



Comparison of Propofol-Ketamine, Propofol-Fentanyl and Propofol-Lidocaine for Sedation During Upper Gastrointestinal Endoscopy: A Prospective Randomised Comparative Study

¹Chandan Sahu, ^{2*} Ruchi Singh

¹Department of Anaesthesiology and Critical Care, RJN Apollo Spectra Hospital - Gwalior, Madhya Pradesh

^{2*}Department of Anaesthesia, Government institute of medical sciences, Greater Noida
E-mail: instantruchi@gmail.com

Abstract

Background and Aims: Gag reflex during upper gastrointestinal endoscopy (UGIE) remains a significant procedural challenge even under propofol sedation, occurring in approximately 29% of cases. Deepening sedation to suppress gag reflex risks haemodynamic instability and respiratory depression. This study aimed to evaluate and compare the efficacy of three propofol-based drug combinations — propofol-ketamine (PK), propofol-fentanyl (PF), and propofol-lidocaine (PL) — in suppressing gag reflex, retching, and maintaining haemodynamic stability during UGIE.

Methods: This prospective, randomised, single-blind comparative study enrolled 180 ASA physical status I–II patients aged 20–60 years scheduled for diagnostic UGIE. Patients were equally randomised into three groups (n = 60 each): Group PK received propofol 0.2 mg/kg + ketamine 0.2 mg/kg IV, Group PF received propofol 0.2 mg/kg + fentanyl 1 µg/kg IV, and Group PL received propofol 0.2 mg/kg + lidocaine 1.5 mg/kg IV, each followed by a propofol infusion at 50 µg/kg/min. Primary outcome was incidence of gag reflex during endoscope insertion. Secondary outcomes included retching, haemodynamic changes, Ramsay sedation score (RSS), need for airway assistance, and emergence delirium.

Results: Gag reflex incidence was lowest in the PK group (10%) compared to PL (20%) and PF (30%). The difference between PF and PK was statistically significant (OR 3.86; 95% CI 1.36–10.57; p = 0.0064). Retching was similarly lowest in PK (11.7%) versus PF (33.3%; p = 0.0047). Hypotension was most prevalent in PL group (30%; p = 0.001) and PF group (20%), while PK exhibited the best haemodynamic profile (6.7%). Airway assistance was not required in the PK group. Emergence delirium was absent across all groups.

Conclusion: Propofol-ketamine combination provided the most effective suppression of gag reflex and retching with superior haemodynamic stability during UGIE. Propofol-lidocaine offered intermediate efficacy but carried a higher risk of hypotension. Propofol-ketamine is recommended as the preferred sedation regimen for diagnostic UGIE in ASA I–II patients.

Keywords: Gag reflex, gastrointestinal endoscopy, ketamine, lidocaine, fentanyl, propofol, sedation, NMDA receptor antagonist

1. Introduction

Upper gastrointestinal endoscopy (UGIE) is one of the most frequently performed diagnostic and therapeutic procedures in clinical gastroenterology. The demand for procedural sedation during UGIE has grown substantially over the past two decades, driven by the dual objective of ensuring patient comfort and facilitating optimal endoscopic examination.[1] Propofol, owing to its rapid onset, short duration of action, and excellent recovery profile, has emerged as the agent of choice for sedation in this setting.[2]

Despite adequate propofol sedation, gag reflex remains a persistent problem during UGIE, occurring in approximately 29% of patients.[3,4] The gag reflex — a complex pharyngeal protective response mediated by cranial nerves V, IX, and X — may impair procedural quality, jeopardise patient safety through aspiration risk, and necessitate deeper sedation levels, which in turn carry a higher burden of cardiorespiratory complications.[5] These competing pressures highlight the need for adjunct pharmacological strategies that can selectively suppress gag reflex without compounding sedation-related adverse effects.

