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Comparative Clinical Study of Intrathecal Low Dose Ketamine Combined With Midazolam versus Fentanyl as Adjuvants to Bupivacaine for Cesarean Section

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ORIGINAL ARTICLE

Comparative Clinical Study of Intrathecal Low Dose Ketamine Combined With Midazolam Versus Fentanyl as Adjuvants to Bupivacaine for Cesarean Section

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Abstract

Background: **General sedation is related with higher death rate in contrast with spinal sedation. Passings in provincial sedation are principally connected with unnecessary high territorial blocks and harmfulness of nearby sedatives. Spinal sedation is the favored means for cesarean area, being easy to perform, affordable, and produces a quick beginning of sedation and complete muscle unwinding.**

Aim: **To look at the hemodynamic impacts, beginning, level, term of the intrathecal block, and occurrence of intricacies on adding a combination of low-portion ketamine and low-portion midazolam to bupivacaine, and on adding fentanyl to bupivacaine during intrathecal infusion for cesarean area.**

Patients and methods: **This imminent, randomized, twofold visually impaired clinical review was done at Al-Azhar College Clinic (Assiut) on 50 parturients going through elective lower-portion crossover-cut CS of singleton pregnancy at greater than 36 gestational weeks under spinal sedation from November 2020 to March 2022.**

Results: **A statistical expansion in the frequency of hypotension in bunch I (fentanyl-bupivacaine, FB) than bunch II (ketamine midazolam bupivacaine, KMB), unimportant contrast in some other difficulty rate between the two groups. Critical lessening in visual analog scale at 2, 4, and 12 h post useable in bunch II (KMB) contrasted with bunch I (FB). Throughout the procedure, there was no significant difference between the sedation score and the Apgar score.**

Conclusion: **Bupivacaine (10 mg) and a mixture of low-dose ketamine (10 mg) and midazolam (2 mg) were administered intravenously. Furnishes delayed post-useable absence of pain with less hemodynamic flimsiness in contrast with expansion of intrathecal fentanyl (25 mcg) to a similar portion of bupivacaine.**

Keywords: Bupivacaine, Cesarean section, Fentanyl, Ketamine, General anesthesia, Spinal anesthesia

1. Introduction

Most anesthetists lean toward spinal sedation over broad sedation general anesthesia (GA) in instances of cesarean segment (CS) conveyance, as it stays away from the gamble of yearning that might happen with GA, evades the neonatal depressant impact of GA, and gives postoperative analgesia.[1]

Spinal sedation is the favored method for CS attributable to its advantages of effortlessness, dependability, low paces of aviation route difficulties and yearning, assistance of postoperative absence of pain, and less neonatal openness to possibly depressant drugs.[2]

Bupivacaine, which is the most ordinarily involved drug for spinal sedation, has a slow beginning, high intensity, and somewhat short postoperative absence of pain. The intrathecal (IT) portion of hyperbaric bupivacaine for CS goes from 12 to 15 mg.[3]

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Peritoneal foothold and treatment of intraperitoneal organs during cesarean conveyance lead to intraoperative instinctive agony. Expanding the portion of hyperbaric bupivacaine prompts decrease of the rate of intraoperative instinctive torment, yet on the cost of the chance of the gamble of higher barricade and its unfavorable effects.[4] To keep away from these downsides, various adjuvants have been used.[5]

Therefore, this study aims to compare the hemodynamic effects, onset, level, duration of the intrathecal block, and incidence of complications on adding a mixture of low-dose ketamine and low-dose midazolam to bupivacaine, and on adding fentanyl to bupivacaine during intrathecal injection for CS.

2. Patients and methods

This prospective, randomized, double-blind clinical study was carried out after local ethics committee approval and written informed consent from the patients. Fifty adult females full-term, aged between 20 and 40 years, undergoing elective cesarean deliveries from November 2020 to March 2022. Patients with BMI greater than 30, emergency CS, twins or more, any congenital anomalies of the fetus, allergy to the study medication, and/or any absolute contraindication for intrathecal anesthesia were excluded from the study.

