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Combination use of intravenous ketamine-midazolam as a sedative agent in endoscopic retrograde cholangiopancreatography: a randomized control trial

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Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive endoscopic procedure that requires deep sedation of the patient. Propofol is the most widely used sedative for advanced endoscopic procedures. However, its use is constrained by high cost and the need for administration by an anaesthetist. Our study aims evaluate the efficacy of ketamine-midazolam as a sedative agent during ERCP, assessing the depth of sedation. This prospective single-blinded randomized control trial (RCT) including patients undergoing ERCP. Patients were randomly assigned to either ketamine-midazolam or midazolam-pethidine combination. Depth of sedation was measured using the Ramsay sedation scale while the endoscopist and patient satisfaction scores, sedation failure rate, sedation-related complication, sedation failure were systematically recorded. A total of 85 patients were included in this study, with 42 in the intervention arm and 43 in controlled arm. The intervention group demonstrated significantly deeper sedation at various stages of the procedure: scope intubation (RSS 5.6 vs. 4.42, *P* < 0.001), common bile duct cannulation (RSS 5.87 vs. 4.9, *P* < 0.001), sphincterotomy (RSS 5.7 vs. 4.95, *P* < 0.005), and scope withdrawal (RSS 5.71 vs. 4.86, *P* < 0.01). Both patients (9.19 vs. 7.31, *P* < 0.001) and endoscopist (4.79 vs. 3.86, *P* < 0.001) reported higher satisfaction scores in the ketamine-midazolam group. The combination of ketamine-midazolam offers a potentially safer and more effective sedation strategy compared to midazolam and pethidine for procedural sedation. This is primarily attributed to ketamine's favourable respiratory and hemodynamic profile along with its combined sedative and analgesic effects.

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Keywords Endoscopic retrograde cholangiopancreatography (ERCP), Ketamine, Midazolam, Procedural sedation, Emergence reaction

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive endoscopic procedure that requires deep sedation of the patient. Since its introduction in 1986, it has gained wide acceptance; it was accepted as a safe, direct technique for evaluating pancreaticobiliary disease[1]. It was created as a result of significant advancements in flexible endoscopic technology. ERCP is primarily used to diagnose and treat diseases affecting the hepatopancreatobiliary tract.

An appropriate sedative agent increases the likelihood of a successful ERCP procedure[2] There are two choices of anaesthesia available for the completion of ERCP: Procedural sedation and general anaesthesia. Procedural sedation is frequently used during ERCP to help the endoscopist accomplish the procedure with minimal patient disruptions. There has been discussion about which sedative should be utilized to produce procedural sedation during ERCP. In general, the best sedative for a procedure should be quick to the onset of action, can be titrated, has a high clearance rate, with side effects, can induce amnesia, and with reversible effects.

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Midazolam, often used in combination with pethidine as the first-line option for procedural sedation, has been associated with a significant probability of sedation failure. Literature indicates that the failure rate ranges between 20% and 45%[3]. While benzodiazepines are therapeutically effective, they can cause significant respiratory depression, which is particularly concerning during endoscopic procedures[4]. Furthermore, midazolam may lead to hypotension and apnoea in 15.4% and 15.7% of cases respectively.

Propofol is the most commonly used sedative for advanced endoscopy. It has been demonstrated to be more effective than midazolam in delivering sedation. However, its use requires administration by trained professionals, as recommended by The American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy[5]. (ASGE). Furthermore, it has a very narrow therapeutic index, and patients may rapidly transition into general anaesthesia, potentially developing complications such as apnoea, hypotension and cardiac arrest. A study on the use of propofol during advanced endoscopic procedures discovered that 12.8% of patients experienced hypoxemia while 14.4% required airway interventions[6]. Another study reported a 3% incidence of unplanned endotracheal intubation in patients receiving propofol for sedation during endoscopy[7]. Given the increased risk of airway complications, especially in individuals with respiratory risk factors, propofol should be used with caution during advanced endoscopy.

Ketamine is a phencyclidine derivative, a non-competitive N- methyl-d- aspartate (NMDA) receptor antagonist that prevents neuronal depolarization by blocking the phencyclidine binding site on the spinal, limbic, thalamus and cerebral cortex NMDA receptors[8]. At lower dosage, ketamine is an effective analgesic and sedative. However, at a higher dose, it induces a state known as 'dissociative anaesthesia' characterized by a detachment from sensory and emotional experiences. Additionally, ketamine exerts secondary actions on opioid receptors that contribute to its analgesic effect rendering it suitable for procedures associated with discomfort or pain, such as ERCP. Furthermore, ketamine does not inhibit the defence reflexes critical for maintaining a patent airway, hence mitigating the danger of airway obstruction or aspiration, which is a prevalent concern associated with sedatives such as propofol[9]. The onset of ketamine's effects is rapid (less than one minute) and lasts for 15 to 20 min[10]. The half-life of dispersion is between 7 and 11 min, but the half-life of elimination is about two to three hours.

