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Double-Blind Multicenter Randomized Clinical Trial Comparing Glucagon Vs Placebo in the Resolution of Alimentary Esophageal Impaction

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This summary reviews de Benito Sanz M, Tejedor-Tejada J, Mangas-Sanjuan C et al. Double-blind multicenter randomized clinical trial comparing glucagon vs placebo in the resolution of alimentary esophageal impaction. Am J Gastroenterol. 2024 Jan 1;119(1):87-96.

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STRUCTURED ABSTRACT

Question: Glucagon has been recommended for medical management of uncomplicated esophageal impaction in order to spare emergent gastroscopy. This recommendation has not been subject to a substantive randomized controlled trial (RCT).

Design: Multicenter, blinded, placebo-controlled RCT.

Setting: Four centers involving 17 endoscopists in Spain.

Patients: Adult patients who were admitted for emergent care for suspected esophageal foreign body impaction (EFBI) while a participating endoscopist

was on call were recruited. An EFBI clinical diagnosis was made if symptoms such as acute onset dysphagia, retrosternal or pharyngeal foreign body sensation, profuse salivation, or intolerance of *per os* intake were present after the last meal. Exclusion criteria included non-food EFBI or having been administered either glucagon or carbonated beverage prior to randomization. Additional participation was excluded for those who were pregnant, with a prior history of esophageal stricture and/or a manometrically-defined disorder of esophageal motility. Participants after randomization were excluded from primary analysis if the wait for gastroscopy exceeded 120-minutes (5 glucagon, 3 placebo).

Interventions/Exposure: After presentation in the emergency department for suspected EFBI, participants were interviewed. After discussion and agreement between the emergency department staff and the on-call endoscopist, patients were randomized to either receiving 1 mg of glucagon or the equivalent volume of saline. Randomization occurred in a stratified fashion, via a computer-generated random sequence. While the on-call endoscopist and study participant were masked as to what agent the participant received, emergency department staff were aware. After enrollment, no further interventions aside from urgent gastroscopy were permitted. All underwent gastroscopy even if there was a sensation of symptom relief, which would be analogous to consensus standard of care. It was at the endoscopists' discretion what maneuvers were to be taken to clinically address EFBI. A standardized telephone interview occurring 7-10-days after gastroscopy was performed, including administration of a variety patient reported outcome measures. The primary outcome was resolution of the EFBI identified on gastroscopy (performed for clinical intent).

Outcome: The primary outcome was resolution of the EFBI identified on gastroscopy (performed for clinical intent). Secondary outcomes included gastroscopy procedure length, the number and type of maneuvers, relevant endoscopic findings, and adverse events.

Data Analysis: Data was captured using the Spanish Digestive Endoscopy Society (ES: Sociedad Española de Endoscopia Digestiva) data capture tool. For the primary aim, the differences in EFBI resolution were assessed, with intention-to-treat and per protocol analysis. Secondary aims were analyzed by chi-squared test.

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Administration of Castile-and-Leon, Spain).

Results: A total of 181 potential participants were screened, of whom 41 were excluded due to declining to participate, non-food-based EFBIs (for which glucagon usage would have been inappropriate), and 6 either had known prior strictures and/or esophageal motility disorders. A total of 72 subjects received glucagon and 68 were administered saline. There were no significant baseline differences between both groups, although prior history of Schatzki ring was more frequently found in the glucagon-administered group. Both groups had gastroscopy performed in slightly under 1-hour. Overall, 23.6% of glucagon subjects had EFBI resolution demonstrated on gastroscopy, compared to 20.6% of participants who had saline administered. Adverse events were distributed similarly across both groups, including some degree of pain, residual dysphagia, and mucosal tears.

COMMENTARY

Why Is This Important?

I think this article is of wide interest to the College's readership for one simple reason: we have all been there! We have all received a phone call overnight with a request for urgent endoscopy for EFBI and have not necessarily known how the consult request will play out. If it is early enough in the evening, do we rush into the hospital to address the EFBI when there are more resources that can be called upon if a complication occurs? Do we wait to see if glucagon will work? How do we translate urgency on the part of our emergency colleagues?