Patients were divided into two equivalent groups, 25 patients each: bunch I (fentanyl-bupivacaine, FB) got 25 μg (0.5 ml) of fentanyl added to 10 mg (2 ml) of hyperbaric bupivacaine 0.5% (sunnypivacaine). Bunch II (ketamine midazolam bupivacaine, KMB) got 10 mg (0.2 ml) of ketamine and 2 mg (0.4 ml) of midazolam (Dormicum, Roche, Switzerland, 5 mg/ml) added to 10 mg (2 ml) of hyperbaric bupivacaine 0.5% (sunnypivacaine). In both groups, the medications were diluted in saline to a total volume of 3 ml.

Preoperatively, all patients were exposed to history-taking, complete actual assessment and research facility examinations, electrocardiogram (ECG) for pulse and musicality, painless estimation of systolic, diastolic, and mean blood vessel circulatory strain (MABP) in mmHg, fringe oxygen immersion (SpO_2%), and oral famotidine 20-mg tablet was regulated with a taste of water 2 h before the medical procedure.

A suitable peripheral intravenous catheter at the dorsum of the hand sized 18 G (two wide-bore cannula) was used to administer spinal anesthesia to patients approximately 10–15 min before the procedure. Lumbar puncture was performed in the sitting position at the L4–L5 or L3–4 intervertebral space using a 25-gauge Quincke spinal needle under complete aseptic technique.

After intrathecal infusion, patients were promptly positioned recumbent with the left uterine dislodging and got 100% O_2 (4 l/min) with facial covering. After the conveyance of the hatchling, oxytocin 20 IU IV was injected at a pace of 1 IU/min.

Information was gathered, coded, updated, and entered to the statistically Bundle for Sociology (Rstudio) adaptation 2.3.2. The data were presented as number and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution and median with interquartile range (IQR) for the quantitative data with nonparametric distribution. Then, the appropriate statistical analyses were applied. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

3. Results

Insignificant statistical difference in weight and age between them (Table 1) statistically diminishing in pulse in bunch I (FB) contrasted with bunch II (KMB) following 5, 10, and 15 min after organization of spinal sedation (Table 2). Statistical decline in MABP (counting both groups I and II) after organization of the spinal sedation in the initial 2 h. Critical decline in MABP in bunch I (FB) contrasted with bunch II (KMB) following 5, 10, and 20 min after organization of spinal sedation (Table 3). Contrasting the two groups with respect to O_2 immersion, there was an immaterial factual distinction between them (Tables 4–7). Bunch I: All out of pain-relieving portion required went from 175 to 320 mg, with a mean worth of 243.8 mg, while in bunch II, complete

Table 1. Comparison between the two studied groups according to demographic data.

	Group I ($n = 25$)	Group II ($n = 25$)	Student t-test
Age (years)			
Minimum–maximum	20–31 years	20–36 years	
Mean (SD)	25.2 (3.1)	25.4 (4.0)	$P = 0.954$
Weight (Kg)			
Minimum–maximum	55–84 Kg	54–82 Kg	
Mean (SD)	67.1 (7.4)	66.5 (8.0)	$P = 0.803$

Table 2. Comparison between the two studied groups according to heart rate.

