ORIGINAL ARTICLE

Effect of Premedication with Glycopyrrolate on Patient Tolerance and Procedure Outcomes in Patients Undergoing Unsedated Upper Gastrointestinal Endoscopy: A Randomized Placebo-controlled Trial

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Received on: 03 August 2023; *Accepted on*: 05 September 2023; *Published on*: 22 December 2023

Abstract

Background and aim: An optimal topical pharyngeal anesthesia (TPA) is required for better patient tolerance and procedural outcomes of an unsedated upper gastrointestinal endoscopy (UGIE). Several additional strategies have been tried to improve patient tolerance with limited success. We hypothesized that premedication with glycopyrrolate would enhance TPA and improve patient tolerance and procedural outcomes of an unsedated UGIE.

Materials and methods: We conducted a randomized, double-blind, placebo-controlled trial between July 2020 and May 2022. Consecutive patients undergoing unsedated UGIE were randomly assigned to receive either intravenous glycopyrrolate or a placebo 30 minutes before TPA. Patient tolerance, comfort level for the endoscopist, cardiorespiratory fluctuations, percentage of failed esophageal intubation, and incomplete examination were studied.

Results: 380 patients were randomized to 190 in each arm. The median (IQR) VAS scores for the overall patient satisfaction in the glycopyrrolate and placebo groups were 8 (1) and 7 (2), respectively ($p = 0.04$). The median (IQR) VAS scores for endoscopist assessment of patient cooperation in the glycopyrrolate and placebo groups were 8 (1.3) and 8 (1), respectively ($p = 0.04$). There was no difference in the percentage of failed esophageal intubation and incomplete examination, fluctuations in heart rate, and oxygen saturation of the participants. However, the mean arterial pressure (MAP) on-table before the start of the procedure at 1 minute and 3 minutes was significantly higher in the glycopyrrolate group ($p = 0.01$, 0.01, and 0.04, respectively).

Conclusion: In unsedated UGIE, glycopyrrolate premedication significantly improves the patient tolerance and endoscopist's comfort, with minimal cardiorespiratory effects. Hence, it could be incorporated into day-care unsedated endoscopy practice.

Trial registration – CTRI/2020/07/026786.

Keywords: Endoscopy, Gastrointestinal, Glycopyrrolate, Premedication, Patient satisfaction.

Euroasian Journal of Hepato-Gastroenterology (2023): 10.5005/jp-journals-10018-1395

Introduction

Upper gastrointestinal endoscopy (UGIE) is a common procedure performed frequently in day-to-day gastroenterology practice. It is a day-care procedure to diagnose upper gastrointestinal cancers, ulcers, and bleeding.[1] However, performing a UGIE can be challenging due to the discomfort to the patient.[2] Sedation can effectively reduce discomfort and intolerance. Nevertheless, it has adverse events, such as transient hypoxemia, aspiration pneumonia, and cardiorespiratory complications.[3–5] It increases the complexity, length of hospital stays, and healthcare expense. Hence, UGIE is often performed under lignocaine topical pharyngeal anesthesia (TPA), which the patients do not tolerate well.[6] Any new strategy enhancing TPA might improve tolerance and procedure-related outcomes. Previous studies demonstrated that using anticholinergic agents significantly improves the outcomes and ease of procedures such as colonoscopy and endoscopic submucosal dissection.[7,8] Glycopyrrolate is widely used as a premedication for endoscopic procedures under intravenous sedation, which reduces oral, tracheal, and gastric secretions, and improves visibility. A study by Watanabe et al. showed that glycopyrrolate prolongs TPA, enhances lignocaine absorption, and helps achieve higher mean peak plasma lignocaine concentration compared with placebo.[9] Hence, the current trial was conducted to find whether premedication with glycopyrrolate could enhance the effect of TPA in patients undergoing unsedated UGIE, thereby improving patient tolerance and procedure-related outcomes. In the current study, we hypothesized that glycopyrrolate

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How to cite this article: Ramalingam R, Senthamizhselvan K, Harichandrakumar KT, *et al*. Effect of Premedication with Glycopyrrolate on Patient Tolerance and Procedure Outcomes in Patients Undergoing Unsedated Upper Gastrointestinal Endoscopy: A Randomized Placebo-controlled Trial. Euroasian J Hepato-Gastroenterol 2023;13(2):55–60.

