Analgesic Efficacy And Side Effects Of Three Different Doses Of Intrathecal Ketamine As An Adjuvant To Intrathecal Bupivacaine In Patients Undergoing Knee Arthroscopy: A Randomized Study

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Abstract

Background: The co-administration of intrathecal ketamine and bupivacaine resulted in a substantial improvement in the time elapsed before the initial request for analgesics. A range of doses, spanning from 0.05 to 0.7 mg/kg, has been utilized in previous studies. We aimed to compare three doses to ascertain the optimal dosage that delivers the most effective pain relief while minimizing potential side effects.

Methods: One hundred and five patients aged 18-70 years, with a body mass index (BMI) of 20-30 kg/m2 and planned for knee arthroscopy were randomly allocated to receive intrathecal heavy bupivacaine 0.5% in addition to intrathecal ketamine at a dose of either 0.1 mg/kg (n = 35), 0.2 mg/kg (n = 35), or 0.3 mg/kg (n = 35). Our primary outcome was the time elapsed to first rescue analgesia.

Results: All groups exhibited comparable time intervals until the first rescue analgesic was requested (11.4 ± 3.99 vs 11.2 ± 4.65 vs 11.63 ± 5.11, p = 0.93). The groups examined also demonstrated similar numeric rating scale (NRS) scores during the 6th, 12th, and 24th postoperative hours. However, a statistically significant difference was observed among the groups regarding the incidence of confusion and dizziness (p = 0.001), with a higher occurrence in the 0.2 and 0.3 mg groups compared to the 0.1 mg group.

Conclusion: Based on our findings, it can be inferred that an intrathecal ketamine dose of 0.1 mg/kg exhibits analgesic efficacy comparable to higher doses while having the fewest side effects.

Keywords

Intrathecal ketamine; Bupivacaine; Knee arthroscopy; Analgesia.

Introduction

Ketamine is a liposoluble phenyl cyclohexylamine derivative that acts as a non-competitive antagonist of the N-Methyl-D-aspartate (NMDA) receptor. It is composed of two enantiomers, (R) and (S) (1). Ketamine can be administered through different routes, including intrathecal (2). In addition to its role as an NMDA receptor antagonist, ketamine exerts various other actions that potentially contribute to its analgesic effects. These actions encompass interactions with calcium and sodium channels, dopamine receptors, cholinergic transmission, and modulation of noradrenergic and serotoninergic reuptake. Importantly, intact descending inhibitory pathways are crucial for the analgesic properties of ketamine. Furthermore, ketamine exhibits opioid-like effects and possesses anti-inflammatory properties (3).

According to a meta-analysis of randomized controlled trials involving adult subjects, it has been noted that adding intrathecal ketamine to intrathecal bupivacaine during spinal anesthesia provides a benefit when compared to using bupivacaine alone. This finding supports the use of intrathecal ketamine as an adjunct to bupivacaine in multimodal analgesia. (4). Nevertheless, there are still gaps in our knowledge and understanding when it comes to determining the appropriate dosing of neuraxial ketamine in this context.

Although higher doses of ketamine, specifically at or above 0.75 mg/kg, were associated with a notable occurrence of side effects like nystagmus, psychological disturbances, and pronounced hallucinations,

the effectiveness of ketamine at lower doses (0.05 mg/kg, 0.1 mg/kg, 25 mg) as part of a multimodal treatment approach has been examined independently in various trials with no adverse events recorded (5-7).

The objective of this study was to compare the postoperative analgesic effects of three different doses of intrathecal ketamine, administered in conjunction with bupivacaine, and explore the associated side effects for each dose to determine the dosage that exhibited superior postoperative analgesic effectiveness while causing minimal adverse effects.

Materials And Methods

This prospective single-center, randomized, double-blind trial was conducted at Assiut University Hospitals following approval from the hospital's Ethical Review Board (IRB17101660) and registered at Clinicaltrial.gov (NCT05074823). All patients provided written informed consent before being enrolled in the study. The study included one hundred and five patients with ASA physical status I – III, aged 18-70 years, with a body mass index (BMI) of 20-30 kg/m2, and admitted for arthroscopic ACL reconstruction.

Patients with a known allergy to local anesthetics, coagulopathy or thrombocytopenia, a BMI greater than 30 kg/m2, infection at the injection site, chronic pain syndromes, pregnant women, regular use of analgesics, those who received analgesics within 24 hours before surgery, or those who refused to participate in the study were excluded.

