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Original Research Article

Subanesthetic Dose of Intravenous Ketamine for Post Cesarean Delivery Analgesia in Spinal Anesthesia Prospective Randomized Study

Shaikh Abdul Nasir[1], Hiral Ranchhodbhai Chavda[2], Chethan L B[3], Ravi Bathia[4], Kiran Rathod[5]

[1]Associate Professor, Department of Anaesthesia, PDU Medical College, Rajkot
[2]Assistant Professor, Department of Anaesthesiology, M P Shah Medical College, Jamnagar
[3]Third Year Resident, Department of Anaesthesiology, M P Shah Medical College, Jamnagar
[4]Senior Resident, Department of Anaesthesia, PDU Medical College, Rajkot
[5]Second Year Resident, Department of Anaesthesia, PDU Medical College, Rajkot

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Corresponding Author: Dr. Ravi Bathia
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Abstract

Poor pain control after caesarean section may interfere with walking, breastfeeding, early attention and nutritional care of the newborn. Multimodal therapy for postoperative analgesia blocks multiple pain pathways. Use of opioid-free analgesia should be preferred in the perioperative period to reduce adverse effects like nausea, vomiting, pruritus, and respiratory depression. Tissue trauma causes central sensitization of the spinal dorsal horn neurons through N-methyl-D aspartate (NMDA) receptor-related mechanisms which in turn produces secondary hyperalgesia. Ketamine is a selective noncompetitive NMDA receptor antagonist. Also, it reduces pain by reducing the NMDA receptors, mediated secondary pain.

Aims and Objectives: To study the Subanesthetic dose of intravenous ketamine for post caesarean delivery analgesia, haemodynamic changes intra-operatively, Total doses of analgesia in 24 hrs. APGAR score after delivery of baby, Time of first rescue analgesic agent given, Adverse effects intraoperatively and postoperatively 24 hours, Ramsey sedation scale and Patients satisfaction during postoperative period.

Material and Methods: 60 females with age group of 18-35 years undergoing cesarean delivery were included and divided. Group A and Group B(n=30): Inj. Bupivacaine 0.5% heavy 2.2cc intrathecally given. After 5 minutes of baby delivery Inj. ketamine 0.2mg/kg intravenously in A group and Saline 0.9% in Group B.

Results: No significant changes in demographic parameters, APGAR score and hemodynamic parameters in both the groups. VAS scores were lower in ketamine group than another group. Higher incidence of nausea vomiting in ketamine group. No patient had Ramsey sedation score more than 2 in both groups. All patients were satisfied for analgesia in ketamine group. Time for rescue analgesics were prolonged in ketamine group.

Conclusion: Subanesthetic doses (0.2 mg/kg) of intravenous ketamine after 5 minutes of baby delivery leads to enhanced postoperative analgesia without any significant side effects, additional benefit in increasing the time to first postoperative rescue analgesic request with excellent satisfaction for postoperative pain.

Keywords: Subanaesthetic dose of Ketamine, Vas score, Post operative analgesia.

Introduction

Pain is one of the most important challenges for the women and health care providers after caesarean delivery. Poor pain control after caesarean section may interfere with walking, breastfeeding, early attention and nutritional care of the newborn. Therefore, effective pain management in women after caesarean delivery is vital and improves the overall quality of life.

Multimodal therapy for postoperative analgesia blocks multiple pain pathways while minimizing side effects of each individual pain medication. Various drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, tramadol, local anaesthetics, and α-2 receptor agonists have been used to control the postoperative pain following CS. Use of opioid-free analgesia should be preferred in the perioperative period to reduce adverse effects like nausea, vomiting, pruritus, and respiratory depression.

Tissue trauma causes central sensitization of the spinal dorsal horn neurons through N-methyl-D aspartate (NMDA) receptor-related mechanisms which in turn produces secondary hyperalgesia. Ketamine is a selective noncompetitive NMDA receptor antagonist. Also, it reduces pain by reducing the NMDA receptors, mediated secondary pain.

Many studies have been done to evaluate the effectiveness of the subanesthetic dose of intravenous ketamine in spinal anesthesia post caesarean delivery analgesia.

Materials and Methods

The present study, a type of prospective study was carried out with 60 adult female pregnant patients in the age group of 18-35 years who are undergoing cesarean delivery are selected after taking Institutional Ethical Committee clearance. While for patients written informed consent are taken in their own language according to institutional protocols and explaining the advantages and disadvantages, consequences of the study process.
60 patients of ASA grade I,II and III belonging to the age group of 18-35 years old females undergoing cesarean delivery surgery. Patients were equally divided into 2 groups by randomisation by double blinding through envelope method given same volume of drug in both groups:

Group A (n=30): Inj. Bupivacaine 0.5% heavy (12.5mg) 2.2cc intrathecally given.