Source of support: Nil

Conflict of interest: None

enhances TPA in unsedated UGIE by decreasing the oropharyngeal secretions, thereby minimizing the dilution of lignocaine in the oropharyngeal secretions and augmenting the direct contact area of lignocaine with pharyngeal mucosa.

Materials and Methods

Study Design

This single-center prospective, randomized, double-blind, placebo-controlled trial was conducted in a tertiary care institute in India. The institutional scientific and ethics committee approved the study, and we performed it as per the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The study was registered at www.ctri.gov.in (CTRI No: CTRI/2020/07/026786). Informed consent was obtained from all the participants, and they were given full freedom to withdraw from the study at any point.

Participants

Eligible participants were patients aged 18–60 years undergoing unsedated diagnostic UGIE from July 2020 to May 2022. The trial excluded patients with glaucoma, cardiorespiratory disease, chronic constipation, obstructive urinary disorders, active upper respiratory infection, pregnant women, intake of anti-anxiety medications, history of prior UGIE or upper gastrointestinal surgery, and those who require therapy during UGIE.

Intervention

The intervention group received intravenous glycopyrrolate (1 mL containing 0.2 mg diluted in 1 mL saline) 30 minutes before TPA, and the placebo group received 2 mL intravenous saline 30 minutes before TPA. And 10% lignocaine spray was used at a dose of 50 mg for TPA (5 puffs each, delivering 10 mg).

Outcome Measures

The primary outcome of our study was to assess the effect of premedication with glycopyrrolate on patient tolerance during unsedated upper GI endoscopy. Other outcomes of the study were to study the level of comfort for the endoscopist, cardiorespiratory fluctuations during the examination, percentage of failed esophageal intubation, and incomplete examination.

Sample Size

Assuming the minimum expected clinically significant difference in the average level of intolerance to the unsedated UGIE between the intervention and placebo arms as 1 in the visual analog scale (VAS) with a standard deviation of 3 at a 5% level of significance and 90% power, the sample size was calculated to be 190 in each arm, and this was achieved using the formula for comparing two independent means, using the OpenEpi software version 3.0.1, Atlanta, USA.

Randomization

Eligible patients were randomized into two groups. Block randomization was used to randomize the patients in a 1:1 ratio to intervention and placebo groups. Computer-generated randomization list was used. Allocation was carried out by using sequentially numbered opaque sealed envelopes.

Procedure

The principal investigator assessed the consenting consecutive patients for eligibility and included them in the study. He took a detailed history and clinically examined all the included patients. The baseline blood reports were noted from the hospital information system. As per the random sequence, the endoscopy nurse allocated patients into the intervention and placebo groups and administered glycopyrrolate and saline to the respective groups. After 30 minutes, both groups received topical pharyngeal anesthesia (TPA) (10% lignocaine, five sprays in each patient). UGIE was done after 5 minutes. The patient was placed in left lateral recumbent position, and a 9.2 mm diameter endoscope (OLYMPUS GIF-Q150) was used for all the cases.

A single expert endoscopist performed all the endoscopic procedures. Endoscope intubation refers to introducing the endoscope through the oropharynx, crossing the cricopharynx to reach the upper esophagus. When the endoscopist could not reach the upper esophagus, it was called a failed intubation. Intubation time was the time taken for intubation of the upper esophagus. The examination time was the time taken from the end of intubation to the withdrawal of the endoscope out of the oral cavity. The total procedure time was the intubation time plus the examination time. Complete endoscopy was an adequate examination of all the parts from the cricopharynx up to the descending part of the duodenum. Failure to tolerate or incomplete endoscopy refers to inadequate visualization or premature endoscope removal due to poor patient tolerance or compromising vitals. If any lesion caused luminal narrowing that precluded a complete endoscopy in an otherwise tolerant patient, we excluded those patients from the analysis. The investigator recorded baseline anxiety scores using the numerical rating scale (NRS).[10] He also recorded the heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SpO_2) at various intervals, namely, at baseline, 5 minutes after giving the drug, on the table just before the procedure, 1 minute, 3 minutes, and 5 minutes per – procedure and 15 minutes after the procedure. Endoscopist and participants reported their assessment using the VAS employed in previous endoscopy studies.[11–13] Immediately after the procedure, the endoscopist reported the failed intubation or incomplete endoscopy. He also gave his assessment based on a 0–10 VAS on the ease of the procedure (0, extremely difficult; 10, very easy), patient cooperation (0 – poor cooperation; 10 – good cooperation), and satisfactory visualization of all areas (0, no; 10, yes). Patients reported the tolerance level for the endoscopic procedure on a similar 0–10 VAS based on discomfort during the procedure (0, extreme discomfort; 10, no discomfort), overall satisfaction (0, not satisfied; 10 satisfied) and willingness to undergo repeat endoscopy (0, certainly no; 10, certainly yes) if clinically indicated.