Randomization:

The patients were sequentially aligned to treatment groups using a double-blind randomization system with a 1:1:1 ratio. A computer software program that generated random numbers and a random number block three design were employed to determine the specific dose of ketamine each patient would receive.

Group I consisted of 35 patients who received 3mL of bupivacaine (heavy) 0.5% along with an additional 0.5 mL of ketamine at a dose of

0.1 mg/kg.

Group II included 35 patients who received 3mL of bupivacaine (heavy) 0.5% in combination with an additional 0.5 mL of ketamine at a dose of 0.2 mg/kg.

Group III comprised 35 patients who received 3mL of bupivacaine (heavy) 0.5% along with an additional 0.5 mL of ketamine at a dose of 0.3 mg/kg.

The allocation sequence was not available to any one of the research team until all data were finalized and secured. Patients, the attending anesthesiologist, and the outcome assessor were unaware of the patient assignments and kept blinded throughout the study. Group allocation was concealed in opaque, sequentially numbered envelopes. A designated investigator with access to the randomization code prepared the study drugs. The volume of the test drug administered remained constant at 3.5 ml for all patients.

Interventions and data collection:

Standard American Society of Anesthesiologists monitoring was applied before anesthesia. Baseline vital sign parameters of heart rate (HR), systolic blood pressure (SBP), and oxygen saturation (SPO2) were recorded. A preload with 10 ml/kg intravenous (iv) normal saline was used for all patients.

While using the aseptic technique, we did the lumbar puncture at L2–3 or L3–4 with a 25-G Quincke's needle. The study drug was injected intrathecally after obtaining a free CSF flow.

The following data were collected: Heart rate, systolic blood pressure, and oxygen saturation were documented every 5 minutes after injection of the studied dose for the first 20 minutes and after that every 10 minutes until reaching the 50th minute. Any decrease in systolic pressure below 90 mmHg was elevated with a bolus of ephedrine (6 mg) IV.

The level of sensory block was evaluated by using a pinprick test in the mid-axillary line every minute until it reached the T10 dermatome. After 20 minutes, the highest extent of the sensory block was determined. The onset of the sensory block was defined as the duration from administering the drug to the point at which the sensory block occurred

at T10. The duration of the sensory block was described as the duration between the onset of the sensory block at T10 and the regression of the sensory block to S2.

The motor block was evaluated using the Modified Bromage score (Zero: No motor loss, one: Inability to flex the hip, two: Inability to flex the knee joint, three: Inability to flex the ankle). This assessment was conducted at one-minute intervals until a Bromage score of three was achieved. The onset of the motor block was determined as the duration from the administration of the drug to the point at which a complete motor block was evident, indicated by a Bromage score of 3. The duration of the motor block was recorded as the time from the initiation of the complete motor block (score 3) to the complete restoration of motor function (score 0).4. Pain was assessed by a numerical rating scale (NRS; 0–10; 0: no pain, 10: worst imaginable pain) which was explained to the patient preoperatively.

After the surgery, pain levels were evaluated at two-hour intervals for the initial 12 hours, then at four-hour intervals for the next 24 hours. If the pain score reached or exceeded 4, intravenous nalbuphine was administered as rescue analgesia, with a maximum single dose of 20 mg for a 70 kg individual(8). The time to the first administration of rescue analgesia was measured starting from the moment the drug was administered intrathecally until the patient required the initial dose of rescue analgesic medication. The total number of rescue analgesic doses needed within 24 hours was also recorded.

Postoperatively, patients were monitored for a period of 24 hours to observe any behavioral side effects, confusion, dizziness, nystagmus (involuntary eye movements), nausea, vomiting, or neurological complications such as pain or numbness in the opposite leg, incontinence or retention of bowel or bladder, and genital dysesthesias.

Outcomes measures:

The primary outcome was the time elapsed to first rescue analgesia. The secondary outcomes included the optimal dose of ketamine with maximum analgesic effect and minimal side effects, onset and duration of sensory and motor blockade, hemodynamic stability, and any postoperative behavioral side effects or neurological complications in the first 24 hours.