After 5 minutes of baby delivery Inj.ketamine 0.2mg/kg is diluted up to 5ml with normal saline 0.9% and is given intravenously.

Group B (n=30): Inj. Bupivacaine 0.5% heavy (12.5mg) 2.2cc intrathecally given.

After 5 minutes of baby delivery Inj. Normal saline 0.9% of 5ml is given intravenously.

Rescue analgesia of inj Diclofenac sodium 1.5mg/kg (75mg) given intramuscular if VAS score is >4. All patients were thoroughly assessed for history and examined in detail; both general and systemic examinations. All subjects fulfilling the inclusion criteria were explained about the purpose, procedure, and side effects of the medications. Informed consent was obtained from them. Venous access was obtained, basic monitors were attached like NIBP, pulse oximetry, ECG and vitals of the patient were recorded.

Inclusion Criteria: Age – 18 – 35years ASA grade - 1,2,3 Patient approval

Undergoing cesarean surgery

Exclusion Criteria

Patient refusal: ASA grade IV and more Sensitivity to the local anaesthetics and ketamine. Age <18 years or >35 years Contraindications to spinal anesthesia- bleeding diathesis, local skin infections, neurological diseases, cardiac or renal insufficiency Contraindications of ketamine use such as significant high Blood pressure and tachycardia, cardiovascular diseases like vessel aneurysms, ischemic heart disease.

History of convulsions, psychiatric illnesses like schizophrenia and features of increased Intracranial pressure. Any history of alcohol, opioid or psychiatric drug intake.

Results

The present study was conducted in the department of Anaesthesiology, Government Hospital during the period of 2020 to 2023 for 3 years.

It was a Prospective Randomized control trial of 60 female pregnant patients who by assessment come under ASA grade I, II and III and also have completed term (37weeks) gestation undergoing caesarean section delivery under spinal anaesthesia.

Table 1: Demographic Characteristics

Parameter	Group A	Group B	Inter group p value
Number of patients	30	30	0
Age (years) (Mean ± SD)	24.93 3.67	25.63 3.85	>0.05
Weight (kg) (Mean ± SD)	58.73 4.79	59.03 3.95	>0.05
Height (cm) (Mean ± SD)	164.66 5.68	163.26± 4.47	>0.05

Both the group were well matched in terms of age, weight, and height. No statistically significant difference was found in both groups. (P>0.05)

Table 2: VAS Score at Rest (MEAN_ SD) in hours

	Group A	Group B	P value
0 hours	0	0	
4 hours	1.13 1.01	3.53 0.89	<0.05
5 hours	2.00 00	2.53 0.9	<0.05
6 hours	3.97 0.18	2.07 0.37	<0.05
12 hours	2.03 0.18	3.85 0.54	<0.05
14 hours	3.97 0.18	2.22 0.67	<0.05
20 hours	2.10 0.31	3.8 0.61	<0.05
24 hours	3.87 0.51	2.2 0.61	<0.05

Table 3: First Rescue Analgesic Time (in Hours)(MEAN_SD)

Group A	Group B	p- value
5.67+0.23	4.21+0.44	<0.001

Time for first rescue analgesic dose was significantly prolonged in group A than group B

Table 4: Total Doses of Rescue Analgesia in 24 Hrs. (Mean_SD)

Group A	Group B	p- value
3.0 ± 0	3.03 ± 0.18	>0.05

Table 5: APGAR Score Recorded at 1 min and 5 Mins After Delivery of Baby

	Group A	Group B	P value
1 min	8.2 ± 1.67	8.93 ± 1.28	>0.05
5 min	9.43 ± 0.86	9.8 ± 0.61	>0.05

No significant changes in APGAR Score was noted in both the groups.

No significant changes were noted in pulse rate, Systolic blood pressure, Diastolic Blood pressure, Oxygen Saturation.

Table 6: Incidence of Adverse Effects and Complications

Complication	Group A	Group B
Bradycardia	0	0
Hypotension	0	0
Tachycardia	0	0
Shivering	0	0

In Group A all patients are said to be satisfied for analgesia while in Group B only 4 patients are satisfied while the rest 26 patients are not satisfied with adequate analgesia throughout 24 hours.

Discussion

The aim of good post-operative analgesia is to produce a long lasting, continuous effective analgesia with minimum side effects. The benefits of adequate postoperative analgesia are clear, and include a reduction in the postoperative stress response, reduction in postoperative morbidity, and improved surgical outcome. Effective pain control also facilitates rehabilitation and accelerates recovery from surgery. A multimodal analgesic regimen is most likely to achieve these goals. However, the optimal components of this regimen continue to evolve. Although single- shot neuraxial analgesic techniques using long- acting opioids, or patient- controlled epidural opioid administration produce effective analgesia but they are associated with a frequent incidence of side effects. IV patient-controlled analgesia (PCA) morphine facilitates a greater degree of patient control, and thereby results in high patient satisfaction levels, the analgesia produced is often incomplete, and opioid- mediated side effects remain common.