Statistical Analysis

The data on categorical variables, such as gender, clinical characteristics, comorbidity, and sociodemographic characteristics were expressed as frequencies and proportions. The quantitative variables, such as age, hemoglobin, vital parameters, cardio-respiratory parameters, VAS for ease of procedure, patient cooperation, satisfactory visualization of all areas during examination, discomfort experienced by the patient, willingness to undergo repeat procedure, and overall satisfaction were expressed as mean with SD or median with the range depending upon the normality of the data. Kolmogorov Smirnov test was used to test the normality of the data. The comparison of the intubation status, examination status, and other categorical variables between the groups was carried out by using the Chi-square test or Fisher's exact test. The comparison of vital parameters and other continuous variables between the groups was carried out using an independent Student

Flowchart 1: CONSORT flow diagram

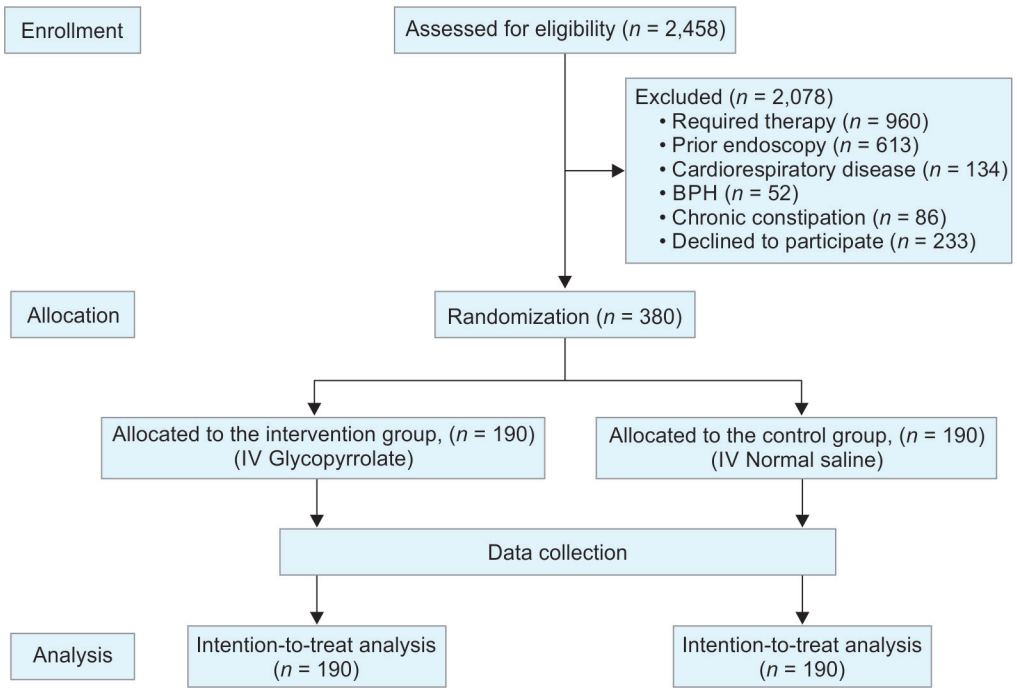

Table 1: Comparison of baseline characteristics between the study groups

Characteristics	*Glycopyrrolate group (N = 190)*	*Placebo group (N = 190)*	*p-value**
Age (years) (mean ± SD)	41.95 ± 12.07	41.65 ± 12.73	0.81
Sex (Male) (*n*) (%)	121 (64%)	123 (65%)	0.83
Hypertension (*n*) (%)	20 (11%)	24 (13%)	0.19
Diabetes mellitus (*n*) (%)	23 (12%)	13 (7%)	0.19
Heart rate (per min) (mean ± SD)	82.98 ± 17.42	84.23 ± 16.18	0.66
Systolic BP (mm Hg) (mean ± SD)	121.61 ± 16.41	119.23 ± 16.29	0.18
Diastolic BP (mm Hg) (mean ± SD)	77.85 ± 9.66	76.99 ± 10.28	0.39
MAP (mm Hg) (mean ± SD)	92.59 ± 10.93	90.85 ± 11.42	0.08
SpO_2 (%) (mean ± SD)	98.74 ± 0.60	98.58 ± 2.69	0.20
Hemoglobin (g/dL) (mean ± SD)	10.99 ± 2.52	10.62 ± 2.55	0.16
Anxiety (VAS) Median (IQR)	2 (3)	2 (3)	0.5

*Student *t*-test; Chi-square test; BP, blood pressure; MAP, mean arterial pressure; SpO_2, oxygen saturation; SD, standard deviation; VAS, visual analog scale

t-test or Mann-Whitney *U* test. All the statistical analyses were conducted at a 5% significance level, and a *p*-value less than 0.05 was considered significant.

