Indian Journal of Clinical Anaesthesia 2025;12(1):22–27

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Indian Journal of Clinical Anaesthesia

Journal homepage: www.ijca.in

Original Research Article

Efficacy of benzydamine hydrochloride on cumulative propofol consumption in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP): A randomized placebo-controlled trial

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ARTICLE INFO

Article history:
Received 16-11-2024
Accepted 09-12-2024
Available online 20-01-2025

Keywords:
Propofol
Benzydamine hydrochloride
Sedation
Cumulative propofol
Endoscopic retrograde cholangiopancreatography (ERCP)

ABSTRACT

Background: The Endoscopic retrograde cholangiopancreatography (ERCP) procedure is utilized for diagnosis and treatment of various biliary and pancreatic disorders. A variety of different drugs with different doses have been used to provide sedation, although they are associated with distinctive pros and cons. Propofol is a widely used sedative agent due to its rapid onset and short duration of action, making it suitable for procedures like ERCP. However, its use is not devoid of risks, including respiratory depression and hypotension. Therefore, strategies to minimize propofol dosage are of clinical significance.

Materials and Methods: After obtaining institutional ethics committee approval and CTRI registration study was conducted on 150 patients posted for ERCP procedure, with random allocation into two groups of 75 in each group. One group received interventional drug and other group received placebo 3 minutes before the procedure. Cumulative propofol consumption in terms of μg/kg/min and incidence of desaturation, hypotension as well as sore throat within 24 hours was recorded.

Results: The results of the study demonstrated that total propofol consumption was significantly lower in the benzydamine hydrochloride group compared to the placebo group, with values of 144.1 ± 27.3 μg/kg/min versus 154.5 ± 30.7 μg/kg/min ($p = 0.03$). The incidence of desaturation was marginally lower in the intervention group (1.3%) compared to the placebo group (2.7%), although this difference was not statistically significant ($p = 0.56$). Similarly, the occurrence of hypotension was 9.3% in the benzydamine hydrochloride group and 12% in the placebo group ($p = 0.59$). Postoperative sore throat within 24 hours was reported in 9.3% of patients in the intervention group and 13.3% in the placebo group, but this difference also did not reach statistical significance ($p = 0.44$).

Conclusion: The study concluded that benzydamine hydrochloride gargles are effective in reducing the cumulative propofol requirement during ERCP procedures. This reduction may help minimize dose-related complications associated with propofol use.

1. Introduction

The Endoscopic Retrograde Cholangiopancreatography (ERCP) procedure is utilized for diagnosis and treatment of various biliary and pancreatic disorders.[1,2] Despite its effectiveness, ERCP is associated with certain challenges such as patient discomfort, requiring adequate sedation to ensure procedural success and patient cooperation. A variety of different drugs with different doses have been used to provide sedation, although they are associated with distinctive pros and cons.[3]

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https://doi.org/10.18231/j.ijca.2025.004

Propofol is a widely used sedative agent, due to its rapid onset and short duration of action, making it suitable for procedures like ERCP. However, its use is not devoid of risks, including respiratory depression and hypotension. Therefore, strategies to minimize propofol dose while maintaining patient comfort and procedural efficacy are of clinical importance.[4]

Several studies have investigated different approaches to optimize propofol dosing in ERCP procedures. For instance, Gillham MJ et al. assessed the efficacy of a target-controlled infusion (TCI) system for propofol administration in ERCP, aiming to achieve a balance between sedation depth and propofol consumption.[5]

A non-steroidal anti-inflammatory drug (NSAID), Benzydamine hydrochloride, has been used for decades in various formulations for its local analgesic and anti-inflammatory properties. A past study has also suggested its potential role in reducing oropharyngeal inflammation and discomfort when used as a gargle solution prior to endoscopic procedures. By reducing discomfort and the need for additional sedation, Benzydamine could contribute to a reduction in propofol dosage during ERCP.[6] But it's use as propofol sparing agent in ERCP has not been studied much.

