

Effectiveness and Safety of Ketamine-Propofol Versus Ketamine-Midazolam Combinations in Endoscopic Cholangiopancreatography: A Prospective Observational Study

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ABSTRACT

Introduction: Endoscopic retrograde cholangiopancreatography (ERCP) requires effective sedation and analgesia. Ketamine–propofol and ketamine–midazolam is commonly used, but comparative data in ERCP are limited.

Objective: To compare the effectiveness and safety of ketamine–propofol (KP) versus ketamine–midazolam (KM) for procedural sedation during ERCP.

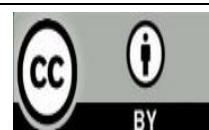
Methods: This prospective observational study included 50 ASA I–II patients aged 18–70 years undergoing ERCP, equally allocated to two groups. The KP group received ketamine–propofol 1:1 (0.5 mg/kg loading dose, 2–3 mg/kg/h infusion). The KM group received ketamine 0.5 mg/kg plus midazolam 0.02 mg/kg, with supplemental doses as required. Sedation was targeted to a Ramsay score of 5. Time to achieve targeted Ramsay Sedation Score after induction, patient needing rescue sedation, hemodynamic variables, recovery time, and adverse events were recorded. Data were analyzed using t-tests and chi-square tests, with $P < 0.05$ considered significant.

Results: Group KP achieved faster sedation than Group KM (184.80 ± 48.74 vs. 314.40 ± 92.11 seconds; P value < 0.001) and shorter recovery time (7.92 ± 1.89 vs. 9.48 ± 2.25 min; P value < 0.05). Discharge time was similar between groups. Hemodynamic parameters were lower in the KP group after induction. Desaturation and airway maneuvers were more frequent with KP while post procedure nausea and vomiting and recovery agitation were more common with KM group, though not statistically significant.

Conclusions: Both regimens were effective for ERCP sedation. Ketamine–propofol provided faster onset, quicker recovery and better-attenuation of sympathetic responses, but with more respiratory adverse events.

Keywords: ERCP; Ketamine; Midazolam; Sedation; Propofol

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INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a sophisticated endoscopic procedure used to diagnose and treat choledocholithiasis, biliary strictures, and pancreatic duct anomalies. [1] Unlike routine upper gastrointestinal endoscopy, ERCP is technically demanding, often prolonged, and commonly performed in the prone position, requiring deep sedation or general anesthesia to ensure patient comfort and immobility. [2,3] An ideal sedation regimen should provide rapid onset, adequate analgesia, hemodynamic stability, minimal respiratory depression, and prompt recovery. [4] However, no single agent fulfills all these criteria, necessitating combination therapy.

Propofol offers rapid induction and recovery but lacks analgesia and may cause hypotension and respiratory depression. [5,6] Ketamine provides effective analgesia and preserves airway reflexes but may lead to cardiovascular stimulation and emergence reactions. [7,8] Ketofol combines these benefits, [9,10] while midazolam reduces ketamine-related adverse effects. [11,12]

Comparative data for these regimens in ERCP remain limited.

Thus, this study compared the clinical effectiveness, hemodynamic profile, and safety of ketofol and Ketamine Midazolam for ERCP procedural sedation.

METHODS

This prospective observational study was conducted in the endoscopic suite of Dhulikhel Hospital, after Institutional Review Committee (IRC) approval on 14th August 2025 (IRC reference no: 209/25). Eligible 50 American Society of Anesthesiologists Physical Status (ASA-PS) I–II patients aged 18–70 years undergoing ERCP of less than 60 minutes were enrolled. The study was conducted between September 2025 and January 2026. Any patient who did not meet above criteria along with neurological disorder like raised intracranial pressure (ICP), seizure disorder, acute stroke within past 3 months, anatomic abnormalities, chronic cardiorespiratory disease were excluded from study.

After informed consent, all patients received 20-gauge IV access, isotonic fluid infusion, supplemental oxygen at 2 liters/min via nasal prongs, and standard monitoring with ECG, pulse oximetry, and non-invasive blood pressure.

