Efficacy of Single Low Dose Ketamine Versus Midazolam for Sedation in Patients Undergoing an Open Inguinal Hernia Repair Under Spinal Anesthesia: A Randomized Controlled Clinical Trial

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Abstract

Background: Discomfort during procedures under spinal anesthesia (SA) can lead to poor posture and autonomic swings, which can be alleviated by sedation. We evaluated the sedative efficacy of intravenous (IV) low-dose ketamine compared to midazolam during SA. We hypothesized that low-dose ketamine may be as effective as midazolam.

Methods: Eighty patients, ASA I-II, aged 18-50 years, undergoing unilateral inguinal hernia repair, were randomly assigned to receive either an IV single bolus dose of ketamine at 0.5 mg/kg or midazolam at 0.03 mg/kg over 10 minutes. Sedation was evaluated up to 90 min after SA using the Modified Observer's Assessment of Alertness/ Sedation (MOAA/S) scale and A-line Autoregressive Index (AAI). Heart rate, mean blood pressure and oxygen saturation were continuously monitored. The time to the first analgesic request, any complications, and patient and surgeon satisfaction were documented.

Results: Patients in the ketamine group achieved a MOAA/S score of 4 (P=0.029) and recovered to an AAI score > 60^{o} (P=0.029) faster than those in the midazolam group. Heart rate and oxygen saturation were similar between the groups. Hypotension occurred significantly more in the midazolam group (P= 0.003), while disruptive movements (P=0.001) and blurred vision (P=0.005) occurred only in the ketamine group. The patient and surgeon satisfaction were similar across groups.

Conclusions: The use of a single low dose of both ketamine and midazolam was effective in providing adequate sedation. However, clinically, ketamine caused a rapid onset of sedation and, instrumentally, led to a faster recovery compared to midazolam.

Keywords: Sedation; spinal; anesthesia; ketamine; midazolam.

Introduction:

Sedation during regional anesthesia (RA) allows for patient cooperation during the block placement and needle puncture (1). It also improves intraoperative patient acceptance of a regional block and enhances comfort, especially during uncomfortable positioning and lengthy operations (2). Procedural sedation reduces postoperative recall, opioid analgesia use, and postoperative vomiting, enhancing the quality of recovery and patient satisfaction (2, 3).

Midazolam is a commonly used short-acting benzodiazepine for ambulatory conscious sedation during spinal anesthesia (SA). It has a rapid onset, quick recovery

time, and a low context-sensitive half-life (4- 5).

Ketamine is a rapid-acting general anesthetic with sedative and analgesic properties. It is used to supplement benzodiazepine sedation in short diagnostic and therapeutic procedures (6), as well as for sedation during SA (7- 10). Small-dose ketamine offers a significant advantage over opioid-based sedation techniques because it produces sedation without causing significant respiratory depression (6).

This study was designed to compare the sedative effect of ketamine versus midazolam, both given as a single low dose, in patients undergoing unilateral inguinal hernia repair under SA. We hypothesized that a single low dose of ketamine would have a comparable or even superior sedative effect compared to midazolam. The primary endpoint was the time to onset of sedation in minutes assessed by MOAA/S.

Methods

This randomized clinical study was conducted in accordance with the Declaration of Helsinki, approved by the local research ethics committee at the Faculty of Medicine, Assiut University (Approval number: 17100917), and registered on Clinical Trials.gov (NCT03133780 on 28/04/2017).

After obtaining written informed consent from each patient, eighty-eight male patients aged 18 to 50 years, with ASA I - II status, scheduled for elective open unilateral inguinal hernia repair under SA, were evaluated for eligibility between July 2018 and March 2020. Exclusion criteria were patient refusal, psychiatric or neurological disorders, deafness or head injury, body mass index > 35 kg/m^2, any known contraindication to the study drugs, patients with intracardiac devices, cardiovascular diseases, coagulation diseases, cerebrovascular disorders, respiratory, renal, or hepatic diseases, allergy to local anesthetics (LAs), and contraindications to neuraxial block.

Patients were randomly assigned, using a computer-generated randomization table enclosed in envelopes, to receive either IV ketamine at a dose of 0.5 mg/kg (ketamine group; N= 40) (11, 12) or IV midazolam at a dose of 0.03 mg/kg, over 10 minutes (midazolam group; positive control; N= 40) (5).

Just before the surgery, an anesthetist who was not involved in the research opened the envelope. This anesthetist had prepared and diluted the tested drugs to a volume of 50 ml in normal saline in identical coded syringes.