	Heart rate (beat/min)		Student t-test
	Group I ($n = 25$)	Group II ($n = 25$)	
Before SP heart rate			
Minimum–maximum	77–104	76–105	$P = 0.639$
Mean (SD)	88.8 (7.3)	89.8 (7.0)	
After SP heart rate			
5 min.			
Minimum–maximum	48–92	56–92	**$P = 0.04$***
Mean (SD)	69.7 (11.3)	75.8 (9.4)	
10 min			
Minimum–maximum	49–84	48–92	$P = $ **0.003***
Mean (SD)	69.8 (8.8)	76.2 (10.0)	
15 min			
Minimum–maximum	61–87	62–90	**$P = 0.017$***
Mean (SD)	72.6 (7.2)	77.6 (6.8)	
20 min			
Minimum–maximum	54–86	68–98	$P = 0.07$
Mean (SD)	72.4 (8.9)	77.8 (6.8)	
25 min			
Minimum.–maximum	62–89	62–92	$P = 0.25$
Mean (SD)	80.2 (6.5)	78.4 (7.0)	
30 min			
Minimum–maximum	65–86	68–90	$P = 0.262$
Mean (SD)	79.8 (4.6)	78.5 (5.8)	
45 min			
Minimum–maximum	63–88	70–88	$P = 0.227$
Mean (SD)	78.9 (5.1)	80.5 (5.0)	
2 h			
Minimum–maximum	70–92	66–86	$P = 0.328$
Mean (SD)	79.3 (5.2)	80.1 (4.5)	
4 h			
Minimum–maximum	72–86	64–89	$P = 0.025$
Mean (SD)	79.9 (3.7)	82.1 (5.6)	

Table 3. Comparison between the two studied groups according to mean arterial blood pressure.

	Arterial blood pressure		Student t-test
	Group I ($n = 25$)	Group II ($n = 25$)	
Before SP arterial blood pressure			
Minimum–maximum	83–97	77–97	
Mean (SD)	89.6 (4.3)	88.4 (5.6)	$P = 0.387$
After SP arterial blood pressure			
5 min			
Minimum–maximum	46–90	50–93	
Mean (SD)	67.6 (12.8)	75.5 (12.0)	**$P = 0.044$***
10 min			
Minimum–maximum	45–92	53–90	
Mean (SD)	68.0 (9.7)	75.1 (11.5)	**$P = 0.004$***
15 min			
Minimum–maximum	53–97	53–90	
Mean (SD)	74.5 (11.2)	75.8 (9.1)	$P = 0.722$
20 min			
Minimum–maximum	55–90	70–90	
Mean (SD)	73.0 (9.2)	79.6 (5.3)	**$P = 0.006$***
25 min			
Minimum.–maximum	68–93	70–87	
Mean (SD)	81.0 (6.3)	78.8 (4.8)	$P = 0.258$
30 min.			
Minimum–maximum	75–93	77–93	
Mean (SD)	84.1 (5.6)	82.9 (3.8)	$P = 0.233$
45 min			

(*continued on next page*)

Table 3. (continued)

	Arterial blood pressure		Student t-test
	Group I ($n = 25$)	Group II ($n = 25$)	
Minimum–maximum	77–97	77–93	
Mean (SD)	85.0 (4.1)	83.6 (3.7)	$P = 0.286$
2 h			
Minimum–maximum	80–93	80–93	
Mean (SD)	85.8 (3.1)	86.3 (3.6)	$P = 0.838$
4 h			
Minimum–maximum	83–100	83–97	
Mean (SD)	88.9 (4.3)	87.4 (4.2)	$P = 0.153$

Table 4. Comparison between the two studied groups according to O_2 saturation (%).

	O_2 saturation		Student t-test
	Group I ($n = 25$)	Group II ($n = 25$)	
Before O_2 saturation			
Minimum–maximum	97–100	97–100	
Mean (SD)	98.6 (0.9)	99.0 (0.9)	$P = 0.05$
After O_2 saturation			
5 min.			
Minimum–maximum	97–100	97–100	
Mean (SD)	99.1 (0.8)	99.4 (0.7)	$P = 0.101$
10 min.			
Minimum–maximum	96–100	96–100	
Mean (SD)	98.9 (1.1)	99.3 (1.2)	$P = 0.05$
15 min.			
Minimum–maximum	96–100	97–100	
Mean (SD)	98.9 (0.9)	99.3 (0.9)	$P = 0.067$
20 min.			
Minimum–maximum	97–100	97–100	
Mean (SD)	99.1 (0.8)	99.3 (0.7)	$P = 0.495$
25 min.			
Minimum–maximum	97–100	98–100	
Mean (SD)	99.0 (0.8)	99.4 (0.6)	$P = 0.125$
30 min.			
Minimum–maximum	97–100	98–100	
Mean (SD)	99.1 (0.9)	99.3 (0.6)	$P = 0.447$
45 min.			
Minimum–maximum	98–100	98–100	
Mean (SD)	99.0 (0.7)	99.3 (0.6)	$P = 0.206$
2 h			
Minimum–maximum	98–100	98–100	
Mean (SD)	98.7 (0.8)	98.7 (0.6)	$P = 0.802$
4 h			
Minimum.–maximum	97–100	98–100	
Mean (SD)	98.6 (0.8)	98.9 (0.6)	$P = 0.141$

Table 5. Comparison between the two studied groups according to sensory block.