Prior research indicates that oropharyngeal anesthesia and analgesia can significantly decrease the requirement for sedative and anesthetic agents during endoscopic procedures. Sugiarto A et al. in 2020, demonstrated that pre-procedural gargling with benzydamine hydrochloride can effectively reduce patient discomfort and sedative requirements during upper gastrointestinal endoscopy.[7]

Despite these promising findings in other endoscopic procedures, the specific efficacy of benzydamine hydrochloride gargles in reducing propofol dosage in ERCP remains largely unexplored. This study aimed to address this gap by investigating the effect of benzydamine hydrochloride gargle in reducing propofol dose among ERCP patients, with the following objectives. The primary objective of this study was to evaluate the effect of benzydamine hydrochloride on cumulative propofol consumption in patients undergoing ERCP. A secondary objective was to assess the incidence of sore throat within 24 hours post-procedure among different study groups.

2. Materials and Methods

This randomized controlled trial was carried out at a tertiary care hospital following approval from institutional Research and Ethics Committee and the study has been registered in Clinical Trail Registry of India (CTRI/2022/09/045354).

The study was conducted between September 2022 to March 2024. A total of 150 study subjects were randomly allocated between group A and group B in the ratio 1:1, after satisfying the inclusion and exclusion criteria (Diagram 1). Allocation concealment was done using opaque sealed envelope technique. Group A, participants received 15 ml of 0.15% benzydamine hydrochloride gargle and Group B, participants received 15 ml of normal saline gargle.

Inclusion criteria were participants who belonged to age group 18-75 years, American Society of Anesthesiologists (ASA) category I, II, III and consenting patients posted for ERCP under sedation. Exclusion criteria include participants who had any history of allergy to the study drug or having any psychiatric illness, any severe hepatic, cardiac, or renal insufficiency, any throat wound, pregnant and lactating women or if procedure expected to take more than 90 minutes.

Cumulative propofol consumption was calculated after dividing total propofol used during the procedure by weight and duration of procedure.

2.1. Anaesthesia technique

All patients were kept fasting as per standard NPO (nil per os) guidelines. In the preoperative section, baseline measurements of heart rate, blood pressure, and pulse oximetry (SpO_2) were recorded.

A nasal prong delivering oxygen at a flow rate of 3 liters per minute was secured before initiating sedation. Sedation was induced with intravenous (IV) fentanyl at a dose of 1 μg/kg and IV propofol at 1 mg/kg. Sedation was maintained using a continuous propofol infusion at 50 μg/kg/min. The propofol dose was titrated based on the Ramsay Sedation Scale (RSS), with additional bolus doses of 0.3 mg/kg administered if the RSS score rose above 4 or if the patient moved.

Standard ASA monitoring protocols were followed throughout the procedure. Hypotension, defined as a decrease in systolic blood pressure (SBP) below 90 mmHg, was managed with intravenous vasopressors. In cases of tachycardia (heart rate >100 beats per minute), incremental doses of 25 μg of fentanyl were administered. The duration of the procedure was measured from the insertion of the endoscope into the mouth until the end of the intervention.

The cumulative dose of propofol was calculated in μg/kg/min at the conclusion of the procedure. Patients were monitored for 24 hours postoperatively to assess the incidence of sore throat.

2.2. Sample size

The sample size for this study was determined based on the results of a preliminary pilot study involving 10 patients in each group. Using Epi Info software, the calculation considered a mean difference of 16.6, with a standard deviation (SD) of 20.2 for the experimental group and 46.0 for the control group. With a significance level of 5% and a statistical power of 80%, the required sample size was estimated to be 144 participants, with a minimum of 72 patients per group, maintaining a 1:1 allocation ratio. To