For decades, endoscopists on call have used glucagon to address some of this uncertainty. It has been thought that glucagon relaxes gastrointestinal smooth muscle and can induce lower esophageal sphincter relaxation[1,2]. Clinically, I have forgone gastroscopy in patients who can clearly delineate a significant/near-complete improvement of symptoms or who can drink water again. Yet, while glucagon has had this role in EFBI management since at least the 1970s, it has not been subjected to the rigors of our investigative discipline – a randomized control trial.

This study has an elegant design, and it is surprising that our profession has not generated it previously. These authors from Spain are to be commended for one of the most robust randomized trials on the use of glucagon in EFBI. This manuscript calls us to question the faith we place in glucagon being a tool we reach for when woken up from deep slumber at 3 AM.

Key Study Findings

Glucagon is no more effective than placebo at resolving EFBI. That being

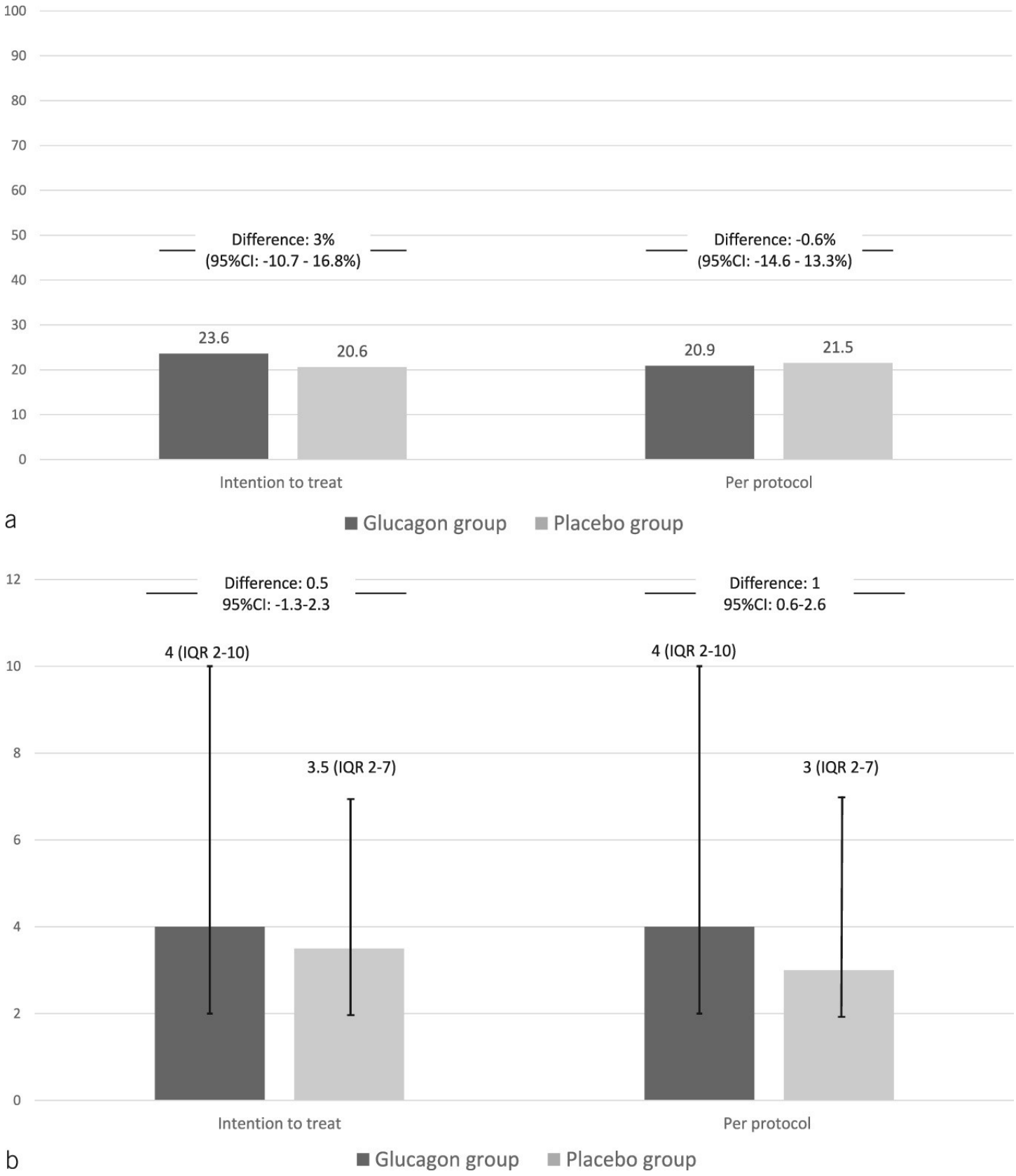

Figure 1. (a) Proportion of resolved esophageal impactions in the glucagon and placebo group (intention-to-treat and per-protocol analysis). (**b**) Duration of upper endoscopy in minutes in the glucagon and placebo group (intention-to-treat and per-protocol analysis). CI, confidence interval; IQR, interquartile range.

said, there does not appear to be any difference in adverse outcomes associated with its use.

It is less likely that glucagon administration is causing harm. It may be delaying inevitable endoscopies, which could lengthen the amount of time patients are spending in emergency departments.

Caution

While this study is a good one, I am not necessarily going to recommend to the emergency department that they chuck their vials of glucagon quite yet. The endoscopy centers represented in this study appear to be exceedingly efficient, with the participants undergoing endoscopy within an hour of either glucagon or placebo administration. Additionally, patients who had an interval of placebo vs glucagon administration greater than 120-minutes were excluded. I wonder if a longer period occurred between glucagon administration and endoscopy, that glucagon would fare better. I do not think that for the average consultation practice around the world that an endoscopy would occur this quickly.

My Practice