Patients, surgeons, anesthetists, medical staff, and data collectors were completely blinded to the group assignment.

Interventions and Anesthesia

No patients received premedication. Upon arrival at the operating room, standard monitoring, including non-invasive arterial blood pressure, electrocardiography, and pulse oximetry, was initiated, and baseline values were recorded.

The baseline sedation level was assessed using the Modified Observer's Assessment of Alertness/ Sedation (MOAA/S) scale and the A-line Autoregressive Index (AAI) (6, 13, 14).

The MOAA/S scale is as follows: 5 = Responds readily to name spoken in a normal tone, 4 = Lethargic response to name spoken in a normal tone, 3= Responds only after the name is called loudly and/or frequently, 2= Responds only after mild prodding or shaking, and 1= Does not respond to mild prodding or shaking (6, 14).

Middle latency auditory evoked potentials (MLAEP) and the AAI were obtained using the A-line® (Software version 1.3, AAI version 4.0) AEP monitor from Danmeter in Odense, Denmark (13, 14).

The skin of the patient's forehead and temples was prepared. Then, three disposable electrodes were placed at the mid-forehead (+), left forehead (reference), and left mastoid (–). The monitor earphones were attached to the patient. The MLAEPs

were evoked by a bilateral click stimulus of 65dB (Sound Pressure Level) intensity, 2 ms in duration, and a repetition rate of 9 Hz. The analysis window for MLAEPs was 20–80 ms.

The AAI ranges from 100° (patient fully awake) to 0° (iso-electric electroencephalogram (EEG)) (13). AAI values ≥ 50° indicate an awake state, 30° indicates light anesthesia, 15° to 25° indicates surgical anesthesia, and AAI values < 15° indicate deep anesthesia (14).

The AAI corresponding to each MOAA/S score was calculated by averaging three readings obtained during the 45 seconds immediately before evaluating the MOAA/S score.

The clinically desired depth of sedation was indicated by a MOAA/S score of 3, while the instrumentally desired depth of sedation was indicated by an AAI of 40° (15, 16).

All subjects were primed with 6 ml/kg of lactated Ringer's solution intravenously 20–30 minutes prior to anesthesia. The study solution was then infused intravenously for 10 minutes.

Five minutes after the study solution administration was completed, participants were placed in a sitting position for SA at either the L3-4 or L4-5 intervertebral spaces. SA was performed using 15 mg of 0.5% hyperbaric bupivacaine and a 25-gauge Quincke spinal needle without local infiltration. Following the SA, patients were repositioned into a supine posture.

IV dexamethasone (8 mg), ranitidine (50 mg), and ketorolac (2 mg/kg) were administered to all patients, along with supplemental oxygen (4 L/min) via a face mask. If a patient experienced discomfort or pain during surgery, or if the initial block failed, they were excluded and given general anesthesia as needed. At the end of the operation, patients were transferred to the postanesthesia care unit (PACU) and discharged once their modified Aldrete score was ≥ 9.

Data Collection

Age, weight, height, ASA class, side of operation, and duration of operation were recorded.

The primary outcome was the onset of sedation, defined as the time taken to reach a MOAA/S score 4, which closely corresponds to the state of minimal sedation (15).

The secondary outcomes measured in the study were as follows: ease of patient positioning for SA (specifically, turning the patient to a sitting position), assessed using a three-point scale (1- patient turned on his own with no person help, 2- patient turned with one person's assistance, 3-patient turned with the help of more than one person); patient response to spinal needle insertion, evaluated on a 4-point scale (1-no patient movement, 2-back muscle contraction, 3-minimal patient movement, 4-gross patient movement); and time to first analgesic request.

Times required in minutes for the patients to achieve a MOAA/S score of 4, to return to a MOAA/S score of 4-5 (the recovery time), to reach an AAI score of 40^{o}; taken for AAI > 60 ^{o}, for MOAA/S score of 4 at AAI > 60^{o}, and MOAA/S score of 5 at AAI > 60^{o} were noted. Mean blood pressure (MAP), heart rate (HR), percutaneous oxygen saturation (SpO_2), MOAA/S scale, and AAI were checked immediately before administration of the tested drugs (baseline); 3 minutes after administration of the tested drugs immediately after the spinal block and 5, 10, 15, 30, 45, 60, and 90 minutes after that. Adverse effects such as vomiting**,** pruritus, shivering**,** hypertension, hypotension, bradycardia, respiratory depression**,** oxygen desaturation (SpO_2< 92%), airway obstruction, vivid dreams, hallucinations, disruptive movements, or blurred vision were noted and recorded if they occurred.

