

Clinical safety and outcomes of glucagon use during endoscopic retrograde cholangiopancreatography (ERCP)



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ABSTRACT

Background and study aims Injectable glucagon enables easier biliary cannulation by inhibiting gastrointestinal mo-

tility and decreasing the frequency and amplitude of phasic activity of the sphincter of Oddi during endoscopic retrograde cholangiopancreatography (ERCP). Data about the safety profile of glucagon use and patient clinical outcomes are scarce.

Patients and methods We used a federated cloud-based network research database, TriNetX, comprising 92 US healthcare organizations to find adult patients undergoing ERCP with glucagon use (Group A) vs. without using glucagon (Group B) from August 1, 2010, to August 1, 2021. The primary outcomes were rates of gastrointestinal bleeding, gastrointestinal perforation, post-ERCP pancreatitis, inpatient hospitalizations, and 30-day overall mortality measured after 1:1 propensity matching of the groups based on the baseline demographics and comorbidities.

Results There were 9,008 patients in Group A compared to 256,597 in Group B. After matching, Group A patients had lower rates of gastrointestinal bleeding (risk ratio [RR], 0.68; CI, 0.52–0.86), post-ERCP pancreatitis (RR, 0.64; CI, 0.58–71), inpatient hospitalization (RR 0.34; CI:0.32 to 0.36) and overall mortality (RR, 0.81; CI, 0.66–0.99). The rates of gastrointestinal perforation (RR, 0.64; CI: 0.34 to 1.19), hyperkalemia (RR, 0.83; CI, 0.64–1.09) and hyperglycemia (RR, 0.65; CI, 0.41–1.03) did not differ between the two groups.

Discussion Glucagon use during ERCP was associated with low rates of gastrointestinal bleeding, post-ERCP pancreatitis, inpatient hospitalization, and overall mortality. Moreover, the rates of hyperkalemia and hyperglycemia did not differ between the two groups even after matching for diabetes, indomethacin use, obesity, and chronic kidney disease.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most commonly performed hepatobiliary and pancreatic duct interventions. Increased duodenal motility could interfere with selective biliary cannulation (SBC), increasing

the risk of post-ERCP pancreatitis (PEP). In most cases, motility is overcome by air insufflation and the short and stable position of the duodenoscope. However, in some cases, even these attempts fail, requiring use of antimotility agents [1]. Multiple duodenal antimotility agents such as hyoscyamine sulfate, atropine, octreotide, and glucagon have been used in the past [2]. Among these, glucagon has been used widely during ERCP to achieve this purpose [3]. However, its action is short-lived

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and multiple doses might be required to reduce the duodenal motility. Furthermore, it can cause electrolyte imbalances such as hyperkalemia and hyperglycemia. Large-scale studies to assess the safety profile and clinical outcomes in patients receiving glucagon during ERCP are non-existent. Hence, we aim to study the incidence of PEP, ERCP-related gastrointestinal bleeding, intestinal perforation, and the need for inpatient hospitalization in patients receiving glucagon during ERCP.

Patients and methods

We used TriNetX (a federated cloud-based network research database) comprising multiple US healthcare organizations (HCOs). A total of 92 HCOs were included for the data extraction. All patients 18 years or older who underwent ERCP with glucagon use were included in Group A (glucagon group). Similarly, patients who underwent ERCP without glucagon use were classified as Group 2 (non-glucagon group). The data were collected from September 1, 2010, to September 1, 2021, over a period of 11 years. The primary outcomes were gastrointestinal bleeding rates, intestinal perforation, PEP, inpatient hospitalizations and 30-day overall mortality. gastrointestinal bleeding was defined as any episodes of hematemesis or melena after the ERCP. PEP was defined based on the revised Atlanta criteria [4]. The clinical outcomes were measured after 1:1 propensity matching of the groups based on the baseline demographics and comorbidities (see supplementary section). A 1:1 propensity score matching was done based on the following variables: patients' age, gender, hypertension (HTN), diabetes mellitus (DM), obesity, chronic kidney disease (CKD), ischemic heart disease (IHD), and chronic obstructive pulmonary disease (COPD).

Results

A total of 9,008 patients were included in the glucagon group (Group A). They were compared with 256,597 patients in non-glucagon group (control, Group B). Demographics, comorbidities of the patients, use of imaging and medications are noted in ► **Table 1**. Male to female ratio was 45.1% vs. 54.9%. Patients in the glucagon group had higher rates of receiving indomethacin but it was not statistically significant (583 [6.5%] vs. 496 [5.5%]; $P=0.086$). After matching, group 1 (glucagon group) patients had lower rates of gastrointestinal bleeding (risk ratio [RR], 0.68; CI, 0.52–0.86), PEP (RR, 0.64; CI, 0.58–0.71), inpatient hospitalization (RR, 0.34; CI, 0.32–0.36) and overall mortality (RR, 0.81; CI, 0.66–0.99). The rates of gastrointestinal perforation (RR, 0.64; CI, 0.34–1.19), hyperkalemia (RR, 0.83; CI, 0.64–1.09) and hyperglycemia (RR, 0.65; CI, 0.41–1.03) did not differ between the two groups (► **Table 2**).