	Group I ($n = 25$)	Group II ($n = 25$)	Significance test
Sensory onset (min)			
Minimum–maximum	4–10	4–8	**Student t-test**
Mean (SD)	6.2 (1.5)	6.1 (1.1)	$P = 0.758$
Sensory levels			
T3	2 (8.0%)	1 (4.0%)	**Chi-square test**
T4	14 (56.0%)	9 (36.0%)	$P = 0.347$
T5	6 (24.0%)	8 (32.0%)	
T6	3 (12.0%)	7 (28.0%)	
Sensory duration (min)			
Minimum–maximum	90–110	120–160	**Student t-test**
Mean (SD)	99.8 (7.6)	136.8 (11.8)	$P < 0.001$

Table 6. Comparison between the two studied groups according to motor block.

	Group I ($n = 25$)	Group II ($n = 25$)	Student t-test
Motor onset			
Minimum–maximum	6–10	6–8	
Mean (SD)	7.4 (1.4)	7.4 (1.0)	$P = 0.794$
Motor duration			
Minimum–maximum	120–160	130–170	
Mean (SD)	138.8 (10.2)	144.8 (10.0)	**$P = 0.043$***

Table 7. Comparison between the two studied groups according to visual analog scale.

	Group I ($n = 25$)	Group II ($n = 25$)	Mann–Whitney test
Postoperative VAS			
Minimum–maximum	0	0	
Median (IQR)	0	0	–
2 h			
Minimum–maximum	1–3	0–2	
Median (IQR)	1.0 (1.0–2.0)	0	**$P = 0.002$***
4 h			
Minimum–maximum	3–5	2–5	
Median (IQR)	4.0 (4.0–4.0)	3.0 (3.0–4.0)	**$P = 0.003$***
6 h			
Minimum–maximum	2–4	2–5	
Median (IQR)	3.0 (3.0–4.0)	4.0 (3.0–4.0)	$P = 0.654$
8 h			
Minimum–maximum	2–6	2–5	
Median (IQR)	3.0 (3.0–3.0)	3.0 (2.0–3.0)	$P = 0.187$
12 h			
Minimum–maximum	2–6	2–4	
Median (IQR)	4.0 (3.0–5.0)	3.0 (2.0–3.0)	**$P < 0.001$***
16 h			
Minimum–maximum	2–6	2–4	
Median (IQR)	3.0 (3.0–4.0)	3.0 (3.0–3.0)	$P = 0.053$
20 h			
Minimum–maximum	2–4	2–4	
Median (IQR)	3.0 (2.0–3.0)	3.0 (3.0–3.0)	$P = 0.868$
24 h			
Minimum–maximum	2–4	2–4	
Median (IQR)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	$P = 0.537$

Table 8. Comparison between the two studied groups according to analgesia required.

	Group I ($n = 25$)	Group II ($n = 25$)	Student t-test
First analgesia (hr)			
Minimum–maximum	4–6	4–8	
Mean (SD)	4.4 (0.8)	5.5 (1.3)	**$P = 0.001$***
Total analgesia (mg)			
Minimum–maximum	175–320	70–160	
Mean (SD)	243.8 (39.0)	116.8 (27.6)	**$P<0.001$***

pain-relieving portion required went from 70 to 160 mg, with a mean worth of 116.8 mg. Contrasting the two groups, there was statistical factual distinction in the absolute pain-relieving portion expected to keep visual analog scale less than 4. More pain-relieving portion was required in bunch I (FB) contrasted with bunch II (KMB) (Tables 8–11). No statistically tremendous distinction in the sedation score all through the methodology. No statistical contrast between the two groups at Apgar score.