In our institution, anesthesiologists use either Ketamine Propofol or Ketamine Midazolam combination as standard practice for sedation in ERCP. So, we are going to observe effectiveness and safety profile between two groups using Ketamine Propofol or Ketamine Midazolam combination for sedation.

Patients were randomly allocated into two groups of 25 each using sealed envelope technique and all the patient received sedation under anesthesiologist supervision. Monitoring and recording were performed by anesthesiologist. The procedures were performed in the prone position after topical pharyngeal lignocaine (15%) spray, with sedation titrated to a Ramsay Sedation Scale score of 5 and time taken to reach it was noted. The endoscope was introduced to the patients once they were adequately sedated in a prone position with the head turned to the right. Hemodynamic variables, patients needing rescue

sedation and adverse events such as desaturation ($\text{SpO}_2 < 90\%$), hypotension, bradycardia, vomiting, and agitation were recorded throughout the perioperative period. Bradycardia was defined as decrease in heart rate of 30 % from baseline and/or an absolute heart rate below 50 beats/min. Bradycardia was treated with atropine 0.6 mg intravenously. Hypotension was defined as either a mean arterial pressure (MAP) below 65 mmHg and/or $\geq 20\%$ reduction from baseline MAP. Hypotension was managed with intravenous crystalloids (200 ml Ringer lactate or normal saline) or incremental doses of mephentermine 3 mg intravenously. Desaturation was managed by initially increasing oxygen flow to 5-8 liters per minute using nasal prongs, followed by chin lift and jaw thrust maneuver until oxygen saturation level was optimized.

Patients in Group KP received ketamine–propofol mixture (ketofol) in 1:1 ratio prepared by combining 2 mL ketamine (50 mg/mL) and 10 mL propofol (10 mg/mL) with 8 mL normal saline to yield a 20 mL solution containing 5 mg ketamine and 5 mg of Propofol for each milliliter.[13] An initial loading dose of 0.5

mg/kg from the prepared solution was given followed by a continuous infusion of 2–3 mg/kg/hr, titrated to achieve the desired depth of sedation.

Group KM received intravenous ketamine 0.5 mg/kg and midazolam 0.02 mg/kg as a slow bolus over 1 minute, with additional boluses of ketamine 0.25 mg/kg and midazolam 0.01 mg/kg if adequate sedation was not achieved; glycopyrrolate 200 mcg was administered to prevent hypersalivation. [14]

After the procedure, patients were transferred to the post-anesthesia care unit once responsiveness to simple verbal commands was confirmed. Recovery was assessed using the modified Aldrete score at 20 and 40 minutes, and patients were discharged when the score exceeded 9 and the Mini-Mental State Examination (MMSE) score was 30.

Sample size calculation was done based on a pilot study of 10 patients (5 in each group). To detect an observed difference of 150 seconds to achieve Ramsay sedation score of 5 after induction between two groups with type I error 5% and

power of study 80 %, the minimum sample size required was 50 (25 in each group).

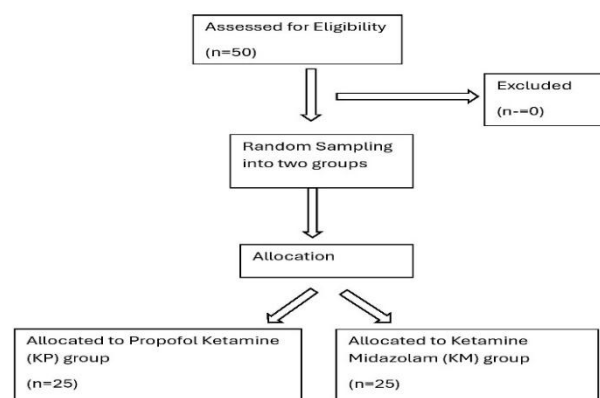


Figure 1: Consort flow diagram showing recruitment of the patients

The collected data was entered into and analyzed with IBM SPSS (Statistical package for social services) statistics software 26.0 Version. Graphs were created with MS Excel. The quantitative data was represented as mean $\pm$ standard deviation and for qualitative data, number, ratio and percentages were used. Demographic data and clinical variables were compared using chi-square test. Hemodynamic parameters at different intervals were compared using an independent samples t - test. A P- value of less than 0.05 was considered significant and -value of less than 0.01 was considered highly significant.