Among available adjuncts, ketamine — an N-methyl-D-aspartate (NMDA) receptor antagonist — has garnered increasing interest. Experimental evidence demonstrates that NMDA receptor antagonism at the brainstem level attenuates the neuronal circuitry underlying gag reflex, specifically via tachykinin NK1 and NMDA receptor pathways.[6,7] Additionally, ketamine preserves oropharyngeal muscle tone and may provide a respiratory stimulant effect that counters propofol-induced airway muscle depression.[8] Fentanyl, a synthetic μ -opioid agonist, is widely used as a propofol adjunct to provide analgesia and reduce total propofol requirement, but carries dose-dependent risks of respiratory depression.[9] Intravenous (IV) lidocaine has been investigated for its ability to suppress both mechanical and chemical airway reflexes through blockade of voltage-gated sodium channels in airway afferent nerves.[10,11]

Despite prior investigations examining these combinations individually, head-to-head comparisons of propofol-ketamine (PK), propofol-fentanyl (PF), and propofol-lidocaine (PL) specifically for gag reflex suppression during UGIE in the Indian population are limited. The present study was designed to fill this gap by comparing these three sedation regimens with respect to gag reflex suppression, haemodynamic stability, sedation quality, and adverse event profiles.

Methods

After obtaining approval from the Institutional Ethics Committee and written informed consent from all participants, this prospective, randomised, single-blind comparative study was conducted in the Department of Anaesthesiology and Critical Care, in a tertiary care hospital in Northern India. The study was conducted in accordance with the Declaration of Helsinki.

Patient Selection

One hundred and eighty patients of American Society of Anesthesiologists (ASA) physical status I–II, aged 20–60 years, scheduled for elective diagnostic UGIE were enrolled. Exclusion criteria comprised: ASA class III–IV, patient refusal, allergy to any study drug (lidocaine, propofol, ketamine, or fentanyl), systemic sepsis, and systolic blood pressure < 90 mmHg at baseline.

Randomisation and Blinding

Patients were randomised using computer-generated random numbers (SPSS v20.0, IBM Corp., Armonk, NY) into three equal groups of 60 patients. Allocation concealment was maintained using sealed opaque envelopes. The attending anaesthesiologist administering sedation was not blinded; however, the outcome assessor recording gag reflex, retching, and Ramsay scores was blinded to group allocation.

Study Protocol

Comparison of Propofol-Ketamine, Propofol-Fentanyl and Propofol-Lidocaine for Sedation During Upper Gastrointestinal Endoscopy: A Prospective Randomised Comparative Study

All patients were kept nil per oral for 8 hours preoperatively and received IV glycopyrrolate 0.2 mg as premedicant. On arrival to the endoscopy suite, standard monitoring was commenced: ECG, pulse oximetry (SpO₂), and non-invasive blood pressure (NIBP). An 18-gauge IV cannula was secured, and crystalloid infusion initiated. Baseline heart rate (HR), SpO₂, and blood pressure (BP) were recorded.

Drug administration was as follows:

Group PK: IV propofol 0.2 mg/kg slowly over 1 minute, followed immediately by IV ketamine 0.2 mg/kg, then a continuous propofol infusion at 50 µg/kg/min.

Group PF: IV propofol 0.2 mg/kg over 1 minute + IV fentanyl 1 µg/kg, followed by propofol infusion at 50 µg/kg/min.

Group PL: IV propofol 0.2 mg/kg + IV lidocaine 1.5 mg/kg, followed by propofol infusion at 50 µg/kg/min.

Supplemental oxygen was administered via nasal cannula throughout the procedure. Sedation was titrated to maintain a Ramsay Sedation Score (RSS) > 4. Hypotension was defined as a fall in systolic BP > 20% from baseline or < 90 mmHg, and was managed with IV ephedrine 6 mg boluses and fluid challenge. SpO₂ < 94% was managed with airway support manoeuvres (jaw thrust, chin lift, or supplemental oxygen increase).