Table 9. Comparison between the two studied groups according to complications' incidence.

	Group I ($n = 25$)	Group II ($n = 25$)	Chi-square test
Complication			
Bradycardia	3 (12.0)	1 (4.0)	$P = 0.014$*
Hypotension	15 (60.0)	8 (32.0)	
Nausea	2 (8.0)	1 (4.0)	
Pruritus	1 (4.0)	0	
Shivering	2 (8.0)	3 (12.0)	
Vomiting	2 (8.0)	1 (4.0)	

Table 10. Comparison between the two studied groups according to sedation score.

	Group I ($n = 25$)	Group II ($n = 25$)	Student t-test
Sedation score beginning			
1	2 (8.0%)	2 (8.0%)	$P = 1$
2	23 (92.0%)	23 (92.0%)	
Minimum–maximum	1–2	1–2	
Mean (SD)	1.9 (0.3)	1.9 (0.3)	$P = 1$
Sedation score after delivery			
2	25 (100.0%)	25 (100.0%)	–
Minimum–maximum	2–2	2–2	
Mean (SD)	2.0 (0.0)	2.0 (0.0)	–
Sedation score after procedure			
2	25 (100.0%)	25 (100.0%)	–
Minimum–maximum	2–2	2–2	
Mean (SD)	2.0 (0.0)	2.0 (0.0)	–

Table 11. Comparison between the two studied groups regarding Apgar score.

	First-minute Apgar score		Fifth-minute Apgar score	
	Group I	Group II	Group I	Group II
Minimum–maximum	7–10	7–10	8–10	8–10
Median (SD)	8.4 (0.9)	8.2 (1)	9.2 (0.7)	9.2 (0.7)
P	0.435		1	

4. Discussion

This study was carried out on 50 parturients aged between 20 and 40 years of the American Society of Anaesthiologists (ASA) physical status I undergoing elective lower segment transverse incision CS of singleton pregnancy at greater than 36 gestational weeks under spinal anesthesia, where they were divided into two equal groups each of 25 parturients.

In the current study, the combination of midazolam and ketamine was used as adjuvants to bupivacaine and compared it with fentanyl, the most used adjuvant to bupivacaine intrathecally in CS, in terms of hemodynamic stability, sensory block, motor block, and postoperative analgesia.

In agreement with this study, Basuni[6] conveyed a concentrate on 50 parturients going through elective CS utilizing midazolam–ketamine blend versus fentanyl as adjuvant to bupivacaine and found that the pulse diminished essentially after intrathecal infusion in bunch fentanyl contrasted with bunch midazolam–ketamine at 10, 15, 20, 25, 30, 45, an hour, and 4 h.

In respect to hemodynamic dependability, we looked at mean blood vessel pulse between the two gatherings, guide was essentially higher in bunch II (KMB) at 5, 10, and 20 min after spinal sedation infusion.

The component of activity prompts more hemodynamic strength, perhaps in light of ketamine, which diffuses into the venous arrangement of the spinal rope and results in cardiovascular feeling that might alienate spinal sedation-actuated vasodilatation.[7]

Murali *et al*.[8] utilized low portion of intrathecal ketamine and midazolam with bupivacaine in spinal sedation in muscular medical procedure and found less hemodynamic unsteadiness in contrast with utilizing bupivacaine alone.

Patel *et al*.[9] added 25 mg of ketamine to intrathecal bupivacaine and contrasted it with intrathecal bupivacaine in patients going through cesarean segment and found that ketamine balances out hemodynamics.

Kathirvel *et al*.[10] found that patients with carcinoma of the cervix going through intracavitary brachytherapy insert (ovoids and couples) inclusion under spinal sedation who got ketamine 25 mg and bupivacaine 7.5 mg had fundamentally higher systolic and diastolic blood pressures at 5 min and 10 min than who got bupivacaine alone after acceptance of spinal sedation.

