Comparison Between Intrathecal Bupivacaine with Ketamine 15 Mg versus Bupivacaine with Ketamine 20 Mg in Postoperative Pain Management after Cesarean Section.

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Abstract:

Background: **Pain associated with cesarean section is the most discouraging side effect that might occur following surgery. When neuraxial anesthesia is being administered, Ketamine, which is a potent analgesic, may be given as an adjuvant. The ideal dosage of intrathecal Ketamine has not yet been completely determined.** ***Aim:*** **To evaluate the best dosage of Ketamine as an adjunct to intrathecal Bupivacaine by comparing the two doses of 15 mg and 20 mg intrathecal ketamine in patients delivering by cesarean section.** ***Materials and Methods:*** **Fifty women undergoing cesarean delivery using neuraxial anesthesia were arbitrarily distributed to receive 2 ml (10 mg) hyperbaric Bupivacaine 0.5% + 15 mg ketamine or 2 ml (10 mg) hyperbaric Bupivacaine 0.5% + 20 mg ketamine. The analgesic effect was evaluated by the Visual Analogue Scale at recovery, 2, 4, 8, 12, 18, and 24 hours after delivery. Request to first analgesic timing, dosage of morphine used, and complications were compared between groups.** ***Results:*** **Increasing the dose of intrathecal Ketamine to 20 mg was associated with prolonged sensory and motor blockage, longer after surgery analgesia, and lower morphine consumption while preserving the patient's hemodynamics.** ***Conclusion:*** **Intrathecal 20 mg ketamine was superior to 15 mg ketamine as an adjunct to Bupivacaine concerning postoperative analgesia, as evidenced by the visual analog score and the total Morphine consumption, with lesser hemodynamic fluctuations.**

Keywords: Cesarean delivery; Postoperative pain; Ketamine.

Introduction:

Pain after cesarean section (CS) is the most distressing complaint occurring after delivery. According to research comparing postoperative pain, CS pain was placed ninth among 179 various operations based on the evaluation of pain severity after surgery on day one. Additionally, the study found that CS pain had a mean numerical rating scale (NRS) of 6, which corresponds to trauma/orthopedic pain. (1) A high-quality analgesic regimen should be effective, associated with reduced medication transfer via breast milk, and increasing the maternal ability to look after of the baby. (2) This increased the need for suitable adjuvants to CS regional anesthesia. Research is being conducted on medications that extend the duration of postoperative analgesia but have fewer adverse effects. For example, Bupivacaine, when administered intrathecally by itself, only causes analgesia for a period of two and a half to three hours. (3)

Ketamine is a non-competitor opponent of the N-methyl-D-aspartate receptor (NMDAR), and it may be delivered by a diverse way, including intravenous, intramuscular, intrarectal, buccal,

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intranasal, intrathecal, or epidural. [4] There are lack of knowledge and expertise about neuraxial Ketamine, even though it has been documented that intrathecal Ketamine may extend the timing of regional anesthetic and pain free time after surgery when it is administered to epidural lidocaine or Bupivacaine. [5] As an additive to epidural or spinal anesthesia, Ketamine has not been widely used because of its potential for neurotoxicity. Variable ketamine dosages were applied as an adjuvant to increase the anesthetic duration. These differed from 0.05 mg/kg, which resulted in no difference, [6] to 0.1mg/kg, which resulted in a prolonged anesthetic effect for one more hour. [7, 8] An amount of Ketamine≥ 0.75 mg/kg were associated with an increased prevalence of central nervous system side effects, including abnormal eye movement, psychomimetic abnormalities, and overt hallucinations. [9] In order to obtain sustained postoperative analgesia with fewer problems, this research aimed to establish the best dose of intrathecal Ketamine that should be administered as an adjuvant to neuraxial block.

Materials and methods

This prospective, randomized, double-blind trial was commenced at the operative theatre at Suez Canal University hospital from January 2024 to October 2024. The research recruited fifty women arranged to undergo elective caesarian section using spinal anesthesia. Patient recruitment was following specified inclusion and exclusion criteria. The inclusion criteria were a) women aged 21-40 years, b) women undergoing elective CS, and c) patients of ASA II (according to the American Society of Anesthesiologists- physical status classification system), which stands for normal physiological pregnancy. The exclusion criteria were a) Patients refusing to participate in the research, b) women refusing spinal anesthesia, c) coagulation and bleeding disorders, d) hypersensitivity to the drugs being studied, e) emergency CS, f) failed spinal anesthesia, g) patients who had communication issues and were unable to comprehend visual analog scale (VAS) measurements, and h) local site infections.