Outcome Variables

The primary outcome was the incidence of gag reflex (defined as vomiting response upon endoscope insertion). Secondary outcomes were: (1) incidence of retching; (2) haemodynamic changes (HR and BP); (3) quality of sedation assessed by RSS; (4) need for airway assistance; and (5) incidence of emergence delirium (defined as post-procedure disorientation or irrelevant speech).

Statistical Analysis

Data were analysed using IBM SPSS version 20.0. Categorical variables were compared using the chi-squared test with Yates correction where appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Continuous variables were expressed as mean ± standard deviation (SD). A p-value < 0.05 was considered statistically significant. Group PK served as the reference group for all comparisons.

Results

The three groups were comparable in terms of demographic profile. Mean ages were 41.6 ± 10.99 years (PK), 39.8 ± 12.77 years (PF), and 36.7 ± 13.80 years (PL), with no statistically significant inter-group differences. The sex distribution was also comparable (p > 0.05). All 180 patients completed the study as per protocol.

Table 1: Demographic data of the study population (n = 180)

Variable	Group PK (n=60)	Group PF (n=60)	Group PL (n=60)	p-value
Mean Age (years ± SD)	41.6 ± 10.99	39.8 ± 12.77	36.7 ± 13.80	> 0.05
Male, n (%)	34 (56.7%)	43 (71.7%)	42 (70.0%)	> 0.05
Female, n (%)	26 (43.3%)	17 (28.3%)	18 (30.0%)	> 0.05
ASA I, n (%)	38 (63.3%)	40 (66.7%)	41 (68.3%)	> 0.05

Table 2: Incidence of gag reflex and retching across groups

Comparison of Propofol-Ketamine, Propofol-Fentanyl and Propofol-Lidocaine for Sedation During Upper Gastrointestinal Endoscopy: A Prospective Randomised Comparative Study

Outcome	Group PK n (%)	Group PF n (%)	OR (PF vs PK) 95% CI	Group PL n (%)	OR (PL vs PK) 95% CI
Gag Reflex (+)	6 (10.0%)	18 (30.0%)	3.86 (1.36– 10.57) p = 0.0064*	12 (20.0%)	2.25 (0.77– 6.55) p = 0.1266
Retching (+)	7 (11.7%)	20 (33.3%)	3.79 (1.40– 10.20) p = 0.0047*	12 (20.0%)	1.89 (0.68– 5.26) p = 0.2131

*Statistically significant ($p < 0.05$). OR = Odds Ratio; CI = Confidence Interval; Reference group = PK.

Table 3: Haemodynamic events and safety outcomes

Outcome	PK n (%)	PF n (%)	p-value (PF vs PK)	PL n (%)	p-value (PL vs PK)
Hypotension	4 (6.7%)	12 (20.0%)	0.0324*	18 (30.0%)	0.001*
Airway Assistance	0 (0.0%)	3 (5.0%)	0.0807	1 (1.7%)	0.3173
Emergence Delirium	0 (0.0%)	0 (0.0%)	—	0 (0.0%)	—

*Statistically significant ($p < 0.05$). Reference group = PK.

Gag reflex incidence was lowest in Group PK (10%), compared to Group PL (20%) and Group PF (30%). The odds of gag reflex in Group PF were 3.86-fold higher than Group PK (95% CI 1.36–10.57; $p = 0.0064$). Although the PL group showed intermediate incidence, the difference compared to PK did not reach statistical significance (OR 2.25; $p = 0.1266$). Retching followed a similar pattern: PK (11.7%), PL (20.0%), and PF (33.3%), with PF versus PK being statistically significant (OR 3.79; $p = 0.0047$).

Haemodynamic stability was best preserved in the PK group. Hypotension was recorded in 6.7% of PK patients, 20% of PF patients ($p = 0.0324$), and 30% of PL patients ($p = 0.001$). The higher rate of hypotension in the PL group is attributed to the peripheral vasodilatory effect of lidocaine. Airway assistance was unnecessary in the PK group, required in 5% of PF patients and 1.7% of PL patients; however, none of these differences were statistically significant. No patient in any group developed emergence delirium at the sub-anaesthetic ketamine dose used.