Hypotension, defined as a decrease in MAP > 20 % from baseline, was treated with Ringer's lactate and ephedrine. Bradycardia, with an HR < 60 beats per minute, was treated with atropine sulfate.

Vomiting was alleviated with IV metoclopramide at a dosage of 10 mg. Any respiratory complications were treated and documented.

Twenty-four hours later, patient and surgeon satisfaction regarding the quality of sedation care was assessed using a four-point verbal rating scale (1= excellent, 2= good, 3= fairly well, and 4= poor) (17). The duration of hospital stay was reported as well.

Sample Size and Statistical Analysis

The primary outcome measured was the onset of sedation, assessed by the MOAA/S scale. Based on a pilot study, the mean ± standard deviation (SD) for the onset of sedation after IV low-dose ketamine was 19.5 ± 5.986 minutes in ten patients and 22.5 ± 10.069 minutes in another ten patients who received IV low-dose midazolam. With a significance level of $\alpha = 0.05$ and a power of $1 - \beta = 80$ %, it was determined that 39 patients needed to be included in each group. To account for potential dropouts, we included 44 patients in each group.

Data analysis was conducted using SPSS version 22 (Statistical Package for Social Science). Data were tested for normal distribution using the Kolmogorov-Smirnov test and presented as mean (standard deviation (SD)) and number (percentage). Qualitative variables between groups were compared using the Chi-square test and Fisher Exact test as appropriate. Independent samples t-test was used to compare quantitative variables between groups for parametric data, while the Mann-Whitney U test was used for non-parametric data. A P value less than 0.05 was considered significant.

Results

Eighty patients were included in the final data analysis (Fig. 1). The patients' demographic data were identical between the groups (Table 1).

Patients in the ketamine group achieved an MOAA/S score of 4 significantly earlier than those in the midazolam group, while patients in both groups reached an AAI score of 40^o at comparable times. Time to return to a MOAA/S score of 4-5 was similar in both groups, while patients in the ketamine group recovered to an AAI score of $> 60^o$ faster than those in the midazolam group (Table 2). Recovery to a MOAA/S score of 4 at an AAI of $> 60^o$ after the spinal block was significantly earlier in the ketamine group compared to the midazolam group (Table 2). Recovery times to a MOAA/S score of 5 at an AAI of $> 60^o$ after spinal block were comparable between both groups (Table 2). MOAA/S scores were similar between both groups throughout the entire study period, except at 3 min after drug administration and 10 min after spinal block, where they were significantly higher in the ketamine group than in the midazolam (Fig. 2a). The AAI scores were significantly lower in the midazolam group compared to the ketamine group immediately after spinal block and at 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, and 90 min after spinal block (Fig. 2b).

The ease of positioning for SA and the response to spinal needle insertion were similar in both groups (Table 3). The total amount of fluids and the number of patients who received ephedrine were significantly higher in the midazolam group than in the ketamine group (Table 3). MAP was significantly lower in the midazolam group compared to the ketamine group at 10 min, 15 min, 60 min, and 90 min after the spinal block (Fig. 3a). Changes in HR (Fig. 3b) and SpO_2 (Fig. 3c) were similar between both groups. The time to the first analgesic request was significantly longer in the ketamine group compared to the midazolam group (Table 2). Hypotension was significantly higher in the midazolam group than in the ketamine group, while disruptive movements and blurred vision only occurred in the ketamine group (Table 4). Patient and surgeon satisfaction were similar between the groups (Table 4), and all participants were safely discharged home 24 hours after surgery.

Table (1): Demographic Data of the Studied Groups

	Ketamine Group (n= 40)	**Midazolam Group (n= 40)**	**P-value**
Age (years)	29.30 ± 7.93	30.30 ± 8.69	0.592
Weight (kg)	75.45 ± 5.40	74.55 ± 6.70	0.510
Height (cm)	173.73 ± 3.06	173.05 ± 2.86	0.312
ASA class:			0.176
ASA I	33 (82.5%)	37 (92.5%)	
ASA II	7 (17.5%)	3 (7.5%)	
Side of operation:			1.000
Right	21 (52.5%)	21 (52.5%)	
Left	19 (47.5%)	19 (47.5%)	
Duration of operation (min)	49.15 ± 11.13	49.68 ± 11.71	0.838

Data are expressed as mean (SD) or number of patients (%). P < 0.05 was considered statistically significant. ASA indicates the American Society of Anesthesiologists.