Discussion

ERCP remains the most commonly used therapeutic intervention for accessing hepatobiliary and pancreatic ducts [5]. Adequate visualization of the ampulla and duodenoscope stability is essential for SBC. Glucagon is the most commonly used med-

ication among all pharmacological agents to decrease duodenal motility.

This study found that glucagon use during ERCP was associated with reduced risk of PEP, post-procedure gastrointestinal bleeding, inpatient hospitalization, and overall mortality. Furthermore, adverse events (AEs) such as development of hyperglycemia, hyperkalemia, and intestinal perforation did not differ between the glucagon and no-glucagon groups.

Glucagon inhibits gastrointestinal motility by relaxation of smooth muscles. It also has sphincter-relaxing properties, enabling SBC [6]. However, its effect is short-lived due to its short half-life, and multiple doses might be needed to achieve its intended effects. ERCP is associated with multiple AEs such as gastrointestinal bleeding, intestinal perforation, and PEP requiring inpatient hospitalization [7]. gastrointestinal bleeding during ERCP could be due to post-sphincterotomy and non-sphincterotomy causes such as duodenoscope-associated trauma to the duodenum, aggressive suction, especially in patients with underlying coagulopathy [8]. Impaired visualization can worsen these effects due to accidental mucosal injury, especially during endoscopic biliary sphincterotomy [9]. Decreasing duodenal motility and stabilization of ampulla could reduce the risk of these adverse events [10]. In our study, the risk of gastrointestinal bleeding after ERCP among glucagon users was reduced by 34% (RR, 0.68; CI, 0.52–0.86). Although this effect could be related to reduced motility by glucagon, the precise mechanisms involved remain to be studied. In addition to nausea and vomiting, reports of biochemical abnormalities such as hyperkalemia and hyperglycemia have been reported with glucagon [11]. Therefore, it remains unclear if the use of glucagon during ERCP can affect its outcomes.

PEP is the most common complication of ERCP, which could be related to patient and procedural factors. Difficult cannulation, papillary trauma by repetitive cannulation, pancreatic sphincterotomy, and contrast injection-induced acinarization of the pancreas contribute to PEP [7]. Most of these complications could be reduced by proper visualization, subtle and skilled movements of the duodenoscope by a skilled endoscopist [12]. Past studies have shown that combined use of sublingual nitroglycerin and IV glucagon has shown to be associated with decreased PEP risk [13]. In our study, the incidence of PEP was significantly lower in the glucagon group (RR, 0.64; CI, 0.58–0.71). Another significant finding of our study is lower post-procedure hospitalizations and overall mortality rates in the glucagon group.

We acknowledge some limitations with our study. First, risk stratification of patients who were at a higher risk of PEP and other AEs could not be performed due to the unavailability of the relevant information in the database. A number of patient and proceduralist factors, such as procedure time, operator skills, and pancreatic duct cannulation, can affect the PEP occurrence. These factors could potentially confound the results of the study. Post-ERCP gastrointestinal bleeding could be related to esophageal, gastric, and duodenal injury, including sphincter trauma. Use of antithrombotic agents can potentiate the effects the gastrointestinal bleeding. Although glucagon can reduce gastrointestinal peristalsis and improve visualiza-

► Table 1 Baseline characteristics and clinical outcomes in patients who has ERCP with glucagon compared to individuals ERCP without glucagon

Characteristic	Before matching			After matching ¹		
	ERCP+ Gluc N=9008 Mean (SD) or n (%)	ERCP no glucagon N=256578 Mean (SD) or n (%)	P value	ERCP+ Gluc N=9008 Mean (SD) or n (%)	ERCP no glucagon N=9008 Mean (SD) or n (%)	P value
Demographics						
Age (SD)	67.72 (11.05)	68.10 (11.69)	<0.001	67.72 (11.05)	67.79 (11.02)	0.67
Female	4846 (53.80)	140785 (54.87)	0.04	4846 (53.80)	4811 (53.41)	0.60
Comorbidities						
HTN	3401 (37.76)	70673 (27.54)	<0.001	3401 (37.76)	3112 (34.55)	<0.001
DM	6446 (71.56)	162541 (63.35)	<0.001	6446 (71.56)	6439 (71.48)	0.91
Obesity	2016 (22.38)	34392 (13.40)	<0.001	2016 (22.38)	1632 (18.12)	<0.001
COPD	6842 (75.96)	157115 (61.24)	<0.001	6842 (75.96)	6864 (76.20)	0.71
CKD	2550 (28.31)	48562 (18.93)	<0.001	2550 (28.31)	2569 (28.52)	0.75
IHD	4057 (45.04)	78282 (30.51)	<0.001	4057 (45.04)	4032 (44.76)	0.71
Radiology						
CT abdomen and pelvis	2856 (31.71)	60069 (23.41)	<0.001	2856 (31.71)	2833 (31.45)	0.71
Medications						
Opioid use	1923 (21.35)	36829 (14.35)	<0.001	1923 (21.35)	1927 (21.39)	0.94
indomethacin	496 (5.51)	10433 (4.07)	0.10	496 (5.51)	583 (6.47)	0.09

ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ID, ischemic heart disease.

¹ A 1:1 propensity score matching was done based on the following variables: age, gender, HTN, DM, obesity, CKD, IHD, and COPD.

► Table 2 Clinical outcomes in the subgroup analysis based on patients with ERCP and glucagon (Group 1) to ERCP without glucagon (Group 2) after propensity matching.

Primary outcome	Before matching			After matching		
	ERCP w glucagon (Group A) N=9008	ERCP w/o glucagon (Group B) N=256578	RR (95% CI)	ERCP w glucagon (Group A) N=9008	ERCP wo glucagon (Group B) N=9008	RR (95% CI)
GIB	100 (1.11)	3420 (1.33)	0.83 (0.68 – 1.01)	100 (1.11)	149 (1.65)	0.67 (0.52 – 0.86)
PEP	638 (7.08)	27725 (10.81)	0.66 (0.61 – 0.71)	638 (7.08)	995 (11.05)	0.64 (0.58 – 0.71)
GI Perforation	16 (0.18)	627 (0.24)	0.73 (0.44 – 1.19)	16 (0.18)	25 (0.28)	0.64 (0.34 – 1.20)
Hyperglycemia	30 (0.33)	1,415 (0.55)	0.60 (0.42–0.87)	30 (0.33)	46 (0.51)	0.65 (0.41–1.03)
Hyperkalemia	95 (1.55)	2017 (0.79)	1.34 (1.09–1.64)	95 (1.06)	114 (1.27)	0.83 (0.64–1.09)
Hospitalization	1243 (13.80)	104237 (40.63)	0.34 (0.32 – 0.36)	1243 (13.80)	3676 (40.81)	0.34 (0.32 – 0.36)
Death	163 (1.81)	4904 (1.91)	0.95 (0.81 – 1.11)	163 (1.81)	202 (2.24)	0.81 (0.66 – 0.99)

ERCP, endoscopic retrograde cholangiopancreatography; CI, confidence interval; RR, risk ratio; GIB, gastrointestinal bleeding; PEP, post-ERCP pancreatitis.

tion, other factors such as time spent during the ERCP procedure, sphincterotomy and hydration status can confound these results.

It is possible that patients with difficult SBC received glucagon and might have additional measures to reduce PEP (pancreatic duct stenting, use of indomethacin, and aggressive hydration). However, we did not find statistically significant high-

er use of indomethacin among patients receiving glucagon. Information about PEP severity, pancreatic duct stenting, procedure time, and number of cannulation attempts was not available. In addition, the information about the total glucagon dose used in each procedure was not available. Also, the information about trainee involvement and skillset and experience of endoscopists was not present in the database. We excluded pa-

tients with postsurgical anatomy and use of enteroscopy-assisted ERCP-related data are unknown. Studies correlating direct evidence of papillary sphincter relaxation and SBC are missing; this is likely dependent of patient, procedure- and operator-dependent factors. Performing studies keeping these variables constant and evaluating correlation between the dose of glucagon and SBC might offer further insights. Finally, retrospective studies are subjected to inherent bias, which could affect the interpretation of this study. Nevertheless, a large sample size with the use of multicentric data could potentially overcome some of these limitations.

Conclusions

Glucagon use during ERCP is associated with low rates of gastrointestinal bleeding, PEP, inpatient hospitalization, and overall mortality. In addition, after propensity matching, AEs related to glucagon use, such as the rates of hyperkalemia and hyperglycemia, did not differ between the glucagon users and non-users. Future prospective large-scale studies are needed to assess the dosing and administration patterns of glucagon that are necessary to achieve these advantages.

Competing interests

Abhilash Perisetti: None. Hemant Goyal: Consultant – Aimloxy. Neil Sharma: Consultant – Boston scientific, MedTronic, STERIS, Mauna Kea, Medical advisory board – endoscopynow, MedTronic, STERIS, Mauna Kea

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