RESULTS

Table 1: Baseline demographic and clinical characteristics. (n=50)

Parameter	Group KP	Group KM	P Value
Age (Year $\pm$ SD)	58.80 $\pm$ 13.33	56.40 $\pm$ 9.97	0.47
BMI (kg/m ² $\pm$ SD)	21.02 $\pm$ 3.92	22.01 $\pm$ 3.22	0.34
Gender (M: F)	12:13	11: 14	0.78
ASA (I: II)	2: 23	6: 19	0.12
Total time taken to complete procedure (Mins $\pm$ SD)	40.00 $\pm$ 9.24	43.80 $\pm$ 6.81	0.10

Independent samples t- test, Chi-square test, P- value < 0.05 – significant

The baseline characteristics of patients in Group KP and Group KM were comparable across several parameters (Table 1, P- value > 0.05).

Table 2: Primary and Secondary Outcomes (n=50)

Parameters	Group KP	Group KM	P value
Time to get Ramsay sedation scale of 5 after induction in seconds (Mean $\pm$ SD)	184.80 $\pm$ 48.74	314.40 $\pm$ 92.11	0.00 #
Patients needing rescue sedation, n (%)	2 (8%)	6 (24 %)	0.12
Time of recovery in minutes (Mean $\pm$ SD)	7.92 $\pm$ 1.89	9.48 $\pm$ 2.25	0.01*
Modified Aldrete Score at 20 minutes) (Mean $\pm$ SD)	7.80 $\pm$ 0.57	7.72 $\pm$ 0.45	0.59
Modified Aldrete Score at 40 minutes) (Mean $\pm$ SD)	10.00 $\pm$ 0.00	10.00 $\pm$ 0.00	-
MMSE (Mini Mental State Examination) (Mins $\pm$ SD)	30.00 $\pm$ 0.00	30.00 $\pm$ 0.00	-
Time to discharge in minutes (Mean $\pm$ SD)	47.40 $\pm$ 7.08	50 $\pm$ 5.77	0.16

Independent samples t- test, Chi-square test, * P- value < 0.05 – significant; # P-value < 0.001- very highly significant.

In table 2, the time to achieve Ramsay sedation scale 5 was significantly shorter in Group KP (184.80 $\pm$ 48.60 secs) than in Group KM (314.4 $\pm$

92.11 secs), $P < .001$; this indicates a faster onset of target sedation with the KP regimen. Rescue sedation was required in 2 of 25 patients (8%) in Group KP vs 6 of 25 (24%) in Group KM; this difference did not reach statistical significance ($P > 0.05$). Time to recovery was significantly shorter in Group KP (7.92 ± 1.89 min) than Group KM (9.48 ± 2.25 min), $P < 0.05$, suggesting faster early recovery with Group KP. Time to discharge did not differ significantly (47.40 ± 7.08 vs 50 ± 5.77 min; $P > 0.05$). There were no statistically significant differences in modified Aldrete scores at 20 and 40 minutes, MMSE scores, or time to discharge, indicating comparable immediate recovery quality and cognitive status.

Table 3: Heart Rate (bpm) at successive time points (Mean $\pm$ SD) (n=50)

Time	Group KP (Mean $\pm$ SD)	Group KM (Mean $\pm$ SD)	P Value
Baseline	81.92 $\pm$ 15.21	84.04 $\pm$ 8.28	0.54
Post-Induction	78.64 $\pm$ 12.92	92.48 $\pm$ 13.15	0.00 #
5 min	77.16 $\pm$ 13.60	94.96 $\pm$ 11.04	0.00 #
10 min	78.12 $\pm$ 11.91	98.80 $\pm$ 14.29	0.00 #
15 min	80.00 $\pm$ 14.59	97.64 $\pm$ 10.88	0.00 #
20 min	82.84 $\pm$ 12.81	98.20 $\pm$ 13.23	0.00 #