Table (2): Recovery Profile in the Studied Groups

	Ketamine Group (n= 40)	**Midazolam Group (n= 40)**	**P-value**
Time to achieve MOAA/S of 4 (min)	19.13 ± 6.09	22.63 ± 7.84	0.029
Time to reach AAI score of 40^{o} (min)	4.44 ± 2.30	5.50 ± 3.16	0.369
Time to return to MOAA/S of 4-5:			0.085
20-35 min.	3 (7.5%)	0 (0.0%)	
35-50 min.	20 (50.0%)	15 (37.5%)	
50-65 min.	17 (42.5%)	23 (57.5%)	
65-80 min	0 (0.0%)	2 (5.0%)	
Time taken for AAI score > 60^{o} (min)	13.88 ± 4.87	17.20 ± 8.09	0.029
MOAA/S score 4 at AAI > 60^{o} (min)			0.036
5 min after spinal block	1 (2.5%)	1 (2.5%)	
10 min after spinal block	15 (37.5%)	5 (12.5%)	
15 min after spinal block	19 (47.5%)	19 (47.5%)	
30 min after spinal block	5 (12.5%)	14 (35.0%)	
45 min after spinal block	0 (0.0%)	1 (2.5%)	
MOAA/S score 5 at AAI > 60^{o} (min)			0.116
30 min after spinal block	3 (7.5%)	0 (0.0%)	
45 min after spinal block	20 (50.0%)	15 (37.5%)	
60 min after spinal block	17 (42.5%)	24 (60.0%)	
90 min after spinal block	0 (0.0%)	1 (2.5%)	
Time to first analgesia request (hours)	5.63 ± 1.13	4.22 ± 0.93	0.001

Data are expressed as mean (SD) or number of patients (%). P < 0.05 was considered statistically significant.

Table (3): Patients' Anesthetic Data

	Ketamine Group (n= 40)	**Midazolam Group (n= 40)**	**P-value**
Total amount of fluids	1533.75 ± 85.78	1638.75 ± 207.08	0.004
Patients received ephedrine	2 (5%)	14 (35%)	0.001
Patients received atropine	0 (0%)	3 (7.5%)	0.241
Ease of positioning:			0.599
Himself	0 (0.0%)	1 (2.5%)	
One person	20 (50.0%)	20 (50.0%)	
Two persons	20 (50.0%)	19 (47.5%)	
Response to spinal needle insertion:			0.901
No movement	3 (7.5%)	2 (5.0%)	
Back muscle contraction	19 (47.5%)	17 (42.5%)	
Minimal movement	15 (37.5%)	17 (42.5%)	
Gross movement	3 (7.5%)	4 (10.0%)	

Data are expressed as mean (SD) or number of patients (%). P < 0.05 was considered statistically significant.

Table (4): Perioperative Adverse Effects and Satisfaction Scores

	Ketamine Group (n= 40)	**Midazolam Group (n= 40)**	**P-value**
Adverse effects:			
Hypotension	3 (7.5 %)	14 (35 %)	0.003
Bradycardia	0 (0 %)	3 (7.5 %)	0.241
Shivering	4 (10 %)	3 (7.5 %)	1.000
Vomiting	2 (5 %)	4 (10 %)	0.675
Disruptive movements	11 (27.5 %)	0 (0 %)	0.001
Blurred vision	8 (20 %)	0 (0 %)	0.005
Patient satisfaction:			
Excellent	33 (82.5 %)	31 (77.5 %)	
Good	4 (10 %)	3 (7.5 %)	0.636
Fairly well	3 (7.5 %)	5 (12.5 %)	
Poor	0 (0 %)	1 (2.5 %)	
Surgeon satisfaction:			
Excellent	34 (85 %)	36 (90 %)	
Good	5 (12.5 %)	4 (10 %)	0.558
Fairly well	1 (2.5 %)	0 (0 %)	
Poor	0 (0 %)	0 (0 %)	

Data are expressed as number of patients (%). P < 0.05 was considered statistically significant.

Fig. 1. CONSORT flow diagram of participants.