This trial has made me consider changing my threshold as it relates to gastroscopy for EFBI. In the daylight, I might be less likely to trial glucagon and potentially waste precious time if a complication occurred during foreign body removal. Overnight, I may still consider a trial of glucagon, as I would like to try to defer a gastroscopy if the patient feels amelioration. I always worry about procedural complications (particularly management of a perforation) when performing a gastroscopy that could wait for the first case of the day. While our colleagues in other service lines do not often appreciate the gastroenterologist's concern for complications, it is infinitely better to wait when rescue is more readily available. That said, this trial makes me question whether glucagon can continue to help serve this role.

While not directly related to my practice surrounding EFBIs, I would be remiss to not offer 3 pearls that the fellows I work with are probably tired of me repeating: (1) one must distinguish acute dysphagia – i.e. impaction – from chronic dysphagia; (2) biopsy the uninvolved portions of the esophagus to identify eosinophilic esophagitis; and (3) recurring dysphagia occurring in the setting of an acute impaction should prompt evaluation for missed stricture or esophageal dysmotility (particularly achalasia).

For fellows reading this article, I have seen nearly missed cases of food impaction that were registered by the primary emergency or medicine departments as "dysphagia" during consultation. Clarify the time course, make sure you are not missing an EFBI as this can then go on to progress to more emergent disease complications. Regarding biopsies, food impactions can be one of the first

signs of eosinophilic esophagitis[3]. In my motility consultation clinic, I have made diagnoses of eosinophilic esophagitis after multiple presentations for EFBI, that could have been avoided had the patient undergone food elimination, proton pump inhibition, swallowed steroids, or dupilumab treatment. In my mind, there must be a very high bar prior to deciding not to biopsy portions of the esophagus not involved in the food impaction. Finally, endoscopists can easily miss strictures that may explain symptoms, but are wider than our gastroscopes' diameters (generally 9-10 mm). Additionally, we do not do enough manometry to identify achalasia that can present as food impacted in the esophagus.

For Future Research

That it took over 50 years from the time that glucagon efficacy in EFBI management has been posited to this trial being performed, I do not imagine further work will be attempted to address the utility of glucagon in management of EFBI. I surmise that some endoscopists will abandon glucagon based on this study, others will still employ it. We must remember that while randomized clinical trials are the gold standard of our field, only the endoscopist can integrate relevant clinical facts and come up with the best resolution at that time.

Conflict of Interest

Dr. Vélez reports no relevant conflicts.

Abbreviations

FBI, foreign body impaction; RCT, randomized controlled trial.

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