Patients were closely monitored for adverse events during the entire study period. The work has been reported per the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Results

The CONSORT diagram describing the participant inflow is shown in Flowchart 1. A total of 380 patients were included in the study, randomized into the glycopyrrolate group (*n* = 190) and placebo group (*n* = 190). The baseline characteristics of the study groups were comparable (Table 1). The mean (SD) age of the glycopyrrolate and placebo groups were 41.9 (12.1) years, and 41.7 (12.7), respectively ($p = 0.81$), and there was a male preponderance [64% vs 65%, $p = 0.83$]. The overall patient satisfaction was better in the glycopyrrolate group, and their tolerance to unsedated endoscopy was statistically significant than the placebo group [VAS 8 (1) vs 7 (2), $p = 0.04$] (Table 2). The patient discomfort due to the procedure and willingness to undergo repeat procedures were not statistically different between the groups [VAS 8(2) vs 8(2), $p = 0.19$] and [VAS 6 (2) vs 6 (3), $p = 0.18$], respectively. The endoscopist felt that patient cooperation was better in the glycopyrrolate group than in the placebo group [VAS 8 (1.3) vs 8 (1) $p = 0.04$]. The easiness of the procedure and satisfactory visualization of all areas were similar between the groups [VAS 8 (1) vs 8 (1), $p = 0.09$] and [VAS 8 (1) vs 8 (2), $p = 0.14$], respectively. The percentage of failed esophageal intubation and incomplete examination were similar between the groups [0% vs 1.1%, $p = 0.5$%] and [0% vs 1.1%,

Table 2: Comparison of outcome measures between the groups

Outcomes	*Glycopyrrolate group (N = 190)*	*Placebo group (N = 190)*	*p-value**
Failed esophageal intubation (%)	0 (0%)	2 (1.1%)	0.50
Incomplete examination (%)	0 (0%)	3 (1.1%)	0.50
Cardiorespiratory parameters			
Heart rate (per minute)	82 (18)	84 (20)	0.66
Mean arterial pressure (mm Hg)	93 (11)	90 (14)	0.08
Oxygen saturation (%)	99 (1)	99 (1)	0.20
Endoscopist comfort (VAS)			
Ease of the procedure	8 (1)	8 (1)	0.09
Patient cooperation	8 (1.3)	8 (1)	0.04
Satisfactory visualization	8 (1)	8 (2)	0.14
Patient tolerance level (VAS)			
Discomfort	8 (2)	8 (2)	0.19
Overall satisfaction	8 (1)	7 (2)	0.04
Willingness to undergo repeat UGIE	6 (2)	6 (3)	0.18