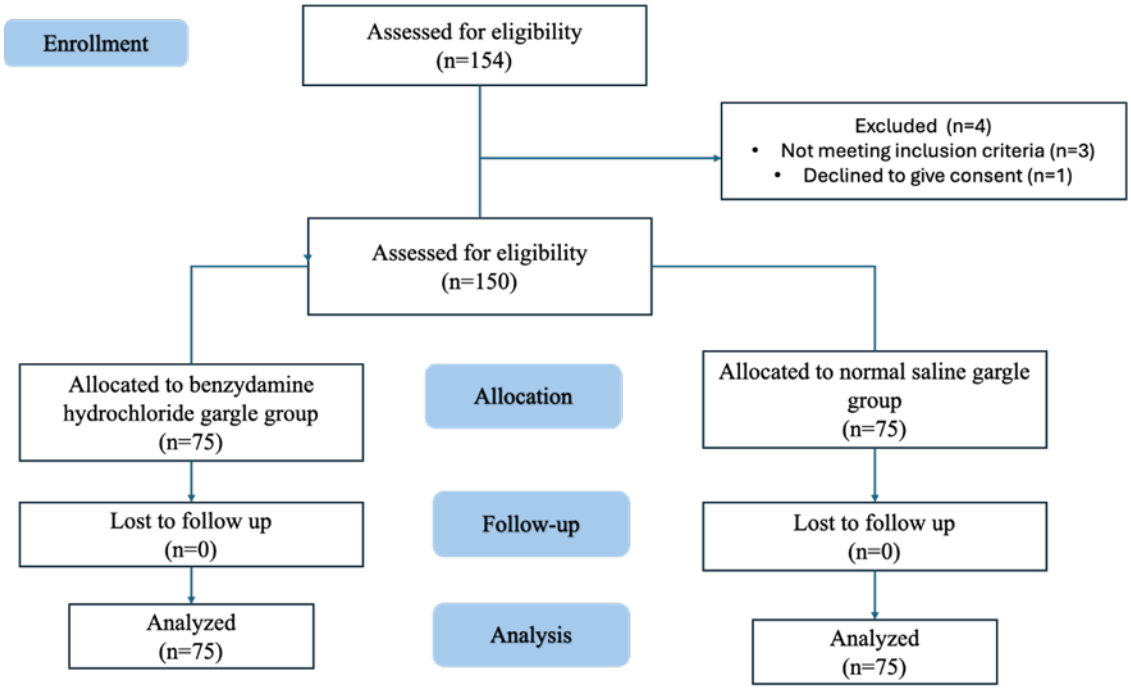

Diagram 1: Consort diagram

ensure robustness and taking 10% attrition rate, a total of 150 participants were ultimately recruited for the study.

2.3. *Statistical analysis*

Data entry and statistical analysis were performed using Microsoft Excel and IBM SPSS Statistics software (version 29.0, trial version). Descriptive statistics were used to summarize qualitative variables as frequencies and percentages, and quantitative variables as means with standard deviations. The Chi-square test was employed for categorical data, while the Student's t-test was used for comparing means of continuous variables. A p-value of less than 0.05 was considered statistically significant.

3. Results

Out of 150 patients, the ratio of male vs female was 72:78. Mean age with Standard deviation (SD) was 49.67 ± 15.77 years in Group A whereas 48.16 ± 14.19 years in Group B. The baseline characteristics in both groups were comparable and there was no statistically significant variation. (Table 1)

Table 2 shows the duration of procedure and cumulative propofol consumption in each group. In group A, mean time of procedure was 44.23 minutes with standard deviation of 15.0 minutes while in group B, it was 44.39 minutes with 14.9 minutes of standard deviation. The difference was statistically insignificant ($p \leq 0.05$).

The dose of propofol used was higher in control group (154.5 ± 30.7μg/kg/min) compared to benzydamine hydrochloride group (144.1 ± 27.3μg/kg/min) with a p value of 0.03 which was found statistically significant. (Figure 1) The findings are expressed in μg/kg/min after dividing total propofol used during the procedure by weight and duration of procedure. The figure represents the mean value with 95% of observation of each group.

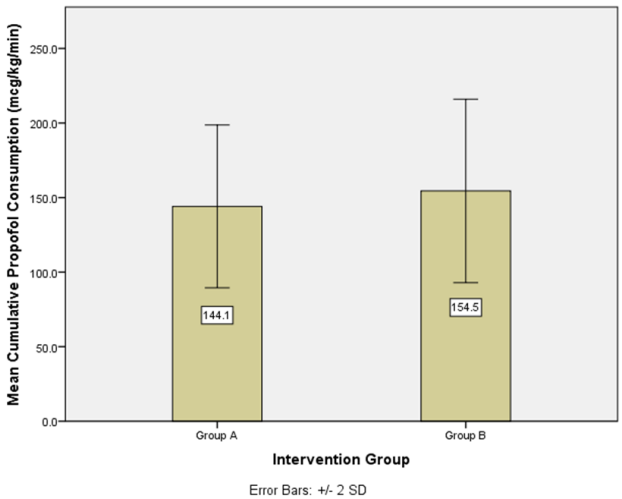

Figure 1: Distribution of the mean with error bars representing cumulative propofol consumption among study subjects

Figure 2 shows, the comparison of incidence of sore throat within 24 hours post-operatively, between the groups. In group A, 7 (9.3%) participants complained of sore throat

whereas 10 (13.3%) in group B complained of the same. The difference was statistically insignificant between groups (p= 0.44), though a greater number of patients in group B reported of sore throat, it can be of clinical significance.