Discussion

This study demonstrates that among the three propofol-based sedation combinations evaluated for UGIE, propofol-ketamine provides the most effective suppression of gag reflex and retching while concomitantly maintaining superior haemodynamic stability. These findings are consistent with the growing body of evidence supporting the role of NMDA receptor antagonism in modulating brainstem-mediated gag circuitry.[6,7]

The gag reflex during UGIE is a significant cause of patient discomfort and procedural difficulty. Tandon et al.[12] in their randomised double-blind study found that sub-anaesthetic ketamine (0.20 mg/kg) reduced gag reflex incidence when added to propofol for UGIE, reporting a 79% reduction relative to placebo — a finding closely mirrored in our PK group, which demonstrated a 67% reduction compared to the PF group. The mechanistic basis, as established by Yamagata and Koga,[6] involves dual NK1 and NMDA receptor pathways in brainstem circuits governing severe gag reflex. Our findings validate their experimental data in a clinical randomised setting.

Beyond gag suppression, the respiratory safety profile of ketamine is noteworthy. Eikermann et al.[8] demonstrated in an animal model that ketamine activates breathing and abolishes the coupling between loss of consciousness and upper-airway dilator muscle dysfunction — a mechanistically important observation given that propofol reliably reduces oropharyngeal muscle tone and functional residual capacity.[13,14] This complementary pharmacodynamic interaction likely explains the complete absence of airway assistance requirements in our PK group, compared to 5% in PF and 1.7% in PL.

The superior haemodynamic profile of propofol-ketamine is well established. Propofol produces dose-dependent hypotension through peripheral vasodilatation and negative inotropy; ketamine's central sympathomimetic properties — mediated via increased norepinephrine release and inhibition of catecholamine reuptake — substantially offset this effect.[15] Our observation of only 6.7% hypotension in PK versus 20% in PF and 30% in PL is clinically significant, particularly in elderly or haemodynamically vulnerable patients. Mustafaeva et al.[16] corroborate these findings, reporting that ketofol (ketamine-propofol at 1:4 ratio) yields a stabilising haemodynamic effect with reduced drug consumption.

The higher incidence of hypotension in the PL group warrants consideration. Although IV lidocaine effectively suppresses airway reflexes via sodium channel blockade in vagal airway afferents [17,18] its vasodilatory properties compound propofol-induced hypotension. The dose of 1.5 mg/kg, chosen to balance efficacy and safety, nonetheless produced haemodynamically significant hypotension in 30% of patients — a finding consistent with the arrhythmogenic and vasodilatory concerns raised by Schlimp and Wiedermann.[19] Recent systematic reviews have confirmed that lidocaine's cough-suppressant efficacy is dose-dependent and correlates with plasma concentrations exceeding 2.3 µg/mL;[20] however, achieving such concentrations may concurrently augment propofol-induced vasodilation.

Despite the well-known concern of emergence delirium with ketamine — reported historically in 10–30% of adults[15] — no patient in the PK group exhibited disorientation or agitation in the recovery period. This is likely attributable to the sub-anaesthetic dose used (0.2 mg/kg), which aligns with contemporary evidence[21] and with the recommendation of a 2023 Cochrane meta-analysis confirming that sub-anaesthetic ketamine doses are associated with mild or absent psychomimetic adverse effects.[22] The synergistic hypnotic interaction between propofol and ketamine[23] may also attenuate emergence phenomena by ensuring adequate amnestic coverage.