The equivalent while utilizing midazolam intrathecally, Bharti *et al*.[11] recommend that expansion of midazolam to bupivacaine does not modify hemodynamics.

Karbasfrushan *et al*.[12] contemplated adding intrathecal midazolam to bupivacaine in contrast with intrathecal bupivacaine alone in parturients going through elective cesarean area and showed that intrathecal organization of midazolam did not influence mother's pulse or circulatory strain.

As per oxygen immersion, there was no tremendous distinction between the two gatherings,

patients in the two gatherings got O2 supply by means of breathing apparatus. No genuinely massive contrast between the two gatherings.

In a prior study, Edwards *et al.*[13] reasoned that the antinoception activity of intrathecal midazolam was because of the interceding job of benzodiazepine–GABA receptor complex inside the spinal rope, which improved gamma-aminobutyric acid (GABA) movement in the essential afferent neurons.

In the ongoing review, as per the postoperative aggravation evaluated utilizing the visual analog scale, the aggravation sensation postoperatively was fundamentally lower in bunch II (KMB) than bunch I (FB) at 2, 4, 8, and 12 h postoperative.

Expansion of fentanyl to low-portion bupivacaine can work on the nature of the absence of pain, just in dosages of 40 μg or more prominent during CS. Be that as it may, pruritus has been displayed to increment by half with fentanyl greater than 35 μg, which is a restricting component for expanding the portion of intrathecal fentanyl as mentioned by Kavak et al.[14]

Apgar scores were inside the ordinary reach in all gatherings at one and 5 min. This could be made sense of by the very brief span between the intrathecal infusion and clasping the umbilical line.

Likewise, Petropoulos *et al.*[15] concentrated on the impact of general, epidural, and consolidated spinal–epidural absence of pain as for the transient result of infants conveyed by elective cesarean segment of sound parturients with ordinary pregnancies.

In abdominal hysterectomies, Neelam *et al.*[16] and Prakash *et al.*[17] discovered that intrathecal low-dose ketamine and midazolam mixture with bupivacaine significantly extended the duration of postoperative analgesia. When combined with bupivacaine for cesarean delivery patients, intrathecal midazolam 2 mg was found to moderately prolong postoperative analgesia.

In lower abdominal and lower limb surgeries, Vasanthi and Santha[18] demonstrated that when midazolam is added to spinal bupivacaine as an adjuvant, postoperative analgesia is superior and of higher quality. Abdul Muthalib *et al.*[19] demonstrated that midazolam added to intrathecal bupivacaine significantly extends the duration of postoperative analgesia in perianal and lower limb surgeries. Shadangi *et al.*[20] contrasted the expansion of midazolam with bupivacaine intrathecally to intrathecal bupivacaine alone and tracked down prolongation of postoperative absence of pain.

In the ongoing review, no genuinely massive contrast between the two concentrated on bunches in respect to complexity occurrences with the exception of hypotension.

In concurrence with the current review, Basuni[6] observed that hypotension rate was altogether lower in bunch ketamine–midazolam–bupivacaine with just 24% of patients who were hypotensive through the concentrate in correlation with 72% of patients in bunch fentanyl–bupivacaine, who experienced times of hypotension throughout the review.

In the ongoing review, there was no measurably massive contrast between the two gatherings in respect to sedation on the start of the technique, after the conveyance of the baby and toward the finish of the methodology.

Bion *et al.*[7] Kathirvel *et al.*[10] and Aloka *et al.*[21] involved ketamine in higher dosages (50 mg, 25 mg, and 1.5 mg/kg separately), and showed higher occurrence of neurological and social secondary effects.

4.1. Conclusion

There was significant decrease in the incidence of hypotension in comparison with administration of intrathecal fentanyl with bupivacaine. Sufficient block, prolonged duration of sensory and motor block, and prolonged postoperative analgesia with a small dose of bupivacaine (10 mg) with less complication incidence than administration of fentanyl as an adjuvant to bupivacaine significantly decreased total analgesic doses needed with minimal side effects.

Conflicts of interest

There are no conflicts of interest.

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