A prospective randomized trial conducted by Varadarajulu et al. and published in Alimentary Pharmacology & Therapeutics evaluated the efficacy of ketamine in comparison to the standard regimen of pethidine, midazolam and diazepam, compared in patients undergoing ERCP and endoscopic ultrasound (EUS)[11]. The inclusion of ketamine resulted in improved depth of sedation, reduced sedation failures, and lowered the requirement for opiates and benzodiazepines. This study found that the ketamine group achieved significantly deeper sedation with a depth of 74.4% compared to 50.5% in the control group ($P = 0.002$)[15].

However, ketamine is also associated with emergence symptoms which are the undesirable psychological sequelae that may occur during reversal from ketamine anaesthesia. They affect visual and auditive perceptions, mood, body image, and time. These effect may lead to a sense of unreality such as feelings of floating, depersonalization, conscious dreaming, or hallucinations[12]. Additionally ketamine is associated with increased oral secretions and sympathomimetic effect distinguishing it from other anaesthetic agent. Study shows the rate of emergence symptoms is between 10 and 20% when ketamine is used as a sole agent[13], but this rate is reduced with the concurrent use of benzodiazepine like midazolam[14].

We hypothesized that combining ketamine with midazolam would be more efficacious in achieving the desired sedative state and offers a better safety profile as a sedative agent for ERCP compared to the midazolam-pethidine combination currently used. The primary objective of this study is to evaluate the efficacy of ketamine-midazolam as a sedative agent during ERCP procedures, specifically assessing the depth of sedation. Additionally, the secondary objectives include comparing the sedation failure rate, safety profile of ketamine-midazolam with midazolam-pethidine, as well as to evaluate both endoscopist and patient satisfaction regarding the quality of sedation. The study will also examine the rate of emergence reactions in both arms to identify any differences between the two sedative combinations.

Methodology

This is a prospective single-blinded randomized control trial (RCT). Patients were recruited from admissions to Hospital Canselor Tuanku Muhriz (Cheras, Malaysia) who required ERCP. The endoscopists were surgeons from the Hepatopancreatobiliary Unit of Hospital Canselor Tuanku Muhriz. The study period was from May 2023 - February 2024. This study was approved by the board of ethical committee members of National University of Malaysia (**JEP-2023-272**) it is registered with clinical trials (**NCT06111872)** and National medical research register (**NMRR ID-23-01931-MKA).**

Patient selection

The inclusion criteria were patients aged over 18 years who required ERCP and could provide valid consent. Exclusion criteria included known sensitivity to ketamine or midazolam, increased intracranial pressure, acute stroke within the past 3 months, intracranial haemorrhage within the past 3 months, severe hypertension defined as a blood pressure of 170/110mmHg, tachycardia defined as a resting heart rate of more than 110 beats/min, acute myocardial infarction or acute coronary syndrome diagnosed within the past 6 months, patients with tachyarrhythmia, pregnant patients, intravenous drug use, history of hallucination and Child-Pugh class C. This trial did not withhold effective routine treatment or intervention for either group of patients. Sample size were collected from 18/7/23–30/6/24, and stopped upon completion of recrutiment.

Sample size calculation

Sample size calculations were derived from a prospective randomized trial by Varadarajulu et al.[11]. which compared the addition of ketamine to a standard regimen of pethidine, midazolam, and diazepam regimen with the use of the standard regimen alone for sedation in patients undergoing ERCP and EUS. The sample size for our study was calculated based on the outcome of this study, specifically the proportion of patients experiencing a deeper level of sedation, using a two-proportion hypothesis testing formula. The proportion of patients in the ketamine group (intervention group) achieving deeper sedation was 0.810 (P_1) while the proportion in the standard sedation group (control group) was 0.505 (P_2). These values were inserted in the formula, with a 95% confidence interval (Za = 1.96) and 80% of the study power (z-score of 0.84). A 20% dropout rate was also factored in the calculation. The sample size required was 37 per arm which excluded the number of dropouts.

Sample size calculated using two proportion hypothesis testing formula.

$$\mathrm{N} = \frac{(\mathrm{Za}+\mathrm{Zb})^2[\mathrm{P}_1\,(1-\mathrm{P}_1)+\mathrm{P}_2\,(1-\mathrm{P}_2)}{(\mathrm{P}_1-\mathrm{P}_2)^2}$$

$$\mathrm{N} = \frac{(1.96+0.84)^2\ \ 0.810\,(1-0.810)+0.505\,(1-0.505)}{(0.810-0.505)^2}$$

$$\mathrm{N} = 37 + 20\%$$

$$\mathrm{N} = 45\,\mathrm{patients\ per\ arm}$$

Patient is randomized according to simple randomization using Microsoft excel, Based on this table, patients will be randomized into 2 groups equally, which are A (Ketamine - Midazolam) and B (Midazolam-Pethidine). This generated code was linked to a code list of treatments assigned, which was kept by the principal investigator in a sealed envelope. The envelope was only opened after recruitment, revealing the unique number code. Based on the number code, the appropriate sedation was prepared. The endoscopists were blinded in this study. However, the patients were not blinded.