Randomization and group allocation were carried out using computer-generated randomization numbers and a closed-seal envelope. The partakers were distributed into two equal groups, with every group comprising twenty-five individuals. Another anesthetist who was not engaged in the research was responsible for preparing the medicines, which were then given to the investigator in a sterile manner and administered. Over the preceding day, each patient was visited and given information on the spinal anesthetic procedure and the VAS. Following the recommendations, the beginning heart rate (HR), blood pressure (Bp), and saturation (Spo2) were evaluated after the parturient had been apprised of the instructions for the day of operation and had fasted for the previous night.

Following the beginning of regular standard monitoring in the operating room, an electrocardiogram (ECG) was performed, oxygen saturation was assessed using a pulse oximeter (SpO2), and non-invasive blood pressure and results were recorded. An 18 G cannula was used to create intravenous access, and an intravenous infusion was started using Ringer acetate solution.

After the parturient was sterilely positioned and placed in a seated posture, another anesthetist prepared the

medicines and then passed them over to the doctor who was doing the study. In the same place, at the L4 interspace, a subarachnoid puncture was done using a Quincke point spinal needle with a gauge of 25.

Parturients were randomly assigned to a) **Group A:** received 2 ml (10 mg) hyperbaric Bupivacaine [10] 0.5% + 15 mg ketamine 0.3 ml + 0.1 ml normal saline total volume 2.4 ml, and b) **Group B** received 2 ml (10 mg) hyperbaric Bupivacaine 0.5% + 20 mg ketamine 0.4 ml Total volume 2.4 ml.

Patient distribution was in a 1-to-1 pattern with the aid of random lists generated by computer systems. It was performed after confirming the patient's suitability for the study. The grouping pattern was hidden from the researcher (recruiting and evaluating patients) using closed envelopes. The senior researcher opened these envelopes in the operating room before the spinal anesthesia. Patients, researchers, outcome evaluators, and data analysts were kept blinded.

Following the injection of the anesthetic agent of each group, the participants were positioned supine rapidly with a 20-degree tilting to the left side. The start of the sensory block was evaluated by pricking the skin after intrathecal injection until stabilization of the level over three times. The start and overall time of motor blockage were evaluated using the Bromage Score where (zero, No difference in legs and feet motility, and 3, Unable to move the lower extremity). [11] The time required to achieve Bromage Score 3 represents when the motor blockade first began, and the time needed to reach Bromage Score 0 is the length of time the motor block has been present.

When the mean arterial blood pressure dropped below sixty millimeters of mercury (mmHg) or when the systolic blood pressure decreased by over twenty percent of the baseline blood pressure, and the heart rate dropped to fewer than 60 beats per minute, intravenous (IV) Ephedrine 5 mg and 0.5 mg of atropine sulfate were administered respectively. Five international units (IU) of oxytocin was given via an infusion after the infant was delivered. [12] The surgical procedure was performed in the same manner on each patient.

Immediately after surgery, one gram of paracetamol was administered to each patient at regular intervals of eight hours, and the VAS was used to evaluate the pain level. The evaluation was done at two, four, eight, twelve, eighteen, and twenty-four hours when the patient requested additional analgesia or a VAS of four or higher, whichever occurred sooner. The patient received rescue pain killers by an intravenous infusion of morphine at a dosage of 2 mg.

The adverse effects that occurred during the operation, such as nausea, vomiting, pruritus, hallucinations, and sedation scores, were documented. The observations continued from when the research medication was administered until the postoperative period.

Sample size:

The sample size was determined using the following equation: [13]

$$n = 2\left[\frac{\left(Z_{\alpha/2} + Z_{\beta}\right) * \sigma}{\mu_1 - \mu_2}\right]^2$$

Where:

n = sample size

Zα/2 = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)

Zβ = 0.80 (The critical value that separates the lower 20% of the Z distribution from the

upper 80%).