Statistical Analysis
1. Sample Size Calculation:

Based on the results of a prior investigation (Study 9), it was established that 33 patients per group were necessary to observe a 25% prolongation in the duration until the initial analgesic request, with a significance level (α) of 0.05 and a statistical power of 85%. To accommodate possible dropouts, 35 patients were enrolled in each group.

Data Analysis:

We used SPSS (Statistical Package for the Social Sciences, version 24, IBM, Armonk, New York) for data analysis. The Shapiro test was employed to assess the normal distribution of the data. Quantitative data were presented as mean ± standard deviation (SD) and compared using ANOVA, followed by post-hoc tests. Nominal data were reported as numbers (n) and percentages (%), and the Chi-square test was utilized for analysis. Changes in heart rate (HR), systolic blood pressure (SBP), oxygen saturation (SPO2), and numerical rating scale (NRS) scores over time within the study groups were evaluated using repeated measures ANOVA, and significant differences were identified using the post-hoc Bonferroni test. A p-value of less than 0.05 was considered statistically significant.

Results

The study enrolled one hundred-five patients, as illustrated in the CONSORT flowchart (figure 1). The demographic data, duration of surgery, and ephedrine dose were similar among the groups (P > 0.05) (Table 1).

The different groups studied exhibited insignificant differences in the perioperative assessment of HR (figure 2), SBP (figure 3), and SPO2 (figure 4). Subgroup analysis also revealed no significant differences (P > 0.05). Furthermore, there were no significant

differences observed among the groups in the measurement points over time for HR [F $(2,102) = 1.88$, P = 0.16], SBP [F $(2,102) = 1.33$, P = 0.27], and SPO2 [F $(2,102) = 1.46$, P = 0.24].

The study's primary outcome revealed that the groups examined had comparable times to first rescue analgesia (11.4 ± 3.99 vs 11.2 ± 4.65 vs 11.63 ± 5.11, p = 0.93). Additionally, no significant differences were observed among the groups in terms of the duration of sensory and motor block, as well as the total number of rescue analgesics required (P > 0.05). However, a significant difference was noted between the studied groups in relation to the level of sensory block at the 20th minute of the intraoperative period (p = 0.006). The 0.2 mg and 0.3 mg groups exhibited a higher level of sensory block (reaching T4 in 71.4% and 80%, respectively) compared to the 0.1 mg group (where T4 was reached in 45.7%), with p-values of 0.02 and 0.004 respectively (table 2).

The study results indicated that the groups examined had similar postoperative numeric rating scale (NRS) scores at the 6th, 12th, and 24th postoperative hours (figure 5). Post-hoc analysis revealed no significant differences between the groups (p > 0.05). Additionally, no significant differences were observed among the groups regarding the NRS scores over time [F $(2,102) = 1.95$, P = 0.15].

There was a statistically significant difference among the groups with regard to the incidence of confusion and dizziness (p = 0.001), with higher incidence in the 0.2 and 0.3 mg groups (3 (8.6%) and 3 (8.6%) vs 10 (28.6%) and 12 (34.3%) respectively) compared to the 0.1 mg group where no cases developed confusion or dizziness (figure 6). The three studied groups did not demonstrate significant differences in the incidence of other side effects.
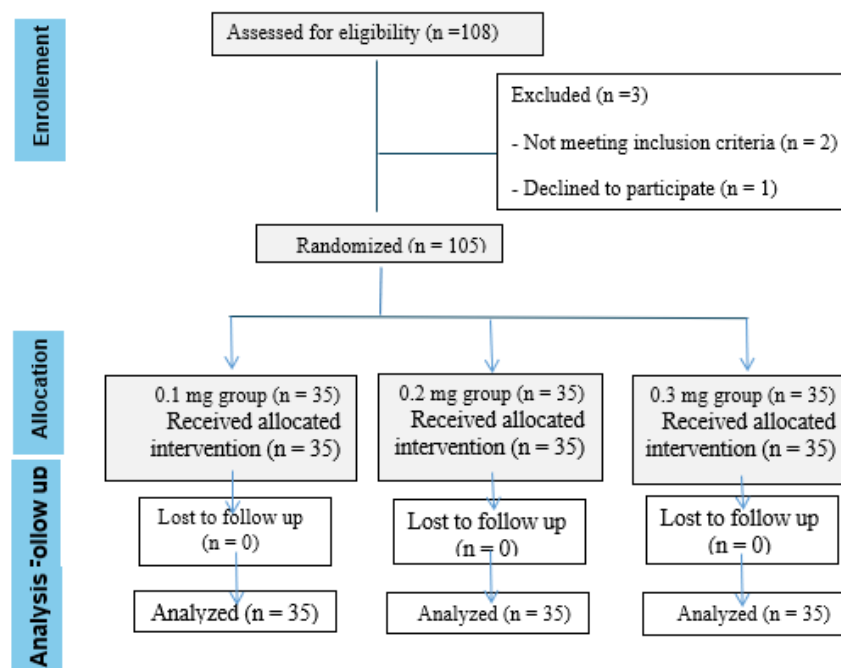