Study process

Patients randomized to the ketamine-midazolam group received IV ketamine 0.5 mg/kg and IV midazolam 0.02 mg/kg slow bolus over 1 min (Fig. 1). If the patients were not adequately sedated after two minutes, another slow bolus of IV ketamine 0.25 mg/kg and IV midazolam 0.01 mg/kg was given, and a reassessment of sedation status was performed after another one minute. This process was repeated until the patient were adequately sedated. If the patient was still not adequately sedated after the maximum dose of IV ketamine 1 mg/kg and IV midazolam 0.04 mg/kg, it would be deemed as a failure of sedation and an ERCP under monitored anaesthesia care (MAC) would be arranged for the patient. Patients aged more than 65 years old were given half of the ketamine dose mentioned as bolus. Patients in the ketamine-midazolam group would also receive intravenous glycopyrrolate 200 mcg during the initial ketamine administration to prevent hypersalivation.

Patients randomized to the midazolam- pethidine group received the initial intravenous midazolam 0.05 mg/kg with IV Pethidine 0.7 mg/kg as an analgesia. If the patient were not adequately sedated, this was followed with IV Midazolam 0.02 mg/kg and IV Pethidine 0.5 mg/kg. Dose adjustments for patients aged over 65-years-old was also made as previously mentioned. As with the intervention group, patients with failure of sedation had arrangements made for ERCP under monitored anaesthesia care (MAC) to complete the procedure.

Four attending surgeon will be performing all procedures. All surgeons performing ERCP have over 5 years of experience performing this procedure. During the procedure, only the surgeons would be kept blinded from knowing a patient's sedation group. The endoscope will be introduced to the patients once they are adequately sedated in prone position with head turned to right. Blood pressure, pulse rate, oxygen saturation and Ramsay Sedation Scale (RSS) will be monitored continuously during the procedure and recorded at specific timepoints of the procedure. This monitoring is done by a trained nurse. These timepoints were chosen as they are the most uncomfortable processes of the procedure for the patient and also to ensure uniformity of data collection. These timepoints are:

1. At the introduction of endoscope to the oropharynx.
2. Cannulation of common bile duct.
3. Initial endoscopic biliary sphincterotomy.
4. Dilatation of biliary stone extraction balloon and trawling.
5. Endoscope withdrawal.

All medications will be administered by the investigator with close monitoring of the patient performed to detect any possible complication. In cases of respiratory/circulatory collapsed, a drop in oxygen saturation to < 90%, a reduction of mean arterial pressure to < 65 mmHg during the procedure or any complication requiring airway management, the diagram below illustrated the sequential steps that was adhered to (Fig. 2). In our study elevation of blood pressure was defined as blood pressure > 140/90, tachycardia HR > 110, bradycardia < 50 and hypoxia when saturation is < 95% .

Data analysis

Data analysis was performed using Statistical Package for Social Science (SPSS) version 26. Descriptive statistics was used to describe the demographic profile The normality of the continuous data was determined using histogram with normal curve. Variables with normal distribution were presented as mean and standard deviation (SD). The association between categorical variables and study groups was determined using a chi-square test. Normally distributed continuous variables were compared between study groups using an independent t-test.

