used pharmacologic agents for EFBI and is thought to decrease lower esophageal sphincter tone by causing smooth muscle relaxation, therefore allowing the foreign body to pass, leading to symptom relief [3,4]. This has been a popular treatment modality in the ED in an attempt to prevent the need for endoscopy. Endoscopy is expensive, can have significant adverse effects, and involves a medical specialty consultant. In addition, this can prolong patient length of stay in the ED. Although there are data supporting the physiologic mechanism of glucagon on lower esophageal sphincter resting pressure, robust literature supporting its clinical efficacy in EFBI is lacking [3,5].

There are a number of previously published studies that attempt to evaluate intravenous glucagon for this indication. The first is a prospective, double-blind, placebo-controlled trial evaluating the use of glucagon in combination with diazepam compared with placebo in patients with EFBI [7]. Nine of 24 patients (38%) in the treatment group had resolution of symptoms compared with 6 of 19 (32%) in the placebo group. This study was not able to show a statistical difference between the glucagon/diazepam compared with placebo groups similar to our study (glucagon success 14.2% vs no glucagon success 10.3%, $P = .586$). It is difficult to draw conclusions about glucagon therapy alone because all patients received combination therapy. In addition, patients with esophageal abnormalities were excluded, which is less representative of the diverse EFBI population because close to 90% of these patients have some underlying esophageal pathology [8].

Mehta et al [9] conducted a 2-phase trial evaluating glucagon use for EFBI. The first phase was a prospective, double-blind, controlled trial that evaluated weight-based intravenous glucagon compared with placebo in children 1-8 years old with coin ingestions. Those that did not have resolution of symptoms in phase 1 were included in the second phase of the trial. The second phase allowed open-label glucagon administration. Overall, those that received glucagon had a lower success rate compared with placebo, 2 of 15 (13%) vs 3 of 5 (60%), respectively. No patients who received additional doses of glucagon had improved success. Of note, 11 of 15 (73%) vomited; however, this was not associated with symptom resolution. Although we had a much lower rate of vomiting in our patient population (16/127, 12.6%), this is still a significant adverse medication event with potential complications. Both of these prospective trials failed to show that using intravenous glucagon for EFBI symptom relief was more efficacious than placebo.

Similar to our study, there are 2 retrospective studies evaluating the use of glucagon for EFBI. A case series of 92 patients found that 30 of 92 (32.6%) patients that received glucagon had symptom resolution (mean time to resolution was 38 minutes [10-95 minutes]) [10]. Based on glucagon pharmacokinetics and known time of glucagon-induced lower esophageal sphincter relaxation, it is difficult to deem glucagon-related success vs spontaneous resolution after 60 minutes. This may account for the higher rate of success in this study compared with our evaluation (32.6% vs 14.2%). Furthermore, there were 19 patients that received a benzodiazepine in addition to glucagon. Concomitant administration was found to improve the rate of symptom relief, which also differs from our results. Once again, this could be a consequence of the extended time frame used to identify therapy success. The second retrospective analysis evaluated 222 patients with EFBI. A total of 106 patients received intravenous glucagon (48%). Only 9% of these patients had complete resolution of symptoms compared with 17% that had spontaneous resolution [11]. This was a study of all patients presenting with EFBI; hence, selection bias may be present due to the absence of a randomization protocol. Nevertheless, the findings once again suggest that glucagon is no better than expectant management. The fact that only 48% of patients with EFBI received IV glucagon is also substantially different from our sample in which 127 of 156 (81.4%) received glucagon as a first-line therapy.