Ketamine exerts its analgesic property in acute pain through reversible antagonism of N-methyl D- aspartate receptors and its effect on μ opioid receptors, muscarinic receptors, monoaminergic receptors and γ- aminobutyric receptors and possesses least psychomimetic effects and in preventing shivering [2,4,5].

Various studies have reported that low dose of IV ketamine (≤0.3 mg/kg) are effective in reducing the analgesic requirements in first 24 hrs after surgery. [3,6,7,8]

Our Present study was a prospective randomized controlled trial, which consisted of 60 patients with ASA grade I, II and III, undergoing caesarean section under spinal anaesthesia. The patients were randomaly assigned, on the basis of double blinding concealed by envelope method.

By above method, the study population was randomly divided in to two groups.

The two groups of our study are:

Group A (n=30): Inj. Bupivacaine 0.5% heavy (12.5mg) 2.cc intrathecally After 5 minutes of baby delivery Inj. ketamine 0.2mg/kg is diluted upto 5ml with normal saline 0.9% and given intravenously.

Group B (n=30): Inj. Bupivacaine 0.5% heavy (12.5mg) 2.2cc intrathecally After 5 minutes of baby delivery Inj. Normal saline 0.9% of 5ml is given intravenously. Rescue analgesia inj Diclofenac sodium 1.5mg/kg IM if VAS score>4. After completion of study observation and results were analyzed statistically using software SPSS (ver. 26.0). Student T test was applied for comparing the inter group results and the p value obtained Statistical significance was assumed at P<0.05.

Demographic Data

Both the groups were comparable with each other with respect to age, weight, height physical status.

The mean age of patients was 24.93 ± 3.67 years in group A and 25.63 ±3.85 years in group B. The mean weight of patients was 58.73 ± 4.79 Kg in group A and 59.03 ± 3.95 kg in group B. The mean height of patients was 166.53 ± 6.57 cm in group A and 164 ± 2.45 cm in group B.

Our study in this regard of Age, weight and height

of the patients are in consonance with the studies of Mojan Rahmanian et al [10] where he compared age and weight in 2 groups while Bhiwal AK et al [9], who had taken 3 groups compared age, weight and height, p value is > 0.05 which are comparable with 2 groups as in our group.

Haemodynamic Changes Intra-Operatively

In our study the Pulse, Systolic BP, Diastolic BP and SPO2 Mean SD of both groups are calculated, and p value is obtained which is >0.05 for each of them and hence there is no significant effect of ketamine in Group A when compared to Group B in view of Hemodynamic changes.

The same is obtained in other studies such as Bhiwal AK et al [9] who had 3 different groups and observed no significant difference in mean arterial pressure (MAP), HR intraoperatively at different time intervals between the three groups. The incidence of hypotension and requirement of ephedrine was also found to be statistically non--significant.

Similarly as in adhikari et al[1] they are comparable VAS Score at Rest.

In our study, VAS score at rest in both groups was 0 at 0 hour. It was statistically insignificant(P>0.05). Subsequently, In group A, VAS score at rest was < 4 at 4 hours but increases to >4 between 5-6 hours in patients and consequently at regular intervals of 6 hours, where rescue analgesia is given at VAS>4.In group B, VAS score is > 4 at 3.5- 4.5 hours and consequently at regular intervals of 6 hours. These regular intervals are observed because the rescue analgesia is given whenever VAS score is > 4 which has a half-life of 6 hours.

As patients are assessed for VAS at 0,4,5,6,12,14,20,24 hours, there were statistically significant difference found at each time in both groups by p value to be < 0.05, this is observed because 1st rescue analgesic given time differs greatly with respect to both A and B groups even though rescue analgesia is given regularly at 6 hours duration thereafter which is observed by VAS score>4 every 6 hours post initial rescue analgesia.