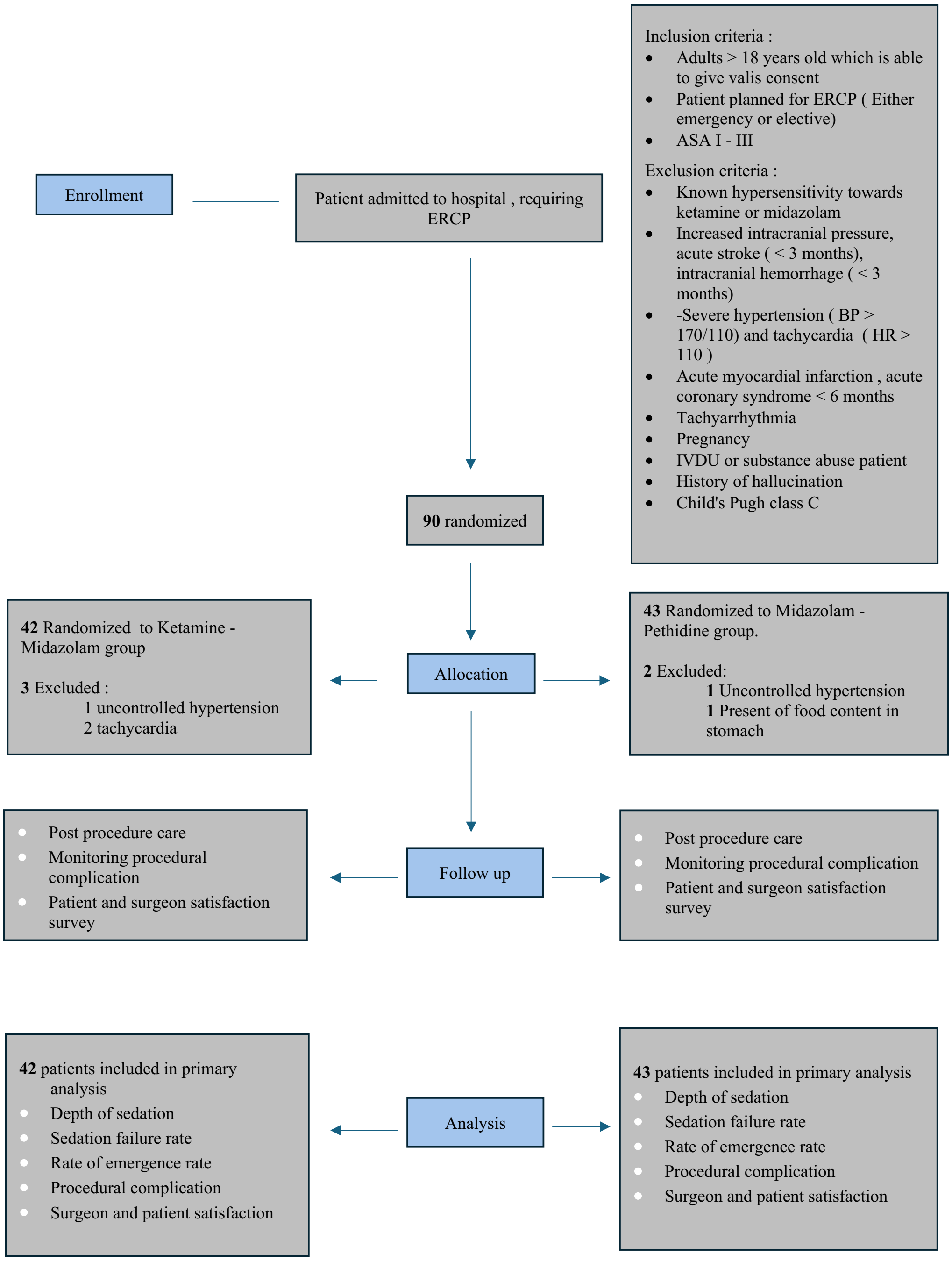

Fig. 1. Flow chart of participant enrollment, inclusion, exclusion criteria, follow up and analysis.

Results

A total of 90 patients were initially randomised for the study. However 5 patients were excluded from this study due to uncontrolled hypertension (two patients) and persistent tachycardia (three patients) prior to receiving sedation. Of the 85 remaining patients, 42 were randomised to the ketamine-midazolam group (intervention group), and 43 were randomised into the midazolam-pethidine group (control group) .

The baseline clinical and demographic characteristics of the 2 groups are summarized in Table 1. The demographic data were similar between the two groups except for the ASA classification. In the intervention group, 61.9% of participants were ASA I; in the control group, 58% were ASA II. The proportion of female patients was higher than that of male patients in the intervention group. Hypertension was the most common comorbidity, present in 65.5% of patients undergoing the procedure.

In both groups, common the most common indication for ERCP was common bile duct stones, which accounted for 56.4% of participants (Table 2). Additionally, 10 patients (11.7%) and 6 patients (7%) underwent ERCP in an emergency setting due to cholangitis.