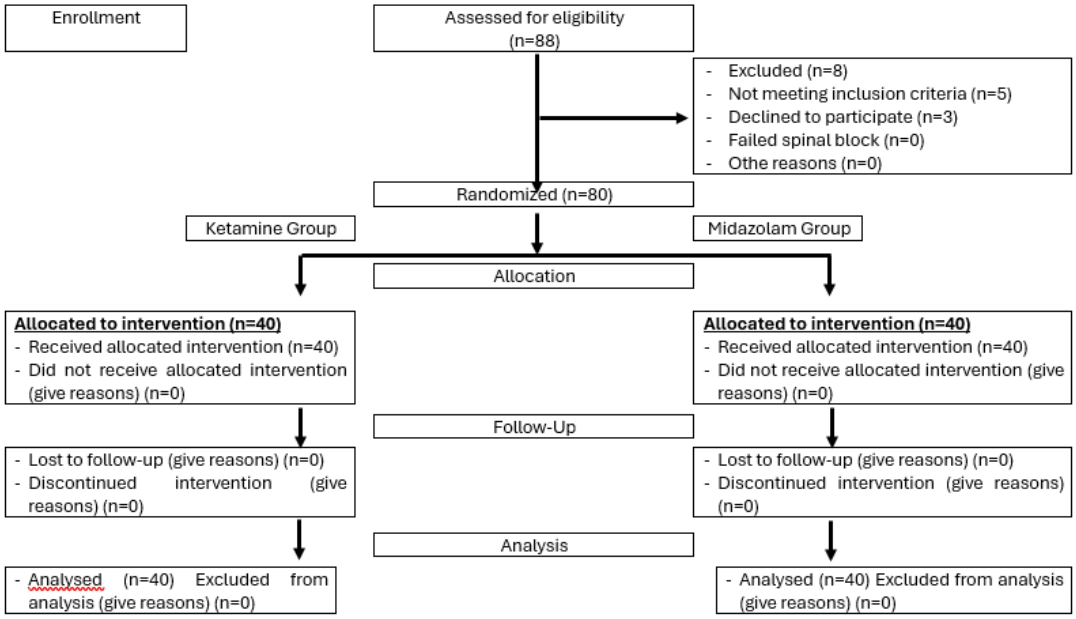


Fig. 2a. Changes in the modified observer's assessment of alertness/sedation (MOAA/S) scale in the two studied groups.

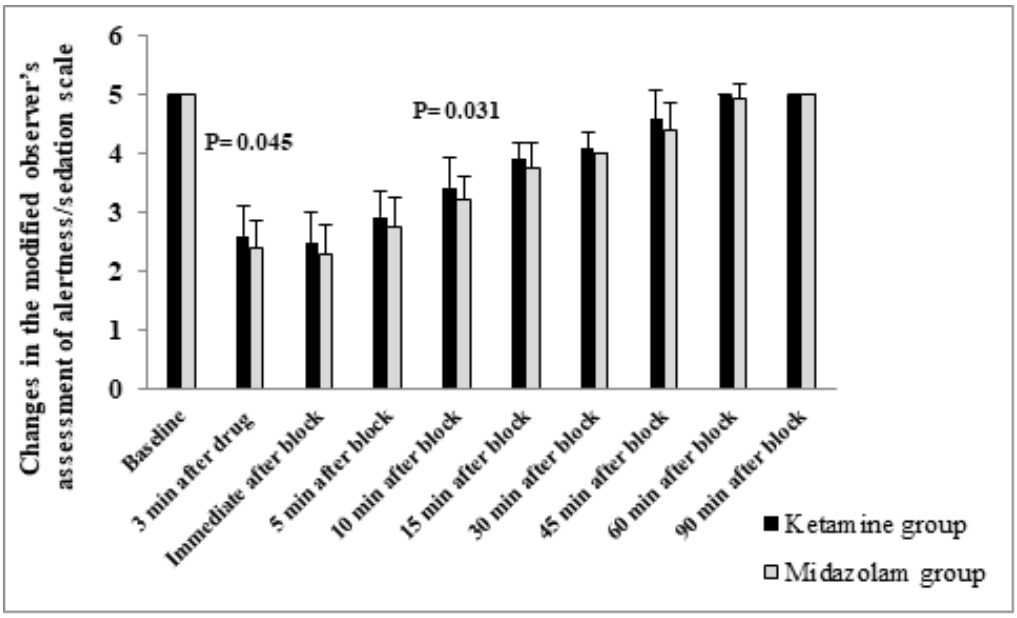


Fig. 2b. A-Line Autoregressive Index (AAI) changes with time in the two studied groups.