Figure 1: The CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trials.
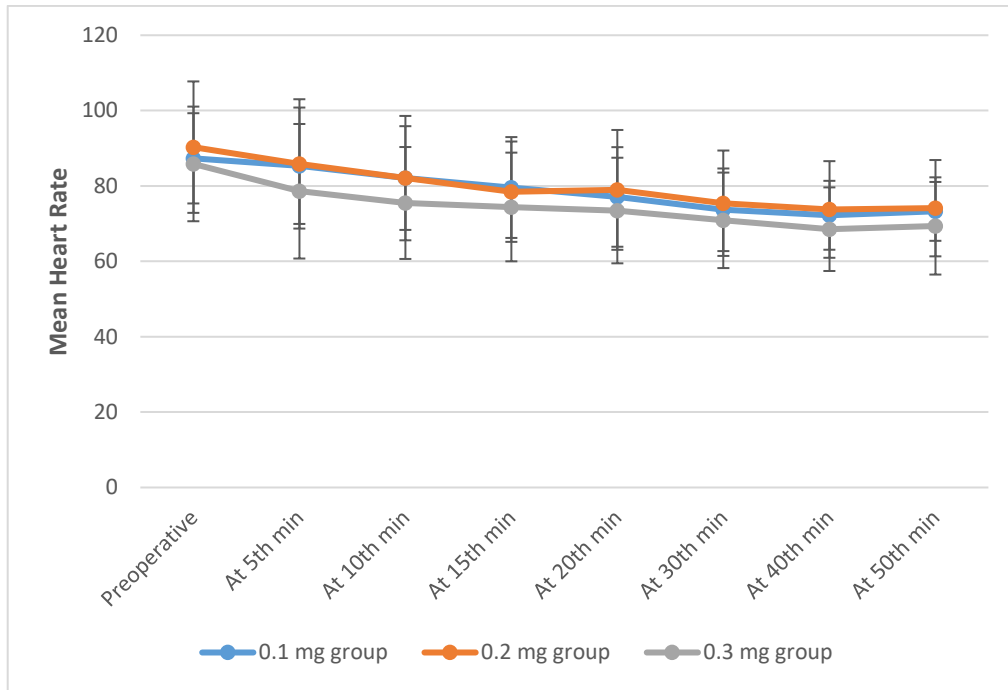
Figure 2: Perioperative assessment of heart rate among the studied groups. Data are shown as mean (standard deviation, S.D.). Serial changes in mean heart rate among groups over time were calculated using repeated-measures ANOVA followed by a post hoc Bonferroni test to identify significant differences. (*) P-value < 0.05 among different groups. (a) P < 0.05 between 0.1 mg and 0.2 mg groups (b) P < 0.05 between 0.1 mg and 0.3 mg groups (c) P < 0.05 between 0.2 mg and 0.3 mg groups. P < 0.05 was considered statistically significant
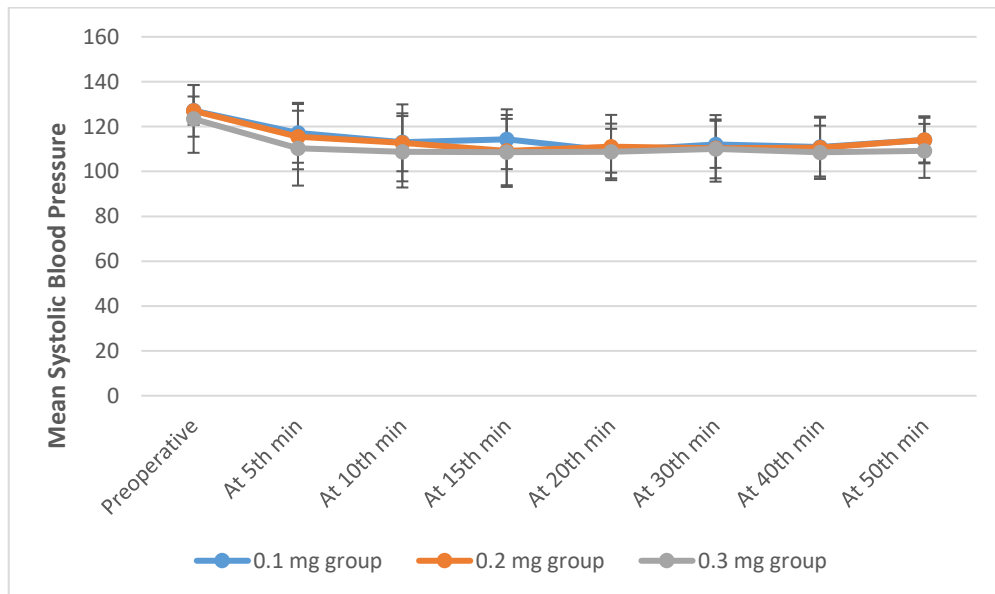