25 min	81.88 $\pm$ 13.75	97.28 $\pm$ 13.76	0.00 #
30 min	82.50 $\pm$ 13.51	97.20 $\pm$ 14.20	0.00 #
35 min	81.94 $\pm$ 12.22	96.56 $\pm$ 14.72	0.00 #
40 min	81.93 $\pm$ 14.49	95.65 $\pm$ 11.68	0.00 #
45 min	78.00 $\pm$ 14.79	98.79 $\pm$ 10.52	0.00 #
50 min	70.00 $\pm$ 10.95	102.17 $\pm$ 9.99	0.00 #
55 min	67.00 $\pm$ 10.53	98.67 $\pm$ 8.08	0.01*

Independent samples t- test, *P-value < 0.05 – significant; # P-value < 0.001 - very highly significant.

In table 3, Heart rate was similar between groups at baseline. Following induction, heart rate remained significantly lower in Group KP than in Group KM at all measured time points from post-induction to 55 minutes ($P < 0.05$), indicating better intraoperative heart rate control in the KP group.

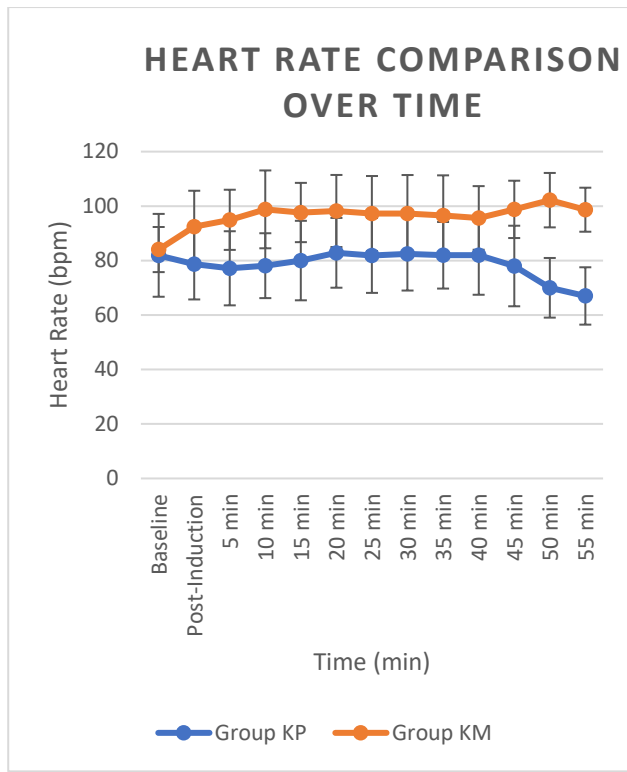


Figure 2: Heart rate (bpm) trend over 55 minutes between Group KP and Group KM.

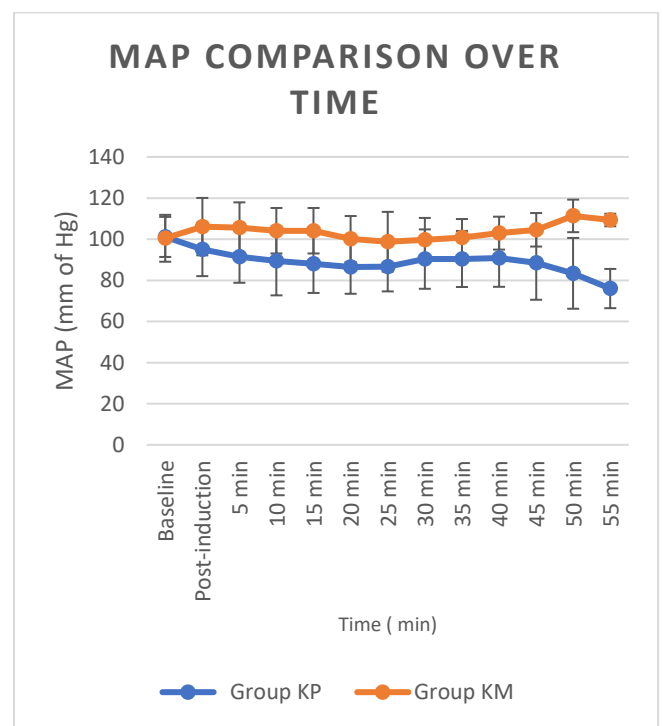
Table 4: Mean arterial pressure (mm Hg) at successive time points (n=50)