Σ = the estimate of the standard deviation (in the study group) = 0.6 **μ1**= mean score of pain, 1 hour after the surgery among patients who received 0.75 mg/kg of 0.25% bupivacaine plus 0.25 mg/kg of Ketamine = 1.47. [14]

μ2= mean pain score, 1 hour after the surgery among patients who received 0.75 mg/kg of 0.25% bupivacaine plus 0.5 mg/kg Ketamine = 0.52. [14]

Therefore, the required sample size was 22 patients; however, after increasing the possible (drop-out) rate (10%), the eventual number was 25 participants in each group.

Ethical approval:

This study was commenced after the research ethics committee of the Faculty of Medicine, Suez Canal University, approved it on 25/7/2023, with a reference number of 5404#.

Statistical Analysis

Data was presented as mean and standard deviation, figures, and percentages when possible. P values smaller than 0.05 were mentioned as statistically noteworthy. The entire statistical operations were performed using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 22 for Microsoft Windows. The Chi-square test was applied for absolute values and the (t) test for quantitative measures with adequate distribution.

Results

Thirty-one patients were suitable for the study. Five declined to take part in the study, and one patient withdrew from group A (15 mg ketamine) **(Figure 1).**

Patients in both groups were comparable demographically **(Table 1).**

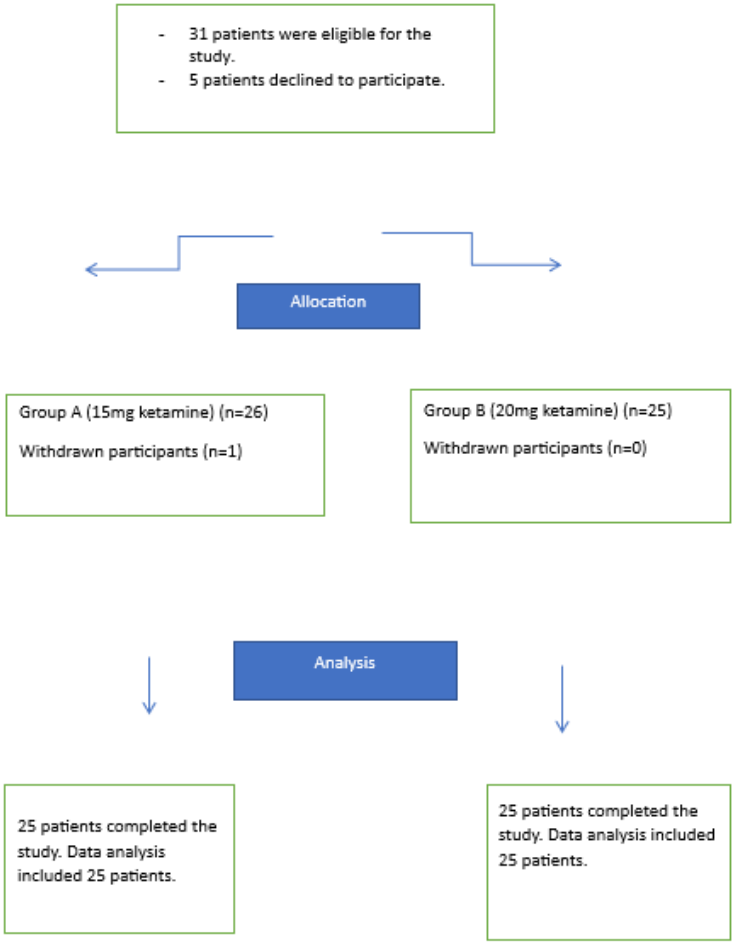

Figure 1: Patients' flow chart

Table (1): Comparison between the two studied groups according to demographic data and anthropometric measurement			
	Group A (15 mg)	Group B (20 mg)	P value
Age (Years) (Mean ± SD)	26.33 ± 2.98	25.89 ± 3.18	0.708
Gestational Age (Weeks) (Mean ± SD)	38.04 ± 1.14	38.32 ± 0.95	0.253
Weight (Kg) (Mean ± SD)	66.12 ± 5.13	70.20 ± 10.26	0.217
Height (Cm) (Mean ± SD)	164.04 ± 4.43	164.68 ± 10.13	0.112
BMI (Kg/M2) (Mean ± SD)	25.32 ± 2.22	25.38 ± 4.30	0.142