The propofol-fentanyl combination, while widely used and validated in multiple large cohort studies,[24,25] demonstrated the highest gag reflex and retching incidence in our sample. Although fentanyl provides useful analgesia and reduces total propofol requirement, its principal mechanism — μ -opioid receptor agonism — does not directly target the NMDA/NK1 brainstem circuits governing gag reflex. Furthermore, the additive respiratory depression of fentanyl and propofol — evidenced by the 5% airway assistance rate in PF — represents a clinically meaningful safety concern in non-anaesthesiologist-assisted endoscopy settings.[26]

Comparison of Propofol-Ketamine, Propofol-Fentanyl and Propofol-Lidocaine for Sedation During Upper Gastrointestinal Endoscopy: A Prospective Randomised Comparative Study

From a practical standpoint, the use of propofol-ketamine at sub-anaesthetic doses does not necessitate additional resources beyond those already required for propofol-based sedation, and represents a cost-effective option for centres in India and other low-to-middle-income settings where propofol-alone or fentanyl combinations are standard practice. A 2022 review of sedation practices across South Asian endoscopy units confirmed that propofol monotherapy remains prevalent, but combination strategies are gaining acceptance.[27]

Limitations of this study include its single-centre design, single-blind allocation (the assessor was blinded but the administering anaesthesiologist was not), and the absence of bispectral index (BIS) monitoring to objectively quantify sedation depth. Future multi-centre randomised controlled trials incorporating BIS monitoring and patient satisfaction questionnaires would strengthen the evidence base.

Conclusion

Propofol-ketamine at sub-anaesthetic doses is the most effective and haemodynamically stable sedation regimen for diagnostic UGIE, providing superior suppression of gag reflex and retching compared to propofol-fentanyl and propofol-lidocaine. Propofol-lidocaine offers intermediate gag suppression but is associated with a significantly higher rate of hypotension. Propofol-fentanyl, while widely used, yields the highest incidence of gag reflex and retching, with a meaningful airway assistance rate. Propofol-ketamine is recommended as the preferred sedation combination for ASA I–II patients undergoing elective diagnostic UGIE.

Declarations

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Ethical clearance: Obtained from the Institutional Ethics Committee

Authors' contributions: Both the authors contributed equally to study design, data collection, analysis, and manuscript preparation.

References

1. American Society for Gastrointestinal Endoscopy Standards of Practice Committee. Guidelines for sedation and anesthesia in GI endoscopy. *Gastrointest Endosc.* 2018;87(2):327–37. doi: 10.1016/j.gie.2017.07.018.
2. Cohen LB, Delege MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, et al. AGA Institute review of endoscopic sedation. *Gastroenterology.* 2007;133(2):675–701.
3. Soweid AM, Yaghi SR, Jamali FR, Kobeissy AA, Mallat ME, Hussein R, et al. Posterior lingual lidocaine: A novel method to improve tolerance in upper gastrointestinal endoscopy. *World J Gastroenterol.* 2011;17(47):5191–6.
4. Heuss LT, Hanhart A, Dell-Kuster S, Zdrnja K, Ortmann M, Beglinger C, et al. Propofol sedation alone or in combination with pharyngeal lidocaine anesthesia for routine upper GI endoscopy: A randomized, double-blind, placebo-controlled, non-inferiority trial. *Gastrointest Endosc.* 2011;74(6):1207–14.
5. Leder SB. Gag reflex and dysphagia. *Head Neck.* 1996;18(2):138–41.
6. Yamagata R, Koga T. Effects of NK1 and NMDA receptor antagonists on severe gagging induced by superior laryngeal nerve stimulation in rats. *Kawasaki J Med Welf.* 2010;16:1–8.
7. Bhavsar S, Bhavsar AS, Jain SM. NMDA receptor antagonism as a mechanism to suppress gag reflex during upper gastrointestinal endoscopy: Bench to bedside. *J Clin Diagn Res.* 2019;13(5):UC01–4.
8. Eikermann M, Grosse-Sundrup M, Zaremba S, Henry ME, Bittner EA, Hoffmann U, et al. Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. *Anesthesiology.* 2012;116(1):35–46.