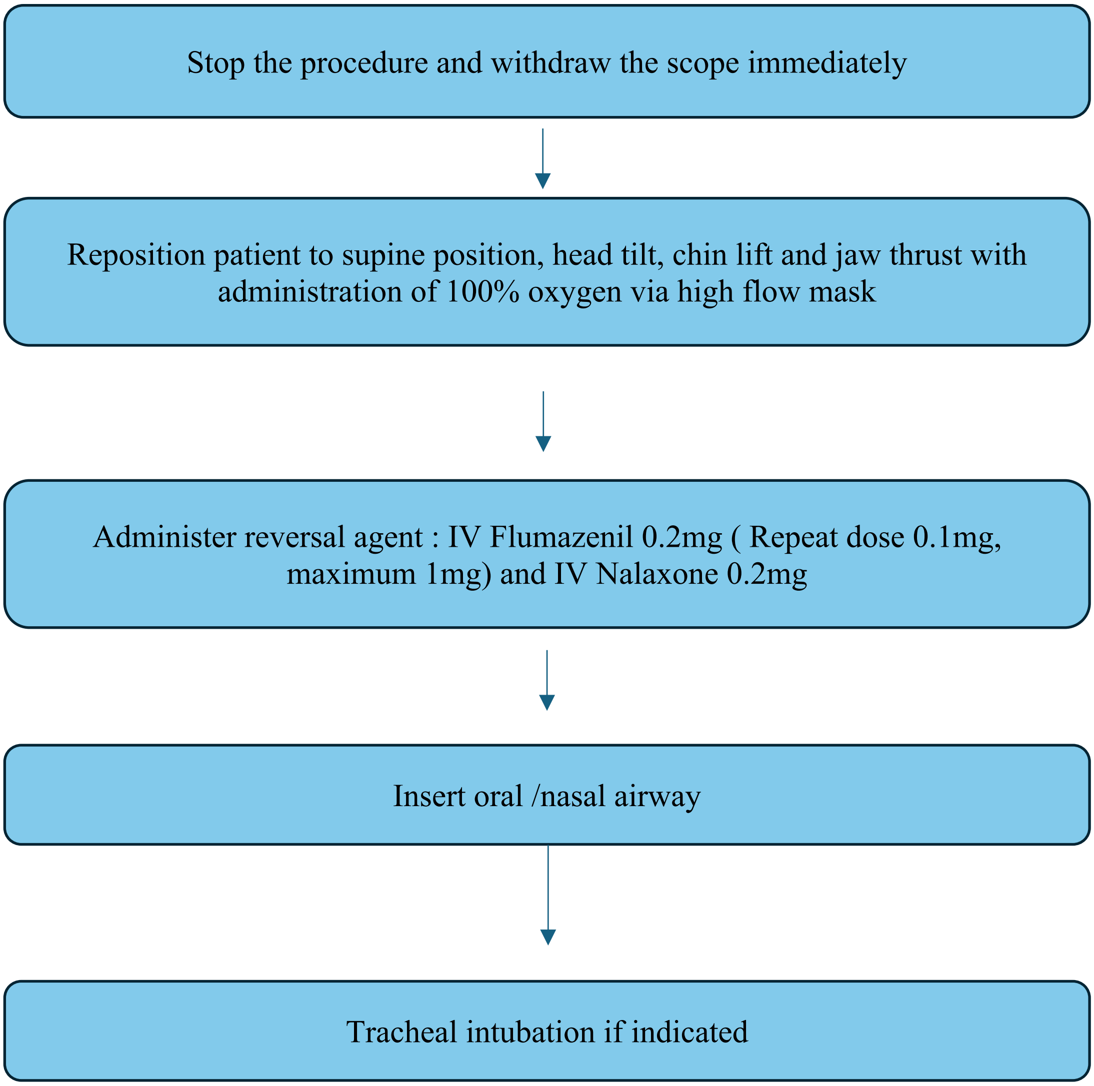

Fig. 2. Rescue protocol for procedure. This outlines the stepwise approach for managing sedation related adverse events and ensuring patient safety during procedure.

Patients in the ketamine-midazolam group exhibited a significantly higher depth of sedation (Ramsay sedation score, RSS) at each significant interval of the procedure, namely scope intubation (RSS 5.6 vs. 4.42, $P<0.001$), common bile duct cannulation (RSS 5.87 vs. 4.9, $P<0.001$), sphincterotomy (RSS 5.7 vs. 4.95, $P<0.005$) and scope withdrawal (RSS 5.71 vs. 4.86, $P<0.01$). (Table 3). Average dose received by the intervention group was IV Ketamine 47 mg and IV Midazolam 2.19 mg, in the controlled group, they received IV Midazolam 5 mg and IV Pethidine 55 mg.

There was no incidence of sedation failure in the Ketamine—Midazolam group (0% vs. 4.7%, $P=0.49$). In the Midazolam-Pethidine group, two patients experienced sedation failure despite receiving the maximum sedation dose and remained restless. (Table 4) Both patients had to be rescheduled for the procedure under monitored anaesthesia care at a later date.

A total of 65 adverse events occurred in 85 patients (Table 5). No serious adverse events, such as cardiac arrest, cardiac arrhythmia, or endotracheal intubation, occurred in either group, and no patient dropped out of the study due to adverse events. In the intervention group, 22 patients (52.4%) patients develop hypertension during the procedure compared to 9 patients (20.9%) in the control group. Notably, 17 of these patients (77.2%) had underlying essential hypertension. Only 5 patients who were undiagnosed with hypertension in the intervention group developed elevation of blood pressure with ketamine administration. Tachycardia was more common in the intervention group, occurring in 9.5% compared to 4.6% in the control group. In the midazolam-pethidine group, 6 patients (14.2%) developed bradycardia, 2 (4%) developed hypotension, and 4 patients developed hypoxia. Among these, 5 patients required reversal agents (11.6% vs. 0, $P=0.05$). No patients in either group required endotracheal intubation supraglottic airway ventilation, highlighting the safety of the sedatives used in this study.