Sensory and motor block characteristics are shown in **(Table 2).** The mean time to reach the T4 sensory block was 2.3 ± 0.08 min in Group A and 2.00 ± 0.16 min in Group B. This difference was insignificant (p=0.161). The maximum level of the block achieved in any group was T4. In the meantime, regression of the block to the T12 level (i.e., mean duration of the sensory block), Group A took 2.2 ± 0.82 hours, while Group B took 2.96 ± 0.20 hours. This difference was significant (p=0.072). The mean time to onset of motor block was **2.20 ± 0.41** min in Group A versus **2.00 ± 0.3** min in Group B. The duration of the motor block (time taken to reach Bromage zero)

was **3.02 ± 0.48** hr in group A and **3.52 ± 0.22** hr in group B (p=0.021). The mean duration of analgesia was 2.88 ± 1.01 Hr in group A and 4.00 ± 1.60 Hr in group B (p<0.001).

Table (2): Sensory and motor characteristics and analgesia requests between both groups:			
	Group A (15 mg)	Group B (20 mg)	P value
T4 Sensory Block (onset of sensory block) (Min) (Mean ± SD)	2.3 ± 0.08	2.00 ± 0.16	0.161
Bromage 3 TIME (onset of motor block) (Min) (Mean ± SD)	2.20 ± 0.41	2.00 ± 0.3	0.843
Return To T12 (duration of sensory block) (Hr) (Mean ± SD)	2.2 ± 0.82	2.96 ± 0.20	0.072
Return To B zero (duration of motor block) (Hr) (Mean ± SD)	3.02 ± 0.48	3.52 ± 0.22	0.021*
Time Of First Analgesic Request (Hr) (Mean ± SD)	2.88 ± 1.01	4.00 ± 1.60	<0.001*

VAS scores at different time intervals showed that Group B exhibited lower VAS scores in the recovery room at 2 hours and a higher VAS score at 4 hours. No significant differences were observed at 8 hours, 12 hours, 18 hours, and 24 hours **(Figure 2).**

Regarding the incidence of adverse effects, none of the patients experienced pruritic reactions, respiratory depression, or neurological symptoms. Nine patients had hypotension more in group A, which was accompanied by nausea and vomiting, and four patients had bradycardia more in group A. All these differences were not statistically significant.

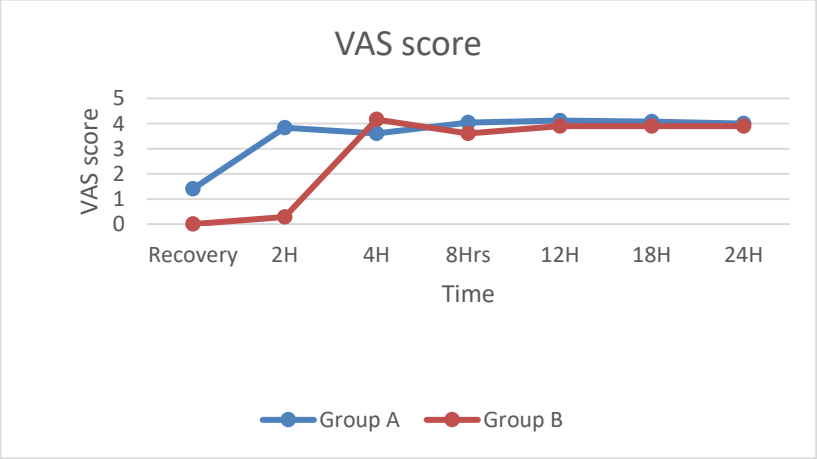

Figure 2: Comparison between study groups according to VAS score measurements.

Discussion:

Ketamine was studied previously and was administered intravenously as an adjuvant to Bupivacaine. These studies were conducted on individuals undergoing obstetrics, lower abdomen surgical

procedures, and lower limb orthopedic treatments. Ketamine was shown to have a longer duration of spinal analgesia when compared to control groups and other adjuvants in several of these investigations. Additionally, the start time of sensory and motor blocks was reduced compared to other groups. It was formerly believed that the neurotoxicity associated with Ketamine was caused by the presence of high dosages of Ketamine (0.75 mg/kg and above). [9] However, recent research has challenged these hypotheses.

