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EVALUATION OF THE EFFECT OF KETAMINE AS AN ADDITIVE TOINTRATHECAL BUPIVACAINE IN PATIENTS UNDERGOING CESAREAN SECTION

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ABSTRACT **Background:** Intrathecal ketamine produces a short period of analgesia with stable haemodynamics. The objective of this study was to assess the effect of a combination of intrathecal bupivacaine and ketamine on the duration of analgesia and haemodynamic parameters

Methods: Eighty patients scheduled for cesarean section under spinal anesthesia were randomly allocated to one of the two groups to receive either 0.5% bupivacaine 1.8ml with ketamine 25mg, or 0.5% bupivacaine 1.8ml with 0.5 mL normal saline intrathecally. All patients were evaluated for block characteristics, duration of pain-free period,total rescue analgesic requirement in the 24-h postoperative period ,the incidences of adverse effects such as hypotension, bradycardia,nausea,vomiting,nystagmus and hypoxemia, were recorded.

Results: Patients who received ketamine (group B) showed better hemodynamic stability compared to patients who received only bupivacaine (group A) which is indicated by lesser fall in blood pressure and lesser variation in heart rate.Incidence of hypotension was 17.5% in group B compared to 65% in group A. Time taken to achieve T5 level is more rapid with group B, 6.15 ±1.3311 min in group A and group B was 3.50±1.2403 min in group B which was statistically significant.

Conclusion: A low dose of ketamine with bupivacaine intrathecally results in prolonged analgesia and less haemodynamic fluctuations. However, the safety of this combination needs to be proved with more clinical trials before its use in clinical practice.

KEYWORDS : cesarean section, spinal, intrathecal, bupivacaine,ketamine,haemodynamic stability,analgesia

Anaesthetic care of pregnant patient is unique in that two patients are cared for simultaneously; the parturient and the foetus..There are different methods of anaesthesia and analgesia practiced all over the world. The different methods are general anaesthesia and regional anaesthesia. In regional anaesthesia, epidural and spinal anaesthesia can be given.

General anaesthesia for the caeserian delivery isassociated with relatively greater maternal morbidity and mortality than regional anesthesia[2].Internationally, obstetric anesthesia guidelinesrecommend spinal and epidural than general anesthesiafor most caesarean sections[3].The main reason torecommend regional blocks in obstetrics is the avoidance of the risk of failedendotracheal intubation, aspiration of gastric contents and drug induced neonatal depressionin pregnant women who receive GA[4]. Other added benefits of RA are facilitation of Postoperative analgesia, inherent benefit in some preexisting medical conditions and avoidance of operation theatre pollution[5].

Spinal Anesthesia is more widely practiced anaesthetic technique in caeserian delivery. It is simple to institute, rapid in its effect and produces excellent operating conditions. It also avoids fetal as well as maternal risks of general anaesthesia, requires minimum postoperative anaesthesia care and provides adequate postoperative analgesia[6]Spinal anaesthesia with local anaesthetic agents, especially bupivacaine, has side effects such as hypotension,respiratorydepression,vomiting and shivering in a dose dependent fashion[7].Hypotension is one of the commonest side effectsand can affect both the mother and the fetus or the neonate. Its side effectsare dose dependent, therefore different approaches have been attemptedin order to avoid spinal-induced complication including the use of small dose of bupivacaine [8,9] or by lowering the dose of local anaesthetic andmixing it with additives like neuraxial opioids[10].Administration of neuraxialopiodscauses fetaland maternal side effects like respiratory depression, emetogenesis, and pruritus[11].

Therefore, the searchfor a new drug that may provide better heamodynamic stability and also has minimal side effects seems mandatory.

In previous studies, it was shown that the addition of ketamine to bupivacaine in spinal anesthesia results in stable haemodynamics[12,13].