		Total	Study groups	
			Ketamine - Midazolam	Midazolam - Pethidine
		(*N* = 85)	(*n* = 42)	(*n* = 43)
Age (Years)	Mean (SD)	57.47(16.24)	56.55(17.02)	58.37 (15.59)
Sex	Male, n (%)	39 (45.9)	17 (40.5)	22 (51.2)
	Female, n (%)	46 (54.1)	25 (59.5)	21 (48.8)
Ethnicity	Malay, n (%)	60 (70.6)	24 (57.1)	36 (83.7)
	Chinese, n (%)	20 (23.5)	13 (31.0)	7 (16.3)
	Indian, n (%)	4 (4.7)	4 (9.5)	0 (0.0)
	Others, n (%)	1 (1.2)	1 (2.4)	0 (0.0)
ASA	I, n (%)	41 (48.2)	26 (61.9)	15 (34.9)
	II, n (%)	33 (38.8)	8 (19.0)	25 (58.1)
	III, (%)	11 (12.9)	8 (19.0)	3 (7.0)
Cardiovascular disease	NA	12	7	5
Hypertension	NA	56	27	29
Diabetes	NA	16	7	9
Chronic kidney disease	NA	3	2	1
Carcinoma	NA	6	5	1
Others	NA	18	11	7

Table 1. Patient characteristics descriptive analysis of demographic characteristics of study patients (*N* = 85).

	Total	Study groups	
		Ketamine-Midazolam	Midazolam - Pethidine
	(*N* = 85)	(*n* = 42)	(*n* = 43)
Bile leak	4	3	1
Biloma post trauma	1	1	0
Cholangitis	16	10	6
Choledocholithiasis	48	22	26
Choledochal cyst	1	0	1
Cholangiocarcinoma	3	1	2
Tumor obstruction	2	1	1
Pancreas carcinoma	2	2	0
Removal of stent	8	2	6

Table 2. Frequencies of indication for ERCP (*N* = 85).

	Study group (Mean, SD)				
Measure	Ketamine- Midazolam	Midazolam - Pethidine	Mean diff	95% CI	*p*-value
Scope intubation	5.60 (0.59)	4.42 (1.31)	1.18	0.74, 1.62	< 0.001
CBD cannulation	5.87 (0.40)	4.90 (1.02)	0.97	0.61, 1.33	< 0.001
Sphincterotomy	5.70 (0.47)	4.95 (1.20)	0.75	0.17, 1.33	< 0.05
Scope withdrawal	5.71 (0.46)	4.86 (1.15)	0.85	0.48, 1.23	< 0.01

Table 3. Depth of sedation: mean difference of RSS between the study groups.

		Total	Study groups			
			Midazolam - Pethidine	Ketamine + Midazolam		
		(*N* = 85)	(*n* = 43)	(*n* = 42)	*P* value	OR
Sedation failure	Yes	2 (2.4)	2 (4.7)	0 (0.0)	0.494	NA
	No	83 (97.6)	41 (95.3)	42(100.0)		

Table 4. Sedation failure rate.

	Total	Study groups		P - Value
		Ketamine-Midazolam	Midazolam - Pethidine	
	N = 85	N = 42	N = 43	
Bradycardia	6	0	6	0.026
Elevation of BP	29	22	9	0.265
Hypertensive	24	17	7	
Non hypertensive	7	5	2	
Nausea	2	2	0	0.148
Hypoxia	4	0	4	0.241
Hypotension	2	0	2	0.494
Tachycardia	6	4	2	0.433

Table 5. Frequencies of adverse events ($N=85$).