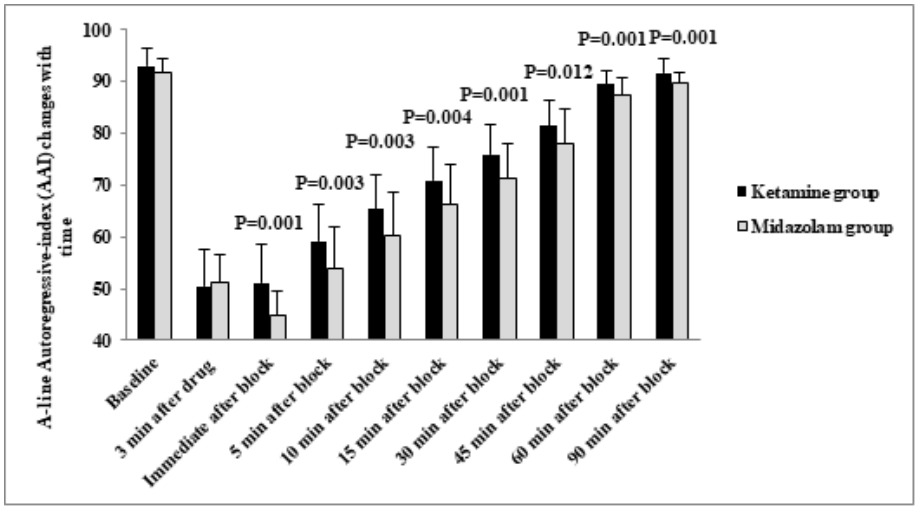


Fig. 3a. Changes in mean arterial pressure (mmHg) in the two studied groups.

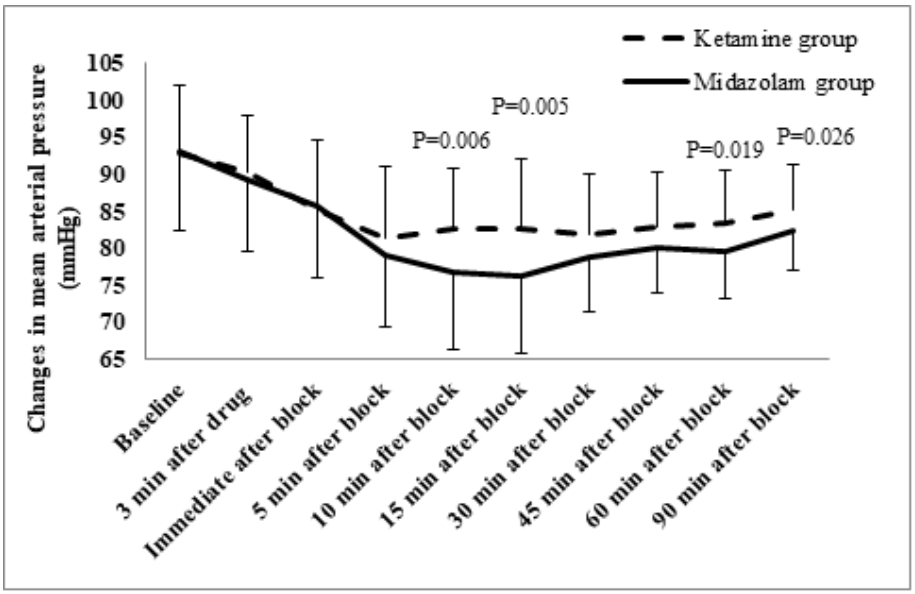


Fig. 3b. Changes in heart rate (beat/ min) in the two studied groups.