*Student's *t*-test; Chi-square test; VAS, visual analog scale

Table 3: Comparison of variation in the heart rate between the groups

Heart rate at different times	*Glycopyrrolate group (N = 190)*	*Placebo group (N = 188)*	*p-value**
Baseline heart rate	82 (18)	84 (20)	0.66
Heart rate 5 minutes after drug	90 (20)	88 (20)	0.28
Heart rate on the table	96.5 (29)	90 (28)	0.17
Heart rate at 1 minute	110 (29)	105.5 (30)	0.42
Heart rate at 3 minutes	96 (24)	100 (26)	0.36
Heart rate at 5 minutes	88 (19)	90 (20)	0.46
Heart rate after 15 minutes	84 (15)	84.5 (12)	0.58

*Mann-Whitney *U* test; Median (IQR)

Table 4: Comparison of variation in the oxygen saturation between the groups

Oxygen saturation	*Intervention group (N = 190)*	*Placebo group (N = 188)*	*p-value**
Baseline SpO_2	99 (1)	99 (1)	0.19
SpO_2 5 minutes after drug	98 (1)	98 (1)	0.50
SpO_2 on the table	98 (1)	98 (1)	0.94
SpO_2 at 1 minute	98 (1)	98 (1)	0.82
SpO_2 at 3 minutes	99 (1)	98 (1)	0.25
SpO_2 at 5 minutes	99 (1)	99 (1)	0.83
SpO_2 after 15 minutes	99 (0)	99 (0)	0.32

*Mann–Whitney *U* test; Median (IQR); SpO_2, oxygen saturation

Table 5: Comparison of variation MAP between the intervention and the placebo groups at different time points

MAP	*Intervention group (N = 190)*	*Placebo group (N = 188)*	*p-value**
Baseline MAP	93 (11)	90 (14)	0.08
MAP 5 minutes after drug	90 (7)	90 (14)	0.08
MAP on the table	90 (7)	90 (17)	0.01
MAP at 1 minute	93 (7)	90 (10)	0.01
MAP at 3 minutes	90 (7)	90 (10)	0.04
MAP at 5 minutes	90 (7)	90 (7)	0.15
MAP after 15 minutes	90 (7)	90 (7)	0.09

*Mann–Whitney *U* test; Median (IQR); MAP, mean arterial pressure

$p = 0.5\%$], respectively. Variations in the HR and oxygen saturation (SpO_2) at baseline, 5 minutes after giving the drug or placebo, on the table just before the start of the procedure, 1 minute, 3 minutes, 5 minutes, and 15 minutes after the procedure) were not statistically significant between the groups ($p > 0.05$) (Tables 3 and 4), whereas the MAP on-table before the start of the procedure, at 1 minute and 3 minutes, was significantly higher in the glycopyrrolate group ($p = 0.01$, 0.01, and 0.04, respectively) (Table 5).

Discussion

A vast majority of the UGIE is done for diagnostic indications, and unsedated procedures can be performed quickly, decreasing hospital stays and the cost of healthcare. As a result, patients can return to work on the same day. Though most of the unsedated UGIE are tolerated well by the patients, 10% experience severe discomfort.[14] Nevertheless, some patients might experience discomfort after intravenous sedation,[15,16] with drawbacks like oxygen desaturation, hypotension, arrhythmias, aspiration pneumonia, and prolonged recovery.[17] Patient tolerance indirectly reflects on procedure outcomes. Hence, endoscopy units tried various strategies to improve patient tolerance in unsedated UGIE, namely, psychological preparation, relaxation music, hypnosis, acupuncture, and allowing a family member to accompany the patient throughout the procedure, have been tried with limited

effectiveness in improving tolerance to UGIE.[18–21] This study aims to find a novel strategy to improve patient tolerance in unsedated UGIE. Enhancing TPA could improve patient tolerance and procedure outcomes since the major contributor to discomfort and poor tolerance happens during endoscope intubation.[22] Lignocaine causes a reduction in sensory function without affecting the motor function of the pharynx and larynx.[23] However, the pharyngeal secretions have reduced their efficacy.[12,24] Lignocaine gets diluted and washed by saliva, decreasing contact with the oral mucosa and increasing the amount swallowed. Hence, glycopyrrolate use before the procedure effectively reduces oral and gastric secretions. As a result, lignocaine gets absorbed faster and topical anesthesia lasts longer.[9] Glycopyrrolate exhibits the onset of action within 1 minute when given intravenously, the elimination half-life is approximately 50 minutes, and the duration of action is 2–4 hours.[25,26] The intravenous route was preferred in this trial since it was proven more effective than the intramuscular or oral route.[27] It also avoided pain to the participants due to intramuscular injection. Since they already had an intravenous cannula placed for UGIE, it would be easier to administer intravenous glycopyrrolate. In the past, glycopyrrolate was tried in bronchoscopy to improve tolerance without much benefit.[28] A study by Kim Eui Joo et al. found that using glycopyrrolate in patients undergoing submucosal dissection improved the ease of the procedure.[8]