Time	Group KP (Mean ± SD)	Group KM (Mean ± SD)	P value
Baseline	101.12 ± 9.75	100.44 ± 11.40	0.82
Post-induction	95.04 ± 13.00	106.12 ± 13.96	0.01 *
5 min	91.52 ± 12.71	105.68 ± 12.24	0.00 #
10 min	89.40 ± 16.71	104.12 ± 11.06	0.00 #
15 min	88.00 ± 14.14	104.12 ± 11.06	0.00 #
20 min	86.40 ± 12.94	100.12 ± 11.15	0.00 #
25 min	86.64 ± 12.02	98.76 ± 14.54	0.00 #
30 min	90.33 ± 14.44	99.72 ± 10.63	0.01 *
35 min	90.39 ± 13.63	100.84 ± 8.98	0.00 #

40 min	90.87 ± 14.02	102.95 ± 8.00	0.00 #
45 min	88.44 ± 17.89	104.57 ± 8.15	0.00 #
50 min	83.40 ± 17.22	111.33 ± 7.91	0.01 *
55 min	76.00 ± 9.54	109.33 ± 3.05	0.00 #

Independent samples t- test, *P-value < 0.05 – significant; # P-value < 0.001- very highly significant

Figure 3: Mean arterial pressure (mm Hg) trend over 55 minutes between Group KM and Group KP.



In figure 3, Mean arterial pressure (MAP) is similar at baseline, but after induction and throughout most of the procedure, it is significantly lower in Group KP than in Group

KM, indicating better attenuation of hypertensive responses in Group KP.

Table 5: Periprocedural adverse events recorded during and after procedure. (n=50)

Side Effects	Group KP n (%)	Group KM n (%)	P value
Hypotension	1 (4%)	0 (0%)	0.31
Bradycardia	0 (0%)	0 (0%)	-
Desaturation	4 (16%)	1 (4%)	0.16
Airway Maneuver	4 (16%)	1 (4%)	0.16
Patient needing intubation	0 (0%)	0 (0%)	-
Post-operative nausea & vomiting	1 (4%)	3 (12%)	0.30
Recovery Agitation	1(4%)	5 (20%)	0.08

Chi-square test, P-value < 0.05 – significant

In table 5, periprocedural adverse events were infrequent and did not differ significantly between Group KP and Group KM.

DISCUSSION

This prospective observational study compared Ketamine- propofol combination (Ketofol) with Ketamine-Midazolam for procedural sedation in ERCP. Our Principal findings are: (a) Ketamine-

Propofol achieved faster loss of consciousness and deeper sedation; (b) emergence time was significantly shorter with Ketofol; (c) Sympathetic attenuation was better with ketofol (d) desaturation were frequent in Ketamine-Propofol group.

The faster onset of sedation with Ketofol (184.80 ± 48.74 secs vs 314.40 ± 92.11 secs; $P < 0.001$) is consistent with pharmacokinetic profile of the drug. Propofol has a rapid effect site equilibrium rate constant, providing plasma to effect site equilibrium within 2-3 minutes. [15] By contrast, midazolam has a slower effect site equilibrium constant, resulting in delayed sedation onset when used in combination with ketamine. [16] The deeper and more consistent sedation in Group KP better fulfills ERCP requirement as deep sedation significantly reduces patient movement and facilitates cannulation. [17] The hemodynamic findings in the present study are noteworthy. Post induction hemodynamics (heart rate and MAP) remained lower in Group KP than in Group KM with hypotension noted only in one case in Group KP. This reflects the unopposed sympathomimetic effect of ketamine and weaker

autonomic blunting in the Ketamine Midazolam combination. Midazolam, unlike propofol, does not adequately counteract ketamine induced catecholamine release. [18] Cardiovascular stimulation may be particularly concerning in elderly ERCP patients, who often have underlying cardiovascular comorbidities and are at increased risk of cardiopulmonary adverse events during ERCP. [19]