Our hemodynamics remained steady over the course of our research, demonstrating that the dosages of Ketamine used were safe and dependable in terms of producing appropriate anesthesia and analgesia. None of the trial participants needed a general anesthetic because they did not get sufficient anesthesia or analgesia.

Regarding the beginning of the sensory and motor block, our findings were comparable to those of Peyyety et al., who utilized varying dosages of Ketamine. Nevertheless, they established sensory and motor blocks simultaneously. [15] This demonstrates that increasing the dose of Ketamine does not hasten the onset of block. The onset of block may be dependent on other factors, such as the rate of injection of drugs that are administered intrathecally, the position of the patient after the injection, and the PH of the prepared solution, which can be altered by adding saline or distilled water, and the characteristics of the patient. Pregnant women tend to achieve a higher level of block for a given dose of intrathecal drugs due to enhanced segmental spread. Among the participants in our study, the administration of 20 mg of Ketamine resulted in a longer duration to return to the T12 sensory level, with a mean of 2.96 ± 0.20 hours.

On the other hand, Bromage zero had a mean of 3.52 ± 0.22 hours, indicating a longer duration of action. This prolongation can be attributed to the gradual release of Ketamine due to liposomal impregnation. The findings of this study were comparable to those found in prior empirical research. [16]

In our investigation, the mean timing of pain free in the 20 mg ketamine group was more significant, measuring at 4.00 ± 1.60 hours. This agreed with previous studies where the analgesic effect was prolonged with increased doses of Ketamine. [8, 17] Analgesia time did not show a positive direct link with increasing the dosage of Ketamine in the previous research; nevertheless, in our investigation, there was a significant difference between the 15 mg and 20 mg group, and the duration was also extended in the Gantasala study when 50 mg of intrathecal Ketamine was administered [17] because of this, it became clear that the outcomes might be affected by several different elements, including changes in the patient and the procedure, which result in varying degrees of discomfort for the patient, and not just the dosage itself.

The reduced incidence of hypotension and bradycardia at the higher dosage may be explained by the transmission of Ketamine into the venous system via the azygos vein of the spinal cord, which leads to hemodynamic equilibrium. This is because Ketamine promotes the release of catecholamines throughout the body. [18] This correlates with the findings of an earlier study where the ketamine group could maintain their hemodynamics more effectively with a lower need for ephedrine. [19]

The present research found that the 20 mg ketamine group had a decreased total morphine intake over 24 hours, with a mean of 4.80 ± 1.00 mg. This finding further supports the improved analgesic effect of the larger dosage. It is possible to explain this phenomenon by stating that the endogenous opioid analgesic system is boosted by pregnancy during labor and the early postpartum period, which results in a decreased need for analgesics. Additionally, it is worth noting that continuous N- methyl-D-aspartate (NMDA) receptor blockage by Ketamine may also improve the efficacy of postoperative morphine. [20]

The research found no evidence of increased adverse effects with a more significant dose. No neurological side effects were observed in any of the groups. The findings of this study are in agreement with those of Bion, [18] who said that intrathecal Ketamine exerts its effects locally at the nociceptors of the spinal cord and does not exert its effects systemically after being absorbed into the circulation. The second probable explanation for this observation is that we employed lower doses of Ketamine compared to previous investigations. Hawksworth and Serpell [9] found psychomimetic signs in fifty percent of their patients when using intrathecal Ketamine at dosages ranging from 0.75 to 0.9 mg/kg, respectively. It was discovered by Togal et al. [21] that a modest dosage of Ketamine (0.1 mg/kg) did not cause any adverse effects. Therefore, it would seem that the occurrence of problems associated with intrathecal Ketamine is a phenomenon that is dependent on the dosage.

Conclusion:

Intrathecal 20 mg ketamine was superior to 15 mg ketamine as an adjuvant to Bupivacaine regarding postoperative analgesia, as evidenced by the visual analog score and the total Morphine consumption, with lesser hemodynamic fluctuations.

Conflict of interest: None.

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