Endoscope size and prior history of endoscopy were crucial factors in determining the patient tolerance to the procedure.[29,30] All the procedures were done by a single expert endoscopist using the same diameter endoscope, and none of the patients had undergone UGIE in the past. Anxiety was the main limiting factor in previous studies that evaluated the patient's tolerance to unsedated endoscopy.[11,31] However, in our study, the baseline anxiety level was comparable between the glycopyrrolate and placebo groups. The key to a safe endoscopy examination is successfully intubating an endoscope into the esophagus. Although there was no statistical significance in our study, all patients had successful intubation and complete examination in the glycopyrrolate group compared with the placebo group. The study by Campo et al. showed that optimal TPA improves patient tolerance and makes examination easier.[12] Our study found that augmentation of TPA with glycopyrrolate results in significantly better overall satisfaction than the placebo group. The discomfort experienced by the patient and willingness to undergo repeat procedures in the future was also better in the glycopyrrolate group; it was not statistically significant.

In our study, HR fluctuation was not significantly different between the groups. It showed that glycopyrrolate has little effect on HR, unlike other anticholinergics. Our study substantiates previous results on the HR effect of glycopyrrolate.[23,27] Unlike previous studies, we observed a higher MAP during the procedure in the glycopyrrolate group.[28] The change in MAP could be attributed to the effect of glycopyrrolate.

Moreover, during the endoscopy, there was no significant change in SpO_2, similar to the previous study by Garg et al.[32] The current trial suggests that frequent monitoring in average-risk patients undergoing unsedated UGIE would not improve patient outcomes because significant changes in cardiorespiratory parameters are rare and brief during endoscopy. However, a large sample size would be needed to determine whether electronic monitoring influences patient morbidity and mortality. Kim Eui Joo et al. demonstrated that the ease of procedure was significantly better with glycopyrrolate in patients undergoing endoscopic submucosal dissection.[8] We observed that patient cooperation was significantly better in the glycopyrrolate group.

In contrast, the ease of the procedure and satisfactory visualization of all the parts of the upper gastrointestinal tract, better in the glycopyrrolate group, were not statistically significant. The procedure might have been easier because glycopyrrolate premedication decreases gastric motility and secretions from the oropharynx and stomach. We did not specifically assess gastric secretion and motility, the ease of the procedure for the endoscopist indicates glycopyrrolate effects on these functions. Furthermore, we found that the endoscopist's assessment score for patient cooperation was significantly better in the intervention group than in the placebo group for the unsedated procedure.

During this trial, there were no major adverse events. The strengths of this study are as follows: all the endoscopic procedures were performed by a single expert endoscopist using the same diameter endoscope, and the baseline anxiety levels were similar in both groups. This study has a few limitations. First, the sample size was relatively smaller. Second, it was a single-center study. We cannot generalize the results to different races and ethnicity. Third, in the current study, outcome variables were not measured objectively. VAS scale was used to measure the outcomes subjectively. However, previous studies have employed similar VAS to measure such outcomes.[12] The results of our investigation must be verified in a large multicenter trial to determine the effect of glycopyrrolate on tolerance to unsedated endoscopy in different populations and ethnicities. The study hypothesis might attract larger, prospective studies with more objective measurements of outcomes.

Conclusion

In unsedated UGIE, glycopyrrolate premedication improves the easiness for the endoscopist due to better patient cooperation. There was a better overall patient satisfaction score. It also allows the endoscopist to examine all areas thoroughly. It is a cheap and effective strategy with a minimal effect on cardiorespiratory parameters; hence, it could be incorporated safely in day-care unsedated endoscopy practice.

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