Figure 3: Perioperative assessment of systolic blood pressure among the studied groups. Data are shown as mean (standard deviation). Serial mean systolic blood pressure changes among groups over time were calculated using repeated-measures ANOVA followed by a post hoc Bonferroni test to identify significant differences. S.D.).(*) P-value < 0.05 among different groups. (a) P < 0.05 between 0.1 mg and 0.2 mg groups (b) P < 0.05 between 0.1 mg and 0.3 mg groups (c) P < 0.05 between 0.2 mg and 0.3 mg groups. P < 0.05 was considered statistically significant.
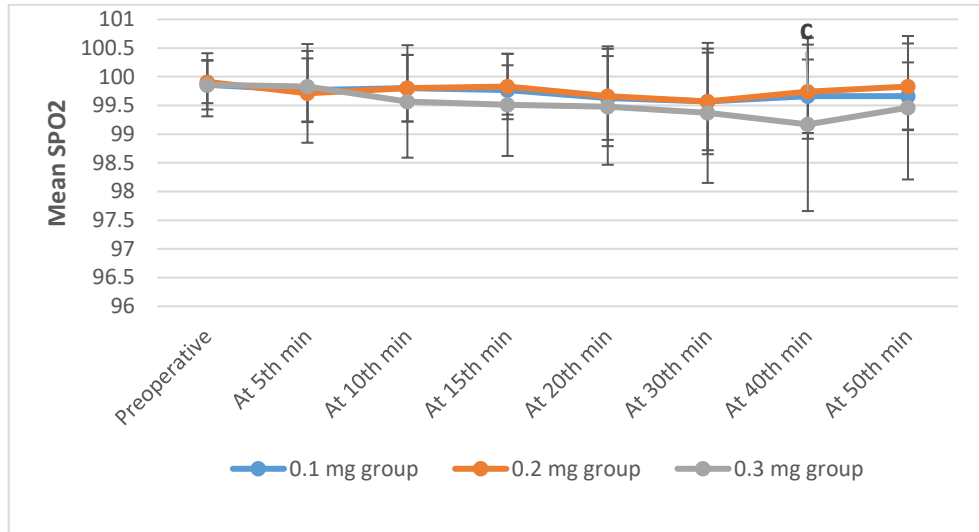
Figure 4: Perioperative assessment of oxygen saturation in the studied groups. Data are shown as mean (standard deviation, S.D.). Serial changes in mean oxygen saturation among groups over time were calculated using repeated-measures ANOVA followed by a post hoc Bonferroni test to identify significant differences. Data are shown as mean (standard deviation, S.D.). SPO2: oxygen saturation. (*) P-value < 0.05 among different groups. (a) P < 0.05 between 0.1 mg and 0.2 mg groups (b) P < 0.05 between 0.1 mg and 0.3 mg groups (c) P < 0.05 between 0.2 mg and 0.3 mg groups. P < 0.05 was considered statistically significant.