In obstetrics, ketamine has no detrimental effect on uterine blood flow, and maternal or fetal hemodynamics[14]. Therefore, thesebeneficial effects may be valuable when ketamine is used as an adjunct for spinal anesthesia in obstetric settings.We hypothesized that ketamine might provide better intra operative heamodynamic stability and post-operative pain relief after cesarean section than conventional anesthetic agents. Inaddition, unlike spinal opioids, ketamine does not produce pruritus, respiratory depression, hemodynamic instability, or hyperalgesia. In order to test our hypothesis, we designed this randomized, double-blind, placebo-controlled study to evaluatethe better intra operative heamodynamic stability postoperative, analgesic effects of intrathecal ketamine added to spinal bupivacaine in patients undergoing cesarean section.

AIM AND OBJECTIVES

Aim

The aimof thestudy was to evaluate the effect of intrathecal ketamine (25 mg) in parturients undergoing caesarean section added with bupivacaine (0.5%) inspinal anesthesia.

OBJECTIVES

Onset of block – both sensory &motor
Duration of block – both sensory &motor
Hemodynamic changes
Side effects - nausea vomiting,sedation,nystagmas.
Duration ofpost-operativeanalgesia

MATERIALS AND METHODS

The study was conducted in our institution after obtaining approval from institutional ethical committee and informed written consent from patients who participated in this study.Using closed envelope method,80 consecutive patients undergoing caeseriansection belonging to American society of anesthesiology (ASA) grade 1 or 2, age between 20-35yrs were randomly allocated to one of the two groups.

Exclusion criteria included significant coexisting complicationssuch as hepatorenal and cardiovascular diseases, any contraindication to regional anesthesia such as localinfection or bleedingdisorders, allergy to ketamine.

Prospective double blind study was conducted on 80 parturient andall patients were categorized as group A (control group) and group B (study group).Patients in group A received 1.8cc of 0.5% bupivacaine with normal saline (0.5cc).Patients in group Breceived bupivacaine1 .8cc 0.5% bupivacainealong with 25 mg preservative free Ketamine (0.5cc).Total volume is 2.3cc in both the groups. All patients were connected to standard multiparameter monitor (DASH 3000/4000 monitor by GE medical monitoring systems) to monitor the ECG, non-invasive blood pressure and pulseoximetry. An 18 G or 20 G cannula was inserted in all patients with a free flowing drip of lactated ringer's solution. All cases were preloaded with 5-7 ml/kg of ringer lactate solution, before performing the lumbar puncture.

Lumbar puncture was done by 25 gauge Quincke spinal needle in L3-4 or L4-5 inter-space in sitting position. Spinal anaesthesia was given in group A with bupivacaine 0.5% 1.8ml + 0.5ml normal saline, Group B with bupivacaine 0.5% 1.8ml + ketamine 25 mg(0.5ml).

Left uterine tilt was given using a wedge under the right hip. Sensory level was determined by a pin prick. O_2 6 liters by Hudson mask was administered till the delivery of the baby.Baseline vitals were measured 5 mins prior to subarachnoid block .After performing the blockpulse, NIBP were measured at 2 mins, 5 minutes and every 5 mins for the first 30 minutes and every 10 minutes thereafter. If maternal systolic pressure dropped below 100 mmHg or more than 20% baseline, it was treated with IV fluids and IV ephedrine.Any intra-operative significant bradycardia (less than 60 bpm) was treated with IV atropine.

Sensory block was tested by pinprick at the left midclavicular line till the block reached T6 when the surgical incision will be allowed. The onset of sensory block was defined as the time from the end of injection of the intrathecal anesthetic to the time at which pain at the T10 dermatome was absent; the duration of sensory block was defined as the time from the maximum block height (T5) to the T10 dermatome to regression of block, as evaluated by the pinprick test after 20 minutes following the completion of injection.Degree of motor block was assessed by using modified Bromage scale (BS). Motor block wasassessed by the modified Bromage score (0 -no motor loss;1 - inability to flex the hip; 2 - inability to flex the knee; and3-inability to flex the ankle); the onset of motor block was definedas the time fromintrathecal injection to Bromage block one,whereas the duration of motor block was assumed when themodified Bromage score was zero. Assessment of sensoryblock onset time, maximum sensory level, onset of motor block,duration of blockade, hemodynamic variables, the incidence ofhypotension, ephedrine requirements, bradycardia, hypoxemia (saturation of peripheral oxygen < 90), pruritus, nausea, andvomiting, sedation and the onsetof postoperative pain were recorded. Theduration of spinal anesthesia was defined as the time from injectionof spinal anesthetic to the first occasion when the patient complained of pain in the postoperative period. Visual analogue scale wasused for evaluatingpain.