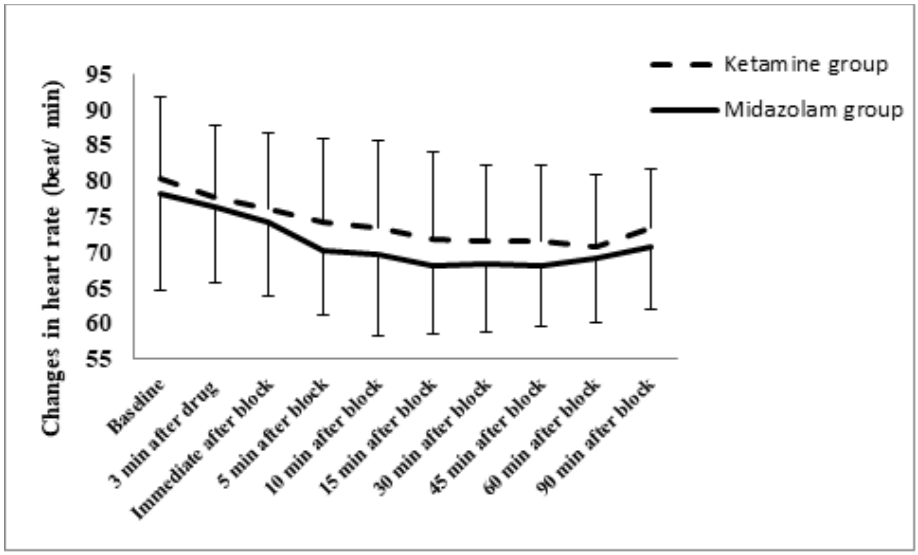
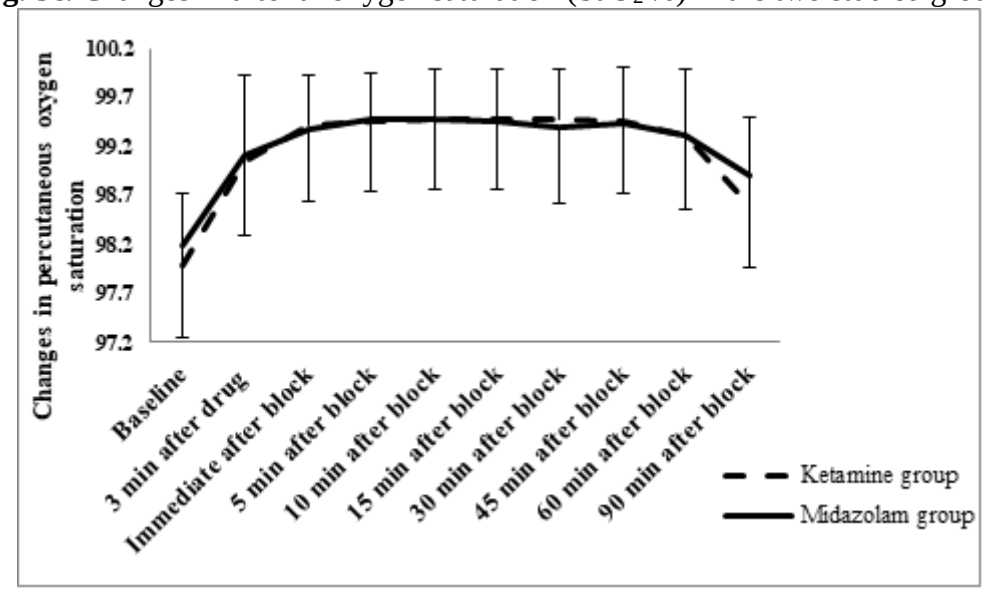


Fig. 3c. Changes in arterial oxygen saturation (SaO_2 %) in the two studied groups.



Discussion

The current study demonstrated that an IV single low dose of ketamine and midazolam during elective open unilateral inguinal hernia repair under SA produced a smooth onset of sedation with an acceptable depth and few side effects. Clinically, the onset of sedation was significantly earlier in the ketamine group than in the midazolam group; however, the recovery was comparable between both groups. Instrumentally, the onset of sedation was comparable between both groups; however, the recovery was significantly earlier in the ketamine group than in the midazolam group. Both groups had similar ease of patient positioning and response to spinal needle insertion. The pain-free time was significantly longer in the ketamine group compared to the midazolam group.

Ketamine and midazolam are two widely used anesthetic drugs that are known to affect specific aspects of brain function, such as memory encoding and pain perception, differently at varying levels of sedation (18).

Midazolam is commonly used for procedural sedation in smaller doses (0.1–0.3 mg/kg) due to its highly reversible anterograde amnestic properties (4, 5, 19-20). Midazolam is a potent benzodiazepine with high lipid solubility and receptor affinity, making it suitable for short procedures (20, 21). However, it can cause respiratory depression, cardiovascular depression, postoperative delirium, and unintentional oversedation (21, 22).

Ketamine, a non-barbiturate dissociative anesthetic, is safer for asthma patients because of its bronchial dilating and anti-inflammatory properties (23, 24). It stimulates the central sympathetic nervous system and is recommended for patients with unstable hemodynamics. Ketamine is preferred for burn patients and children and may help reduce postoperative delirium. However, rapid IV administration of ketamine can cause apnea. It may also cause dose-dependent psychometric adverse effects (22).

Ketamine is a popular analgosedative in the intensive care unit (ICU), aiding in recovery (25), and is useful in traumatic brain injuries because it does not raise intracranial pressure and could increase cerebral perfusion pressure (22). It is effective in emergency medicine (26), in acutely agitated patients (27), and in arthroscopic knee surgery under SA (7- 9).