		Total	Study groups		P value	OR
			Ketamine- Midazolam	Midazolam - Pethidine		
		(N = 85)	(n = 42)	(n = 43)		
Gag reflex	Present	40 (47.1)	5 (11.9)	35(81.4)	< 0.001	32.4
	Absent	45 (52.9)	37 (88.1)	8 (18.6)		
Procedure time	Mean (mins)	NA	22.4 (9.1)	29.0 (13.6)	0.012	NA
Patient satisfaction	Mean (SD)	NA	9.19 (0.74)	7.31 (1.33)	< 0.001**	NA
Surgeon satisfaction	Mean (SD)	NA	4.79 (0.41)	3.86 (0.86)	0.001**	NA
"If you were to repeat the procedure, would you like to use the same sedative agent?"	No	15 (17.9)	1 (2.4)	14 (32.6)	< 0.001	18.6
	Yes	70 (82.1)	40 (97.6)	30 (67.4)		
"Do you remember anything about the endoscopy?"	Yes – introduction of the endoscope	8 (9.4)	0 (0.0)	8 (18.6)	< 0.001	NA
	Yes – part of the endoscopy	17 (20.0)	0 (0.0)	17 (39.5)		
	Yes – the entire process	2 (2.4)	0 (0.0)	2 (4.7)		
	No	58 (68.2)	42(100.0)	16 (37.2)		
Reversal used for sedative agent	Yes	5 (5.9)	0 (0.0)	5 (11.6)	0.055	NA
	No	80 (94.1)	42(100.0)	38 (88.4)		
Need to restraint patient during procedure	Yes	36 (42.4)	4 (9.5)	32 (74.4)	< 0.001	27.6
	No	49 (57.6)	38 (90.5)	11 (25.6)		
Emergence reaction	Yes	5 (5.9)	5(11.9)	0(0.0	0.026	NA
	No	80(94.1)	37(88.1)	43(100.0)		

Table 6. Association between independent categorical variables and study groups ($N=85$).

The mean endoscopist satisfaction rating in ketamine-midazolam group was significantly higher at 4.79 vs. 3.86, ($P<0.001$) on a scale where 0 represents "poor" and 5 represents "excellent." Patient satisfaction (Table 6) was also significantly greater in the intervention group with a rating of 9.19 vs. 7.31, ($P<0.001$) on a scale where 0 represents "bad" and 10 represents "excellent."

Upon recovery, patients were asked if they would like to use the same sedative agent if the procedure were to be repeated in the future. In the ketamine-midazolam group, 40 participants were keen (97.6% vs. 67.4%, $P<0.001$) (Table 6). This included participants who experienced emergence reactions; only one patient was not keen to use ketamine-midazolam in the future due to nausea sustained post-procedure which was self-limiting and resolved within a few hours. Five patients in the ketamine - midazolam group developed a self-limiting emergence reaction; all the patients described it as pleasant, vivid dreams.

Furthermore, 32 patients in the midazolam-pethidine group required restraint during the procedure (74.4 vs. 9.5%, $P<0.001$, OR 27.6) (Table 6). The procedure time was shorter in the ketamine-midazolam group, with a mean time of 22.4 min compared to 29 min in the control group ($P=0.012$). Additionally 37 patients of the intervention group did not exhibit a gag reflex during scope intubation (88.1 vs. 18.6%, $P<0.001$).

Discussion

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced endoscopy procedure recommended to be conducted by deep sedation or general anaesthesia[15]. Another paper by Azimaraghi et al. also recommends that short ERCP procedures of low complexity should preferably be conducted under monitored anaesthesia care. In contrast, the expected complicated ERCP should be conducted under general anaesthesia[16]. However, this is not feasible in all centres, especially in low and middle-income countries where resources and financial limitations have always been problematic. At the time of writing this paper, there have only been 2 other pilot studies compared ketamine-midazolam vs. midazolam pethidine. Both studies concluded that ketamine may have a potential as a sedation agent[9,17].

In our study, we have shown that Ketamine-Midazolam usage as a sedative agent in ERCP is safe and more efficacious in producing a desirable sedative state than Midazolam - Pethidine, where procedural sedation is a concern. This sedation regime where all patients were successfully sedated (100% vs. 95.3%, $P < 0.4$) and the intervention group had a deeper level of sedation at all intervals. The procedures included in this study ranges from stenting, stone removal to complex procedures such as controlled radial expansion balloon (CRE) and choledochoscope. A combination of Ketamine and midazolam provides a deeper level of sedation due to the properties of each agent itself. Midazolam, a benzodiazepine, is used for its sedative and amnestic effects, but it does not provide significant pain relief on its own[15]. Ketamine provides both pain relief and sedation, allowing for potentially lower doses of other medications and simplifying the sedation regimen[18].

Ketamine is a phencyclidine derivative that blocks the N-methyl-D-aspartate receptor (NMDA) and is classified as a dissociative anaesthetic, providing both amnesia and analgesia. Besides this, another intriguing property of ketamine is its potential anti-inflammatory properties[19]. Ketamine may provide additional benefit in patients with biliary sepsis undergoing ERCP. A pilot study published by Jason M Reese et al. examined the use of ketamine as a sedative in adult patients with septic shock who required mechanical ventilation[20,21]. The study found that patients who received ketamine as their primary sedative tended to require lower doses of norepinephrine and vasopressin. Furthermore, the group receiving ketamine needed less fentanyl for pain relief and fewer benzodiazepines (lorazepam and midazolam) or dexmedetomidine for sedation compared to the control group.