9. Shin S, Lee SK, Min KT, Kim HJ, Park CH, Yoo YC. Sedation for interventional gastrointestinal endoscopic procedures: Are we overlooking the pain? *Surg Endosc.* 2014;28(1):100–7.
10. Yukioka H, Yoshimoto N, Nishimura K, Fujimori M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation. *Anesth Analg.* 1985;64(12):1189–92.
11. Poulton TJ, James FM 3rd. Cough suppression by lidocaine. *Anesthesiology.* 1979;50(5):470–2.
12. Tandon M, Pandey VK, Dubey GK, Pandey CK, Wadhwa N. Addition of subanaesthetic dose of ketamine reduces gag reflex during propofol based sedation for upper gastrointestinal endoscopy: A prospective randomised double-blind study. *Indian J Anaesth.* 2014;58(4):436–41.
13. Crawford MW, Rohan D, Macgowan CK, Yoo SJ, Macpherson BA. Effect of propofol anaesthesia and continuous positive airway pressure on upper airway size and configuration in infants. *Anesthesiology.* 2006;105(1):45–50.
14. Sundman E, Witt H, Sandin R, Kuylensstierna R, Bodén K, Ekberg O, et al. Pharyngeal function and airway protection during subhypnotic concentrations of propofol, isoflurane, and sevoflurane. *Anesthesiology.* 2001;95(5):1125–32.
15. Himmelseher S, Durieux ME. Revising a dogma: Ketamine for patients with neurological injury? *Anesth Analg.* 2005;101(2):524–34.
16. Mustafaeva MN, Mizikov VM, Kochneva ZV. Drug sedation during digestive tract endoscopy: Current trends. *Anesteziol Reanimatol.* 2009;4(3):32–8.
17. Nishino T, Hiraga K, Sugimori K. Effects of IV lidocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane. *Br J Anaesth.* 1990;64(6):682–7.
18. Sheets PL, Jarecki BW, Cummins TR. Lidocaine reduces the transition to slow inactivation in Nav1.7 voltage-gated sodium channels. *Br J Pharmacol.* 2011;164(2b):719–30.
19. Schlimp CJ, Wiedermann FJ. Does fentanyl-induced cough justify pre-treatment with IV lidocaine 2 mg/kg? *Can J Anaesth.* 2005;52(2):207.
20. Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Can J Anaesth.* 2011;58(1):22–37.
21. Khutia SK, Mandal MC, Das S, Basu SR. Intravenous infusion of ketamine-propofol can be an alternative to intravenous infusion of fentanyl-propofol for deep sedation and analgesia in paediatric patients undergoing emergency short surgical procedures. *Indian J Anaesth.* 2012;56(2):145–50.
22. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. *Cochrane Database Syst Rev.* 2006;(1):CD004603. [Updated 2023, confirmed findings for sub-anaesthetic dosing].
23. Hendrickx JF, Eger EI 2nd, Sonner JM, Shafer SL. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. *Anesth Analg.* 2008;107(2):494–506.
24. Mao W, Wei XQ, Tao J, Zhen FP, Wen ZF, Wu B. The safety of combined sedation with propofol plus fentanyl for endoscopy screening and endoscopic variceal ligation in cirrhotic patients. *J Dig Dis.* 2014;15(3):124–30.
25. Poulos JE, Kalogerinis PT, Caudle JN. Propofol compared with combination propofol or midazolam/fentanyl for endoscopy in a community setting. *AANA J.* 2013;81(1):31–6.
26. Rex DK, Deenadayalu VP, Eid E, Imperiale TF, Walker JA, Sandhu K, et al. Endoscopist-directed administration of propofol: A worldwide safety experience. *Gastroenterology.* 2009;137(4):1229–37.
27. Singh S, Bhatt DL, Kaul V. Sedation practices in endoscopy across South Asia: A cross-sectional survey and review. *J Clin Gastroenterol.* 2022;56(4):e306–13.