Figure 5: Postoperative assessment of numeric rating scale in the studied groups. Data are shown as mean (standard deviation, S.D.). Serial changes in the mean numeric rating scale among groups over time were calculated using repeated-measures ANOVA followed by a post hoc Bonferroni test to identify significant differences.(*) P-value < 0.05 among different groups. (a) P < 0.05 between 0.1 mg and 0.2 mg groups (b) P < 0.05 between 0.1 mg and 0.3 mg groups (c) P < 0.05 between 0.2 mg and 0.3 mg groups. P < 0.05 was considered statistically significant
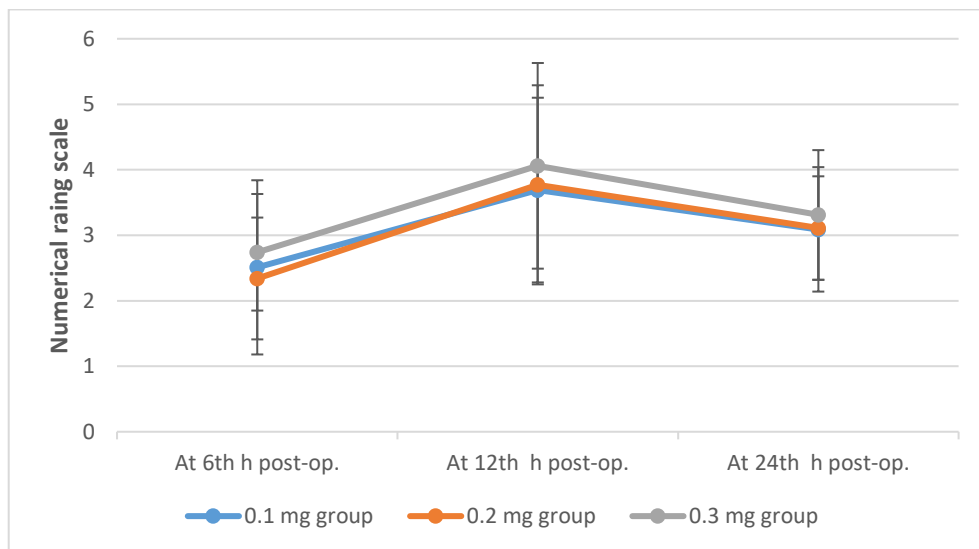
Figure 6: The reported side effects among studied groups. (*) P-value < 0.05 among different groups (a) P < 0.05 between 0.1 mg and 0.2 mg groups (b) P < 0.05 between 0.1 mg and 0.3 mg groups (c) P < 0.05 between 0.2 mg and 0.3 mg groups. P < 0.05 was considered statistically significant.
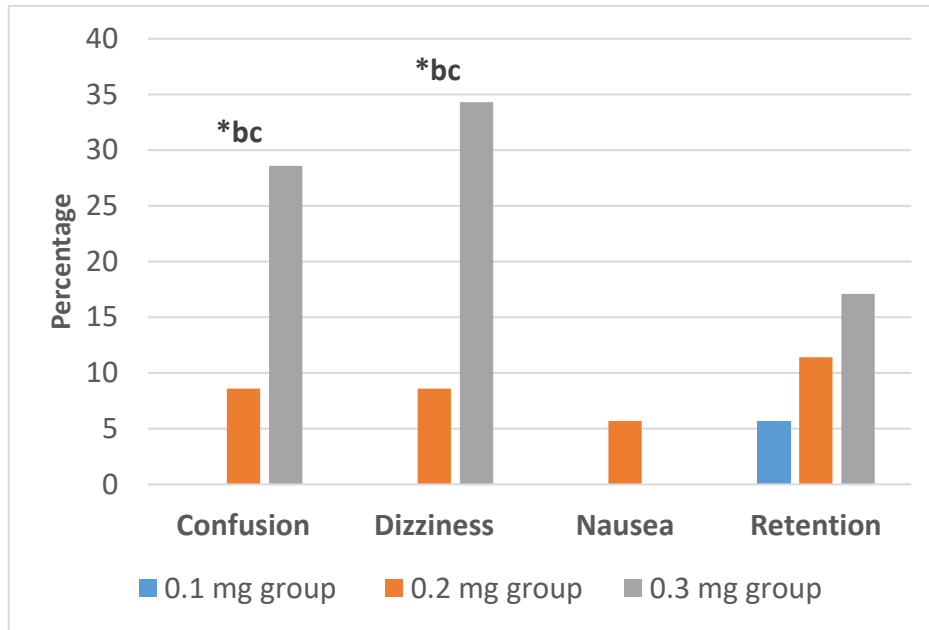
Table 1: Demographics and operative data of the studied groups