This is particularly relevant in septic shock, where maintaining stable blood pressure preserves respiratory drive with effective sedation and analgesia; however, it should be used with caution in patients who have myocardial infarction, recent haemorrhagic stroke, tachyarrhythmia, and severe hypertension. The rise in systolic and diastolic blood pressure occurs within minutes of administration, often increasing the blood pressure by 10–50% above the pre-anaesthetic levels[20]. In our study, blood pressure elevation was observed in 22 patients in the intervention group (52.4% vs. 20.9%). Notably, only 11.9% were non-hypertensive. However this elevation in blood pressure did not affect the treatment administered to the patient, no intervention was needed, it was self limiting and resolved post procedure.

Emergence reaction occurred in 5 (11.9% vs. 0%, $p < 0.02$) patients in the Ketamine-Midazolam group. In these patients, emergence reactions were described as pleasant and vivid dreams. Emergence reactions are not universally bad; events such as 'vivid dreams' are unlikely distressing for patients. In our study, all participants who experienced an emergence reaction did not object to using the same sedation protocol if the procedure were to be repeated.

A review of adverse events associated with ketamine by Strayer and Nelson estimated that the incidence of emergence phenomena when ketamine is given as a sole agent ranges up to 20%[13]. In our study, the rate of emergence reaction was reduced by co-administering midazolam as a sedative agent. The severity of the emergence reaction varies widely, and the more severe form is almost always related to the higher dose of ketamine given (anaesthetic dose >2 mg/kg intravenously)[13]. In our study, doses were titrated to a maximum of 1 mg/kg. Based on our findings, we recommend co-administering ketamine with Midazolam to reduce the risk of severe emergence reactions.

Our results showed that ketamine - midazolam enhances the quality of sedation as perceived by endoscopists and endoscopy room nurses based on reduced gagging and retching[22] and the need for lower need for physical restraint during the procedure. Patient movement during ERCP can significantly increase radiation exposure to medical staff, particularly those who may need to restrain the patient[23]. This suggests that patient movement is also likely to increase the risk to the patient by necessitating longer procedures and increasing the likelihood of complications[24]. In our study, the procedure time was significantly shorter in the ketamine -midazolam group.

Despite being blinded, it is interesting to note that endoscopists were able to predict the type of sedation received by the patients by the absence of gag reflex although this finding was not formally analysed. A struggling and gagging patient who is not properly sedated mid procedure would be distressing to the endoscopists as it affects their ability to perform a safe procedure efficiently. We believe that the lack of gag reflex and deeper sedation of the patients due to the use of ketamine-midazolam. It is the main reason for the higher satisfactory score among endoscopists in the intervention group In an ideal situation, anaesthesiologist-administered sedation for patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) will be superior in comparison procedural sedation[25], however, this is not feasible in the majority of developing countries due to resource limitation and high cost.

A major limitation of this study, the sedation was given by the investigator which could introduce bias and variability on how the sedation was given potentially affecting the result. Moreover, this may not replicate the real world clinical condition where sedation is typically administered by a trained anaesthetist or trained personnel. Other limitations were it was conducted by a single centre and there were instances where the endoscopists were able to discern the sedation regimen given to the patients due to its distinct clinical characteristics such as absence gag reflex.

In conclusion, the combination of ketamine and midazolam offers a safer and more effective sedation strategy compared to midazolam and pethidine particularly where procedural sedation is required. We recommend this sedation regime (Ketamine - Midazolam) for patient previously experienced difficulties with conventional sedation protocols. This protocol demonstrated superior sedation quality, enabling improved patient tolerance, shorter procedure duration and a higher likelihood of procedural completion. Additionally it is a feasible option for administration by trained personnel in settings where anaesthetic support is not readily available. It is an alternative safe treatment by Non Anaesthesiologist sedation (NAS) even in such complex procedure as ERCP. This is primarily due to ketamine's favourable respiratory and hemodynamic profile and its combined sedative and analgesic effects. The use of ketamine-midazolam in ERCP may be advocated in local institution where procedural sedation is the preferred approach.

Data availability

All data generated or analysed during this study are included in this published article.

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Author contributions

R.S.S.S. - Writing original draft, editing, conceptualization , analysis , methodology , data analysis A.A. - Writing original draft, Editing draft , Supervision , investigation , data curationJ.T. - Writing original draft , Supervision , editing draft , formal analysis C.I. - Editing , prepared figures , Data curation H.S.B - Editing, prepared figures, supervision R.J. - Editing, prepared tables , Supervision F.F.J. - Editing, prepared tables , supervision.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics
All methods were carried out in accordance with local guideline and accordance to the ethics committee of National University of Malaysia. All protocols we approved by ethics committee of National University of Malaysia. Informed consent were obtained from all patients.

Additional information
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