Our retrospective evaluation found that glucagon-related symptom resolution was evident in 14.2% of patients. Although our study has a similar design to the other retrospective studies available in the literature, there are a number of key differences. Glucagon is administered to the majority of EFBI in our EDs, decreasing selection bias. In addition, we included patients of all ages, of all types of foreign body ingestions, and with known esophageal abnormalities, making our sample more consistent with the general EFBI patient population and those that receive glucagon. Our data also represent the only controlled trial in the last 10 years and show that although efficacy data are lacking, the use of glucagon is still prevalent in the ED. Furthermore, based on available medication properties and previous literature, we used a definition of patient-reported symptom relief within 60 minutes to describe success from glucagon. This was used to ensure that EFBI symptom relief was most likely attributed to glucagon administration and not spontaneous resolution. We did identify that those patients in whom glucagon was administered were also significantly more likely to also receive concomitant therapy (benzodiazepines or nitroglycerin) (55.9% vs 6.9%, $P < .0001$). However, we also found that despite additional pharmacotherapy in addition to glucagon, these patients were less likely to have glucagon-related EFBI resolution. These results are different from previous publications and may be somewhat counterintuitive. A reason for this finding may be that some patients, possibly based on anatomy or size of the foreign body, will not have resolution of symptoms regardless of the medications administered. It also may represent a selection bias for those patients presenting with a more critical constellation of symptoms or more impressive impaction leading physicians to prescribe a more aggressive therapy.

4.1. Limitations

These results are not without limitations. This is a retrospective review, and as a result, the data obtained are limited by the documentation available. We attempted to collect data in a uniform manner using a single abstractor at each institution, a standardized extraction form, defined study definitions, and a code book. However, we were not able to blind the medical record reviewers because they were also investigators, and we did not test interrater agreement to evaluate selective abstraction bias. Lastly, although we attempted to define a time frame for glucagon-related EFBI symptom resolution, it is still possible that there were spontaneous resolutions within 60 minutes and glucagon success beyond 60 minutes.

5. Conclusion

In our EDs, glucagon-related resolution of EFBI occurred in 14.2% of patients. This rate of resolution was not significantly different from the control group of patients that did not receive glucagon. Concomitant medication administration with a benzodiazepine or nitroglycerin was also found to be associated with a lower success rate. Our data represent the largest, multicenter, sample of patients evaluating glucagon use for EFBI and suggest that glucagon has a relatively low success rate, has potential to result in adverse effects, and does not offer additional advantages to promote EFBI resolution.

References

[1] Leopard D, Fishpool S, Winter S. The management of oesophageal soft food bolus obstruction: a systematic review. Ann R Coll Surg Engl 2011;93:441–4.
[2] Arora S, Galich P. Myth: glucagon is an effective first-line therapy for esophageal foreign body impaction. Can J Emerg Med 2009;11:169–71.
[3] Colon V, Grade A, Pulliam G, Johnson C, Fass R. Effect of doses of glucagon used to treat food impaction on esophageal motor function of normal subjects. Dysphagia 1999;14:27–30.
[4] Hogan WJ, Dodds WJ, Hoke SE, Reid DP, Kalkhoff RK, Arndorfer RC. Effect of glucagon on esophageal motor function. Gastroenterology 1975;69:160–5.
[5] Weant KA, Weant MP. Safety of efficacy of glucagon for the relief of acute esophageal food impaction. Am J Health-Syst Pharm 2012;69:573–7.
[6] Glucagon for injection (rDNA origin) prescribing information. Lilly Corporate Center, Indiana: Eli Lilly and Company; 2005.
[7] Tibbling L, Bjorkhoel A, Jansson E, Stenkvist M. Effect of spasmolytic drugs on esophageal foreign bodies. Dysphagia 1995;10:126–7.
[8] Lacy PD, Donnelly MJ, McGrath JP, Byrne PJ, Hennessy TP, Timon CV. Acute food bolus impaction etiology and management. J Laryngol Otol 1997;111:1158–61.
[9] Mehta DI, Attia MW, Quintana EC, Cronan KM. Glucagon use for esophageal coin dislodgement in children: a prospective, double-blind, placebo-controlled trial. Acad Emerg Med 2001;8:200–3.
[10] Al-Haddad M, Ward EM, Scolapio JS, Ferguson DD, Raimondo M. Glucagon for the relief of esophageal food impaction: does it really work? Dig Dis Sci 2006;51:1930–3.
[11] Sodeman TC, Harewood GC, Baron TH. Assessment of the predictors of response to glucagon in the setting of acute esophageal food bolus impaction. Dysphagia 2005;19:18–21.