	0.1 mg group (n= 35)	0.2 mg group (n= 35)	0.3 mg group (n= 35)	*P* value*
Age (years)	31.89 ± 11.80	32.91 ± 12.54	32 ± 12.45	0.93
BMI (kg/m^2)	26 ± 2.10	25.47 ± 2.09	25.40 ± 2.37	0.45
ASA class				0.59
Class-I	32 (91.4%)	34 (97.1%)	33 (94.3%)	
Class-II	3 (8.6%)	1 (2.9%)	2 (5.7%)	
Sex				0.62
Male	26 (74.3%)	26 (74.3%)	29 (82.9%)	
Female	9 (25.7%)	9 (25.7%)	6 (17.1%)	
Duration of surgery (minute)	49 ± 17.56	47.57 ± 15.54	47.57 ± 13.31	0.91
Ephedrine dose (mg)	9.26 ± 1.39	7.20 ± 1.29	7.54 ± 1.29	0.50

Data expressed as mean ± SD, frequency (percentage). *P* value was significant if < 0.05. **ASA:** American society of anesthesiologists; **BMI**: body mass index. ***** ***P* value** compares between different groups. *[a]* P < 0.05 between 0.1 mg and 0.2 mg groups. *[b]* P < 0.05 between 0.1 mg and 0.3 mg groups. *[c]* P < 0.05 between 0.2 mg and 0.3 mg groups.

Table 2: Motor and sensory block and time to first rescue analgesia in studied groups

	0.1 mg group (n= 35)	0.2 mg group (n= 35)	0.3 mg group (n= 35)	*P* value*
Sensory block (minutes)	283.09 ± 60.9	299.37 ± 64.28	284.37 ± 62.15	0.48
Sensory level after20 minutes				**0.006**
T4	16 (45.7%)	25 (71.4%)[a]	28 (80%)[b]	
T7	19 (54.3%)	8 (22.9%)	6 (17.1%)	
T10	0	2 (5.7%)	1 (2.9%)	
Motor block (minutes)	237.17 ± 57.99	243.74 ± 54.24	235.37 ± 57.91	0.81
Time to first rescue analgesia (hours)	11.4 ± 3.99	11.2 ± 4.65	11.63 ± 5.11	0.93
Analgesic doses' number in the first 24 hours	1.26 ± 0.44	1.26 ± 0.51	1.26 ± 0.44	1.00

Data expressed as mean ± SD, frequency (percentage). *P* value was significant if < 0.05. *** *P* value** compares between different groups. [a] P < 0.05 between 0.1 mg and 0.2 mg groups. [b] P < 0.05 between 0.1 mg and 0.3 mg groups. [c] P < 0.05 between 0.2 mg and 0.3 mg groups.

Discussion

In this clinical trial, we aimed to evaluate analgesic efficacy, hemodynamic stability, and the incidence of different side effects associated with three different doses of ketamine (0.1, 0.2, or 0.3 mg/kg) in patients undergoing knee arthroscopy under spinal anesthesia with bupivacaine.

Regarding the primary outcome measure, which assessed the time to first rescue analgesia, no significant differences were observed among the three dose groups (p = 0.93). This indicates that all three doses of ketamine yielded similar analgesic effects during the postoperative period. These findings align with a comprehensive meta-analysis conducted by Sohnen et al. (4), which included studies administering ketamine at 0.1 mg/kg and higher doses. The meta-analysis consistently demonstrated that patients receiving ketamine experienced significant prolongation in time to the first analgesic request. Meanwhile, it is worth noting that a single study conducted by Unlugenc et al. (5) utilized a combination of the lowest dose of intrathecal ketamine, administered at 0.05 mg/kg, along with bupivacaine. This particular study didn't find significant prolongation in the time to the first analgesic request. Nonetheless, it is important to consider that this study's dosage differs significantly from the dosages used in

other studies and may contribute to the observed disparity in results. In summary, this finding of our clinical trial, along with the evidence synthesized in the meta-analysis by Sohnen et al., supports the notion that all doses of ketamine at or above 0.1 mg/kg yield comparable analgesic effects in the postoperative period.