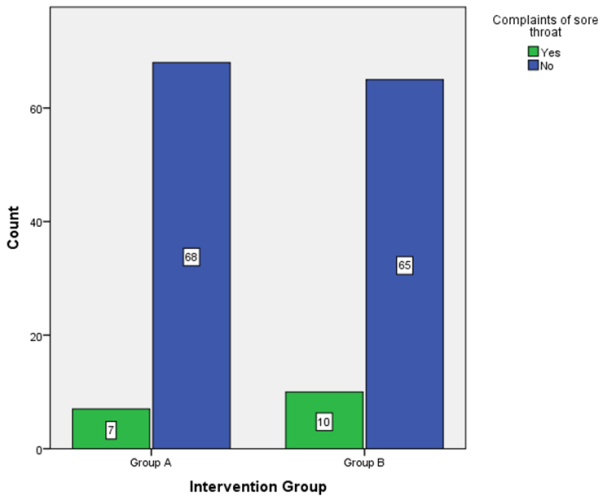

Figure 2: Distribution of sore throat complaints among study subjects across the groups

The incidence of hypotension amongst the groups was found statistically insignificant (Table 3). All the patients of either group who developed hypotension managed with multiple doses of phenylephrine (10μg/dose) or ephedrine (6mg/dose) based on heart rate, to maintain MAP of minimum 65 mmHg during the procedure.

During the procedure, single patient in intervention group had the episode of desaturation whereas two subjects in the control group. The incidence was managed by increasing the FiO2 level, without the need for endotracheal intubation. Although the results are not statistically significant for hypotension and desaturation, vigilant monitoring during sedation is essential to take prompt action if necessary.

Table 1: Demographic characteristics of study participants

	Group A (n=75)	Group B (n=75)	p value
Gender (Male:Female)	37:38	35:40	0.744
Age (Years) (Mean ± SD)	49.67±15.77	48.16±14.19	0.540
Weight (Kg) (Mean ± SD)	55.67±8.08	56.27±9.79	0.694
Height (Cm) (Mean ± SD)	165.20±7.62	164.79±8.24	0.750
BMI (kg/ sq.mt) (Mean ± SD)	20.50±3.60	20.80±3.78	0.621
ASA Grade (I:II:III)	31:37:7	34:29:12	0.298

Table 2: Comparison of duration of procedure and propofol consumption amongst the groups

	Group A Mean ± SD	Group B Mean ± SD	p value
Duration (mins)	44.23±15.0	44.39±14.9	0.94
Cumulative propofol consumption (μg/kg/min)	144.1±27.3	154.5±30.7	0.03

Statistically significant (<0.05)

Table 3: Comparison of hypotension incidence across the groups

	Group A n (%)	Group B n (%)	p value
Yes	9 (12%)	7 (9.3%)	0.59
No	66 (88%)	68 (90.7%)	

4. Discussion

Studies have demonstrated that anesthetist-directed moderate to deep sedation leads to better procedure outcomes and higher patient satisfaction compared to conscious sedation.[8,9] However, targeting deeper sedation levels during ERCP raises safety concerns. Studies indicate that the incidence of cardiovascular and respiratory complications, such as hypotension (ranging from 0.8% to 7.2%) and hypoxemia (5.3% to 13.4%), is higher during ERCP than in other gastrointestinal procedures, even when anesthesia professionals manage the moderate to deep sedation.[10,11]

This study findings indicated that the group receiving benzydamine hydrochloride required significantly less cumulative propofol in contrast to the control group. Dose of propofol used was 144.1 ± 27.3μg/kg/min (mean ± SD) in benzydamine hydrochloride group and in control group, it was 154.5 ± 30.7μg/kg/min. The results are consistent with the studies carried out by Soweid et al. in 2011, which explored the use of topical anesthetics in endoscopic procedures, and by Basturk et al. in 2017, who utilized lidocaine in spray or gel form.[12,13] However, it is important to note that lidocaine spray can potentially cause side effects such as irritation, nausea, vomiting, and difficulty swallowing. Due to anti-inflammatory properties of benzydamine hydrochloride, it is effective in reducing the mucosal inflammation and alleviating the sore throat episodes.[14]

A study done by Wang P et al. amongst 400 patients scheduled for ERCP, where one group received the propofol with nalbuphine and other group propofol with fentanyl. In the fentanyl group, respiratory depression occurred in 12.06% of cases, and 14 patients experienced hypoxia. Of these, 5 developed severe hypoxia, with 2 requiring endotracheal intubation.[15] These findings contrast with the current study, where desaturation was observed in only 2% of cases. In those instances, it was managed by increasing

the FiO2 and performing the jaw thrust manoeuvre.