IM Injection Diclofenac, 75 mg given as rescue analgesic when the VAS >=4. Injection Tramadol 100 mg IM, given after one dose of Diclofenac.Number of rescue analgesics in 24 Hours of post-operative period was recorded.Apgar score of all the babies at 1, 5 and 10 minutes and maternal depression were also recorded.

All patients were followed after surgery up to 24 hfor any behavioural side-effects, confusion, dizziness, nystagmus, nausea, vomiting or any neurological complications like pain or numbness in theopposite leg, incontinence or retention of bowel or bladder or genital dysaesthesias.

RESULTS

Eighty pregnant patients belonging to ASA I and II aged between 20-35 years, posted for caeseriansurgery under spinal anaesthesia were selected for the study. The study was undertaken to evaluate the efficacy of Ketamine (25mg) as adjuvant to Bupivacaine (0.5%) in comparison with plain Bupivacaine (0.5%),intra-thecally.

There were no significant differences in age, height, and weight between the two groups.The duration of surgery was also similar inthe two groups (Table 1).

Table1.Patient Characteristics

VARIABLES	GROUP A	GROUP B	P VALUE
AGEIN YEARS	25.7±3.94	25.5±3.48	0.857
WEIGHT IN KG	63.52±5.32	63.55±6.65	0.985
HEIGHT IN CM	157.7±5.20	157.05±5.19	0.577
DURATION (HRS)	1.01±0.15	0.97±0.22	0.345

The mean time to reach highest level of sensory block (T5) in group A 6.15 ±1.3311 min and in group B was 3.50±1.2403 min which was statistically significant.Time to reach T5 level is more rapid with group B.

The mean duration of sensory block in group A was 2 hrs 52 mins and group B 3hrs 27 mins.therefore mean duration of sensory block in group B is higher than group A.mean duration of motor block was 2.46 hrs in group A and 2.52 hrs in group B. In this study, there is no significant difference on duration of motor block between two groups. Since the spinal analgesia time is more for group B, requirement of post-operative analgesia is less in group B over 24 hours (graph 2).Despite volume loading prior to anesthetic block, transient hypotension occurred at various time points in the two groups. Incidence of hypotension with group-A was 26 times while with group-B was only 7 times (table 6, graph 1). This is a very significant advantage with group-B. These patients were treated with 5 mg boluses of intravenous ephedrine to maintain the fall of SBP within 20% of thebaseline value or at 90 mmHg.

Haemodynamicvariables (SBP, DBP,MAP, tables 2,3,4)were statistically significant at 5 and 10 minutes interval.

Systolic B.P at 5 mins in group A and group B was 93.5±13.6 mmHg and 104.3±8.81 mmHg.

Systolic B.P at 10 mins in group A and group B was 95.7±11.5 mmHg and 103.5±8.17mmHg.

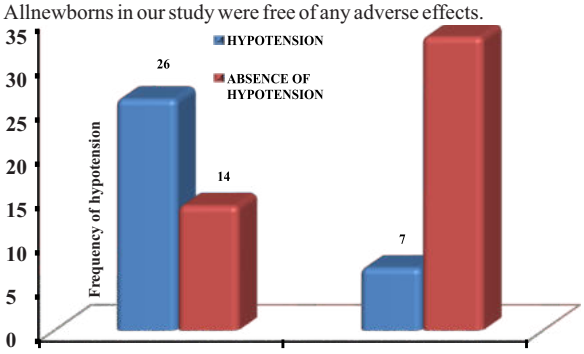
Diastolic B.P at 5 mins in group A and group B was 48.6±10.2mm Hg and 60.9±10.1mmHg.

Diastolic B.P at 10 mins in group A and group B was 52.3±9.77mmHg and 56.6±7.65 mmHg.