Ketamine, a Nmethyl-D-aspartate (NMDA) receptor antagonist, has been shown to possess central, regional, and local anesthetic properties, as well as analgesic effects. In addition to these effects, ketamine may exert peripheral actions through various mechanisms. These include binding to variable opioid receptors (ORs), interacting with monoamine transporters, inhibiting muscarinic and nicotinic cholinergic receptors, binding to D2 and 5-HT2 receptors, modulation of ion channels (such as Na^+, Ca^{2+}, and K^+ channels), reduction of activation and migration of microglia, and inhibition of inflammatory mediator production (10).

When considering the secondary outcome measures, specifically the hemodynamic stability indicated by the ephedrine requirement to treat hypotension, no significant differences were found between the three groups (P=0.5). This suggests that all three doses of ketamine had comparable effects on maintaining hemodynamics

throughout the perioperative period. Previous research investigating intrathecal ketamine administration at doses of 0.1 mg/kg and higher has consistently emphasized the cardiovascular stability associated with intrathecal ketamine (7, 11, 12). This mostly results from systemic absorption of ketamine and resultant cardiovascular stimulation.

Regarding neurological complications within 24 hours postoperatively, no significant differences were observed between the three groups, except for a lower incidence of dizziness and confusion in group I (0.1 mg/kg). Notably, the incidence of dizziness and confusion was significantly higher in group II compared to group I, and it was also significantly higher in group III compared to both group I and group II. These findings suggest that a lower dose of ketamine may be associated with a reduced occurrence of these particular side effects.

In support of this observation, a study conducted by S. Kathirvel et al. investigated 30 healthy female patients undergoing intracavitary brachytherapy applicator insertion for carcinoma of the cervix under spinal anesthesia. In their study, they utilized intrathecal ketamine at 25 mg. The researchers documented that a significantly higher number of patients in the ketamine group experienced adverse events, including sedation, dizziness, nystagmus, "strange feelings," and postoperative nausea and vomiting (13). In agreement with our results, Abd El-Rahman et al. stated that the addition of intrathecal ketamine at a dose of 0.1 mg/kg to morphine at a dose of 0.3 mg in patients undergoing major abdominal cancer surgery resulted in satisfactory postoperative analgesia, and there were no side effects observed except for sedation (10).

In contrast to our findings, Sohnen et al. reported that studies utilizing a dosage of 25 mg of ketamine (equivalent to 0.3 mg/kg) or doses ranging from 0.05 mg/kg to 0.1 mg/kg were not associated with significant neuropsychiatric side effects (4). However, it is important to interpret these findings cautiously and consider each study's specific context and patient population.

Intrathecal ketamine can potentially have neurological side effects. Common neurological side effects associated with intrathecal ketamine administration include dizziness, confusion, sedation, nystagmus (involuntary eye movements), and, in rare cases, hallucinations or delirium. These side effects are generally transient and resolved independently as the medication is metabolized and eliminated from the body. It is important to note that the incidence and severity of neurological side effects can vary depending on the dosage of ketamine used and individual patient factors (14).

It is important to acknowledge the limitations of this study. Firstly, the sample size used in this trial may have limited the ability to detect smaller differences between the dose groups. Future studies with larger sample sizes could provide more robust evidence. Additionally, the study was conducted in a specific patient population undergoing a particular procedure, which may limit the generalizability of the findings to other patient populations or surgical interventions. Despite these limitations, to our knowledge, this trial is the first documented study that compares three distinct intrathecal ketamine to determine the optimal intrathecal dosage that achieves a longer duration of analgesia and fewer postoperative side effects.

In conclusion, our findings suggest that different doses of ketamine, ranging from 0.1 mg/kg to 0.3 mg/kg, provide comparable analgesic efficacy and hemodynamic stability. Furthermore, a lower dose of 0.1 mg/kg may be associated with a lower incidence of postoperative dizziness and confusion. These results can guide clinicians in selecting appropriate doses of ketamine for perioperative pain management. This clinical trial adds to the growing body of evidence supporting the use of ketamine in perioperative analgesia. Upcoming studies with larger sample sizes and diverse patient populations are warranted to confirm our results regarding the optimal dosing strategies and potential benefits of ketamine in different surgical contexts.

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