Sore throats are a common complaint after the procedure due to inflammation of the mucous membranes. In this study, incidence of sore throat was observed for 24 hours post-operatively and it was found that, in group A, 7 (9.3%) participants complaints of sore throat vs 10 (13.3%) in group B. Zubarik R et al., found the incidence of sore throat in 9.5%, when 30 days follow up for complications was done in 473 patients after endoscopy procedure.[16] The findings of this study align with those of the current research. However, in contrast, Sugiarto A et al. in 2020 reported a 36% incidence of sore-throat in the control group four hours after the procedure.[7] This inflammation typically subsides over time and generally improves within 72 hours post-procedure.[17] The agent used may provide a topical anesthetic effect lasting up to 90 minutes following administration. Additionally, the sore throat incidence significantly reduced because of anti-inflammatory properties of the drug.

In the present study, desaturation and hypotension reported in both the groups. The observed side effects are likely linked with the use of propofol during the ERCP procedure and not because of study drug. Propofol is recognized for its potential to cause hypotension, desaturation, apnea, allergic responses, and cardiac arrest.[18,19] Nonetheless, the control group experienced a higher incidence of desaturation and hypotension compared to the study group. This discrepancy might be attributable to a slightly higher amount of propofol administered in the control group.[20]

Problem of nausea and vomiting were similar in both the groups. In group A, 4 (5.3%) participants and in group B, single participants (1.3%) had complaints of nausea/vomiting. The ERCP procedure itself can trigger nausea and vomiting, either due to the contrast media used during the procedure or as a result of pancreatic inflammation, which is a serious complication.[21] Additionally, the administration of fentanyl during the ERCP anesthesia may lead to nausea and vomiting after the procedure.[13]

In our study, the average propofol consumption for patients undergoing ERCP was 149 μg/kg/min. These dosages were administered to achieve a level of deep sedation, ensuring patient immobility and comfort while allowing the endoscopist to perform the procedure effectively. The total dosage was carefully titrated based on patient responses and procedural requirements.

Liu J et al. in 2020, also reported an average propofol consumption of approximately 148 μg/kg/min in their double-blind prospective trial among ERCP patients which aligns closely with our findings.[21] A study by Peprah K et al. assessed the use of propofol and ketamine for sedation during ERCP.[22] They found that the combination of propofol and ketamine was effective for sedation with minimal adverse events. The similar use of propofol in both studies suggests that our sedation protocols align with those used in other high-volume centers. However, Varadarajulu et al. observed a slightly higher incidence of hypotension, which may reflect differences in patient populations, procedural techniques, or variations in the dosing and administration of sedative agents.[23]

5. Conclusion

Based on the results of our study, we conclude that benzydamine hydrochloride gargles, administered three minutes before patients undergo an ERCP procedure under sedation, are effective in reducing the overall propofol requirement and minimizing subsequent complications. Additionally, the incidence of sore throat is lower due to the anti-inflammatory properties of benzydamine hydrochloride. Therefore, benzydamine hydrochloride gargle could be particularly advantageous for patients scheduled for ERCP under sedation.

6. Limitation

The study was conducted at a single center due to time and logistical constraints. Future research on this topic involving multiple centers is essential. Another limitation was the use of the Ramsay Sedation Scale to assess sedation depth, which could have been more objectively measured using the Bi-spectral Index (BIS). BIS monitors are widely recognized for their ability to help anesthesiologists accurately assess sedation levels in patients.

7. Sources of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Gaur BPS, Nayak LK, Das M, Mohapatra PS, Nath P. Efficacy of benzydamine hydrochloride on cumulative propofol consumption in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP): A randomized placebo-controlled trial. *Indian J Clin Anaesth* 2025;12(1):22-27.