Ketamine, when administered at a low-dose infusion (0.3 to 0.5 mg/kg) in acute clinical settings, induces a dissociated mental state, profound analgesia, and adequate sedation while still maintaining

airway reflexes. It also has favorable cardiorespiratory effects and is preferred over opioid administration (6- 12, 18, 21-28).

The current study found that patients who received ketamine reached a MOAA/S score of 4 earlier and recovered to a MOAA/S score of 4 at AAI > 60^o faster, taking 13.88 minutes to reach an AAI score > 60^o. Patients who received midazolam experienced deeper sedation than those who received ketamine. Both drugs effectively provided intraoperative sedation, but the difference in onset and recovery was minimal, and its clinical importance is likely minor.

Despite LA infiltration and preoperative counseling, discomfort and pain often accompany spinal needle insertion during SA. This is attributed to patient positioning, the procedure, and fear of pain (29).

Ketamine at a dose of 0.3 mg/kg provided sufficient sedation, easing positioning and resulting in high patient satisfaction. However, patients receiving 0.5 mg/kg required assistance from two persons due to increased sedation. Prick response scores were significantly higher in patients receiving 0.3 mg/kg, with three experiencing gross movement (29, 30).

Imbelloni et al. found that patients' comfort during spinal procedures improved with lower doses of ketamine, showing a negative correlation between increasing the dose and prick response scores (29). In the current study, none of the patients who received ketamine turned on their own without assistance, while one patient in the midazolam group did. Additionally, 50% of patients in both groups turned with the help of one person, but 50% of ketamine patients versus 47.5% of midazolam patients required the help of two persons. Only three patients in the ketamine group versus four patients in the midazolam group experienced gross movement during spinal needle insertion.

Midazolam directly affects the affective-emotional component of pain and inhibits limbic and reticular systems (31, 32). It enhances the action of local anesthetics and opioids when administered in neuraxial blockade (33). Additionally, it improves the quality of anesthesia and perioperative analgesia (34).

Ketamine is a potent analgesic used in acute pain management due to its ability to provide amnesia, procedural sedation, and potent analgesia. It activates serotonin and noradrenaline receptors and binds to opiate receptors in the spinal cord. A low dose of ketamine (IV 0.2-0.8 mg/kg) is widely used as an alternative to opioids (10, 28), reducing pain intensity and postoperative analgesic consumption (24, 28, 35, 36). In the current study, the time to the first analgesic request was prolonged in both groups; however, it was significantly shorter in the midazolam group compared to the ketamine group.

Nuotto et al. found that IV midazolam at a 0.15 mg/kg dose effectively sedated patients without causing changes in HR or MAP (31). Sivachalam et al. used a loading dose of 0.03 mg/kg of midazolam and a maintenance dose of 0.03 mg/kg/h for sedation during SA without causing desaturation or excessive sedation (32). Additionally, IV midazolam at 0.05 mg/kg dose provided sufficient sedation without affecting hemodynamics or respiration (20).

Ketamine is a non-competitive inhibitor at the NMDA receptor, causing non-dose-dependent stimulation of the cardiovascular system. It attenuates the baroreceptor reflex in the nucleus tractus solitarius, leading to central stimulation of the sympathetic nervous system and inhibition of norepinephrine reuptake (37).

In the current study, hypotension, total fluid intake, and ephedrine intake were significantly higher in the midazolam group compared to the ketamine group. Changes in HR and SpO_2 were similar in both groups, with only three patients in the midazolam group developing bradycardia and requiring atropine. No patients in either group developed respiratory complications.

Ketamine increases hallucinations, vivid dreams, disorientation, and confusion when used alone. These effects are decreased when used in small doses and combined with other sedatives (38). However, when ketamine is combined with midazolam, it may not significantly reduce emergence events, but it can increase recovery times and respiratory events (39). In the present study, patients in the ketamine group experienced disruptive movements and blurred vision.

The study has limitations, including assessing the agents' amnestic effects from the provider's perspective, not the patient's. It also only included adult male patients with ASA I-II undergoing elective procedures. Therefore, the safety and efficacy of the studied drugs cannot be applied to higher ASA classes, different age groups, or patients with comorbidities. There is a lack of previous research on the optimal single low dose of IV ketamine and midazolam for sedation during SA.

Conclusion

The use of IV single low-dose ketamine versus low-dose midazolam resulted in acceptable levels of sedation, with rapid onset and recovery and minimal adverse effects.

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None

Conflicts of interests

None

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