Desaturation occurred in 4 patients (16%) in KP group versus 1 (4%) in KM group ($P < 0.05$). This finding, while clinically important, is consistent with the respiratory depressant properties of propofol. Importantly all desaturation were brief and responded to airway maneuvers (chin lift and jaw thrust) without requiring intubation or reversal agents. Similar desaturation with ketofol have been reported in the literature and are considered manageable with appropriate monitoring and airway equipment. [9,19] This also suggests that while ketamine may mitigate propofol's respiratory depressive effects at certain dosages, the specific drug ratios and individual patient responses are critical determinants of respiratory outcomes. [20] Given the prone

positioning in ERCP, vigilant respiratory monitoring is mandatory when ketofol is used.

Furthermore, incidence post procedural nausea vomiting was more with Group KM compared to Group KP, which is consistent with previous reports showing Propofol has antiemetic properties and that ketofol regimens are associated with lower rates of nausea and vomiting. [13]

Recovery agitation (20 % vs 4 %) and rescue sedation requirement (28 % vs 8%) were higher in Group KM group, although these did not reach statistical significance. Recovery agitation is a well-documented complication of ketamine-based sedation, attributable to dissociative effects during emergence. [21] Midazolam partially attenuated this phenomenon through GABA- A receptor modulation but remains inferior to propofol in this regard. [22] Higher rescue sedation in Group KM reflects the less predictable sedation depth achieved with Ketamine Midazolam, which may necessitate additional doses to maintain the target RSS during prolonged ERCP procedures.

Discharge time was comparable between groups (47.4 vs 50.0 min, $P > 0.05$), and both groups achieved full Modified Aldrete scores (10/10) and normal MMSE score (30/30) prior discharge, indicating complete cognitive recovery. The shorter emergence time with ketofol (7.92 vs 9.48 min; $P < 0.05$) does not translate to significantly earlier discharge, because the postprocedural observation period standardized discharge timing as per institute in both groups.

Our findings have direct clinical implications. ketofol, with its superior sedation quality, better attenuation of sympathetic response and faster emergence, represents an efficient and safe sedation regimen for ERCP. The desaturation rate was 16% in Group KP compared to 4% in Group KM which necessitates preparedness with airway adjuncts, capnograph monitoring, and trained personnel. Conversely Ketamine -Midazolam may be preferred in patients with Propofol allergy or significant hypotension risk, such as patients in shock.

The study has several limitations. The study was concluded at single center. Depth of sedation was assessed using Ramsay Sedation Scale;

Bispectral index (BIS) monitoring was not employed due to resource constraints. Sedation was guided by clinical scales, which can be influenced by inter-observer variability. Long term cognitive outcomes and patient satisfaction score were not formally assessed. Future multicenter trials with larger samples incorporating BIS monitoring, capnography and patient reported outcomes are warranted. Patients with significant cardiopulmonary disease and higher ASA status were excluded, so the safety of these combinations in higher-risk populations remains uncertain.

CONCLUSIONS

Ketofol (Ketamine- Propofol 1:1) provides superior procedural sedation for ERCP compared to Ketamine -Midazolam, with significantly faster loss of consciousness, deeper and more consistent sedation, shorter emergence time, and better attenuation of sympathetic response. Although desaturation rates are higher with ketofol as compared to ketamine midazolam, all events were readily managed with simple airway maneuvers. Recovery agitation and rescue

sedation requirements were lower with ketofol. These findings support the adoption of ketofol as a preferred sedation regimen for ERCP, provided that appropriate monitoring and airway management capabilities are in place.

CONFLICT OF INTEREST

None

SOURCES OF FUNDING

None

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