MAP at 5 mins in group A and group B was 63.3±10.9mmHg and 74.6±7.62mm Hg.

MAP at 10 mins in group A and group B was 66.7±9.74mmHg and 72.7±6.67 mmHg.

As shown in table 6, the two groups did not differ significantly in intraoperative and postoperative side effects including pruritus, nausea, vomiting, headache, shivering, and respiratory depression. Allnewborns in our study were free of any adverse effects.



Graph 1: Incidence of Hypotension in both the groups

Table 2: Changes In Systolic Blood Pressure

TIME (MIN)	GROUP A	GROUP B	P VALUE
BASIC	118.8±8.86	120.4±10.9	0.473
2	108±8.15	108.5±9.39	0.790
5	93.5±13.6	104.3±8.81	0.000*
10	95.7±11.5	103.5±8.17	0.001*
15	101.1±10.9	104.1±7.14	0.159
20	102.1±5.83	103.1±6.22	0.438
30	103.2±7.66	104.5±6.45	0.405
40	104.6±5.99	104.7±6.36	0.957
50	104.4±3.47	104.7±6.77	0.087
60	105.1±3.59	106.8±7.13	0.197
75	106.2±3.96	112.7±10.4	0.210
90	109.5±4.95	109.5±6.36	1.000

Table 3: Changes In Diastolic Blood Pressure

TIME (MIN)	GROUP A	GROUP B	P VALUE
BASIC	72.02±10.1	70.2±9.75	0.414
2	59.2±9.37	59.3±9.85	0.945
5	48.6±10.2	60.9±10.1	0.000*
10	52.3±9.77	56.6±7.65	0.034*
15	57.9±8.78	57.7±8.52	0.887
20	55.2±6.88	56.7±6.28	0.312
30	55.5±7.86	57.2±6.57	0.297
40	58.7±7.51	56.4±7.75	0.177
50	58.7±7.77	59.3±10.6	0.781
60	59±6.48	58.9±8.80	0.961
75	60±10.3	65.6±9.66	0.341

Table 4: Changes In Map

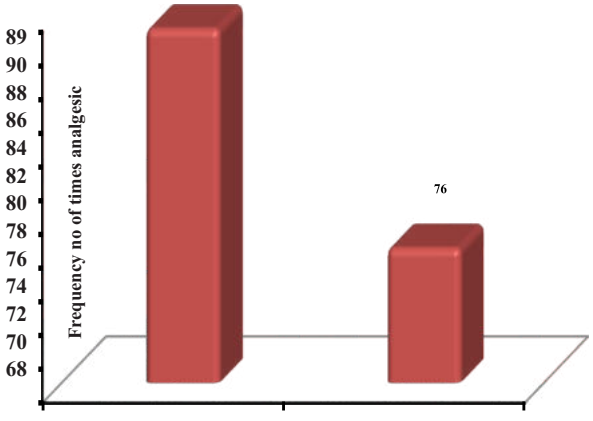
TIME (MIN)	GROUP A	GROUP B	P VALUE
BASIC	87.5±8.72	85.9±10.6	0.463
2	75.1±7.85	75.6±8.93	0.771
5	63.3±10.9	74.6±7.62	0.000*
10	66.7±9.74	72.7±6.67	0.002*
15	72.6±8.79	73.1±7.16	0.792
20	71±5.97	72.7±5.45	0.175
30	71.5±6.47	72.9±5.58	0.312
40	73.7±5.44	72.5±6.29	0.345
50	73.8±6.34	73.7±6.73	0.955
60	74±4.52	73.8±7.10	0.915
75	76.2±8.68	77.4±10.1	0.834
90	83±5.66	71.5±3.53	0.135

Table 5: Changes In The Heart Rate

TIME (MIN)	GROUP A	GROUP B	P VALUE
BASIC	100.1±6.0	97.9±10.3	0.247
2	107.9±6.01	97.6±10.4	0.000*
5	100.7±5.39	101.2±9.13	0.744
10	87.6±5.53	95.8±6.15	0.000*
15	85.2±4.71	94.4±3.95	0.000*
20	79.1±6.79	90.4±4.57	0.000*
30	77.7±5.55	86.7±4.39	0.000*
40	72.7±6.16	79.2±3.86	0.000*
50	71.1±6.86	75.8±3.87	0.000*
60	72.9±7.64	75.6±3.47	0.064
75	75.4±8.35	75.6±6.09	0.956
90	67±4.24	76±0	0.095

Table 6: Complications

COMPLICATION	GROUP A	GROUP B	Chi square	P – Value
Nausea	7	8	0.082	0.775
Vomiting	2	4	0.721	0.396
Shivering	11	3	5.541	0.018*
Nystagmus	0	5	5.333	0.021*
Sedation	4	12	5.000	0.025*
Bradycardia	1	0	1.013	0.314
Hypotension	26	7	18.620	0.000*



Graph 2: Total number of analgesic intervention of both the groups

DISCUSSION

Based on the data found in the present study, it could beconcluded that in Group B the administration of intrathecal ketamine with spinal bupivacaine could provide better hemodynamic stabitity compared to group A as indicated by lesser fall in blood pressure , lesser variation in heart rate and also lesser incidence of hypotension in group B compared to group A(table 2,3,4,5) .This finding is consistent with MuraliKrishna et al[15],Ila Patel et al[18] concluded a similar finding in their study of 60 patients for LSCS[18]. Kathirvel S, Sadhashivam S, SaxenaA, et al[16] found that requirement for intravenous fluids in the perioperative period were less in the ketamine group. Togal, S. Demirbilek, A. Koroglu, et al[17] studied intrathecal ketamine with bupivacaine for prostate surgery in elderly patients and observed that lack of cardiovascular depression with intrathecal ketamine, provided definite advantage in an elderly population.

The second observation in our study was that the time taken to achieve T5 level is more rapid with group B than group A.Similar findings were recorded by Singh et al andUnlugenc et al. Singh SP, Sinha AK, Jha AK[1] studied preservative free ketamine (50 mg) mixed with 2 – 2.5 ml of 0.5% bupivacaine and injected intra-thecally. They found that mixture produced quick sensory loss. UnlugencH, Ozalevli M. Gunes Y, etal[19] studied the double-blinded comparison of intrathecalS (+) ketamine combined with bupivacaine 0.5% for caesarean delivery. In patients undergoing caesarean section with spinal anesthesia, the addition of S (+) ketamine (0.05 mg/kg) to 10 mg of spinal plain bupivacaine (0.5%) lead to rapid onset of sensory blockade and enhanced the segmental spread of spinalblock. Khezri[20] et al noted that the administration of 0.1 mg/kg intrathecal ketamine with spinal bupivacaine prolonged the onset of sensory block. However, these apparently controversial results may be due to thedifferent populations, doses of ketamine, and methodologies .Our third observation from the study was that the duration of sensory block was prolonged and thereby the requirement of post-operative analgesics was lesser in group B compared to group A (graph 2). The duration of sensory block in group A and group B was 2 hours 52 min; 3 hours and 27 min respectively. Therefore the duration of sensory block in Group B is higher than Group A. Similar findings was observed by Yang et al, Singh et al and Bhattacharya et al also. Post operatively, total consumption of analgesics in 24 hrs was less with group B. This finding is consistent with Khezri et al [20].

In our study, there is no significant difference on duration of motor block between two groups. Similar finding was noted in Ila Patel et al study as well. Where as in the study conducted by Khezri et al[20], it was observed that there was prolongation of the duration of motor block but sensory block was unaffected.

In the present study,it was observed that the incidence of nausea,vomiting and sedation was more with group B than in group A which is similar to that found in Kathirvel et al[(16)] and Ila Pateletal[18].

It was observed that all newborns in our study were free of any adverse effects. In conclusion, the addition of preservative-free ketamine to bupivacaine intrathecally in caesarean section decreases the onset of block, providesstable hemodynamics with fewer fluctuations in blood pressurethough the duration of postoperative analgesia was not significantly prolonged but it improves the quality of analgesia in post-operative period.

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