In Bhiwal AK et al[9] study 3 groups are taken and they are divided as Group C, who received 2 ml of 0.9% normal saline; Group Ka, received 0.15 mg/kg of ketamine (2 ml) and Group Kb, received 0.3 mg/kg of ketamine (2 ml) Intravenously after 5 mins of baby delivery who were induced with spinal anesthesia, post op pain was evaluated by VAS score at 2,6,10,12,24 hours and rescue analgesia as tramadol 100 mg iv given when VAS>4, it was found to be highly statistically significant between the three groups after 2 h (P < 0.001) and statistically significant after 10 h and 12 h (P < 0.05) but there was no significant difference in VAS score at 6 h and 24 h among the three groups (P > 0.05) Adhikari et al [1] study, NRS score is used to obtain assessment of pain post operatively

During the stay at the Post anesthesia care unit (PACU; On arrival, 1 and 2hours thereafter), if NRS score was >3, the patient received IV fentanyl 15µg, and it was repeated every 5min until NRS was ≤3. In the postoperative ward (6, 12, and 24 hours) intravenous morphine 2mg was administered for NRS score >3, and it was repeated until NRS≤3.

Results were that Significant differences between the two groups in terms of postoperative pain scores at rest were observed only at 2hours and 6 hours. Likewise, the pain scores during movement between the two groups were significant at 2hours and 6hours after surgery.

This is comparable with our study as in our group A(Ketamine) group had mean SD of at 4,5,6 hours are 1.13, 1.01, 2.00, 3.80018.

However, after adjustment for multiplicity (p=0.008), the difference in the pain scores after surgery between the two groups was only significant at 2 hours at rest and 2hours and 6hours during movement. The median (range) time to the first perception of pain in the KET group was 6 (1–12) hours whereas in the NS group this period was reduced to 2 (0.5– 6) hrs(p<0.001).

First Rescue Analgesic Time

we have used rescue analgesia when VAS score is > 4, Inj Diclofenac sodium 1.5mg/kg is given intramuscular postoperatively. In our study, Mean_SD of 1st rescue analgesia was 5.67 0.23 hrs. in group A and 4.21 0.44 in group B. It is found to be highly significant statically (p < 0.001).

In Bhiwal et al [9] study the time to the first analgesic requirement (hours) was prolonged in Ka (0.15mg/kg) group (5.44 ± 1.45) and Kb (0.3mg/kg) group (6.18 ± 1.61) as compared to the control group (4.97 ± 1.48) and was found to be statistically significant (P < 0.05). This results are similar to our study results.

Total doses of Rescue analgesia in 24 hrs

In our study mean SD of total doses given in first 24 hours is 3.03 0.18 in group B and 3.0 0.0 in group A hence in our study there is no statistically significant difference found in both groups.(P> 0.05).This is observed because after 1st rescue analgesia dose every 6 hourly there is VAS score>4 and hence rescue analgesia is given which signifies sub anesthesia dose used is having effects up to first rescue analgesia given time , thereafter ketamine is not that prominent analgesic afterwards which is explained and justified by measuring blood levels of ketamine at different intervals done by clinical trials like in Domino et al [11] studies, it can also explained by Low dose IV ketamine used in our study may have reduced pain and delayed the onset of central sensitization. Although this effect of ketamine may be due to antagonism of spinal NMDA receptor sites, it can also act on sev-

eral opioidergic and cholinergic receptor types but the development of secondary hyperalgesia is induced by peripheral sensitization when facilitation of A-α and A-β nerve fibers occurs which by chemical mediators continue to be released following the initial insult, their effects must be prevented for a longer time than the duration of action of single dose of analgesia administered. Overall ketamine if given in pre incision time, it's analgesia action is more pronounced.

Study done by Bhiwal AK et al[9] showed that the total dose of rescue analgesic required in 24 hours was less in the Ka(0.15mg/kg) group and Kb(0.3mg/kg) group as compared to the group C(NS) which was found to be highly statistically significant (P < 0.001). However, when Ka and Kb group was compared the significant difference was found only in time to first analgesic request (P =0.045), this is because the rescue analgesia used was Inj Tramadol(100mg) which is an opioid and also used diclofenac sodium suppository, a multimodal analgesia.

Similarly in Adhikari et al[1] study The median (range) time to the first perception of pain in the KET group was 6 (1–12) hours whereas in the NS group this period was reduced to 2 (0.5–6) hours (p<0.001). The difference is very much more significant than our study because of following 2 reasons 1) used fentanyl 10 ug intrathecally in spinal anesthesia as an adjuvant along with Bupivacaine heavy 0.5% 2.5cc. 2) NRS score is used when >3, rescue analgesia is given. Though the study results differ in both of our study statistically; the goal of the study of ketamine at subanesthetic dose has decreased the time for 1st rescue analgesia request is achieved in both of our study.

In our study Mean SD of total doses given in first 24 hours is 3.03 0.18 in group B and 3.0 0.0 in group A hence in our study there is no statistically significant difference found in both groups.(P> 0.05).This is observed because after 1st rescue analgesia dose every 6 hourly there is VAS score>4 and hence rescue analgesia is given which signifies sub anesthesia dose used is having effects up to first rescue analgesia given time, thereafter ketamine is not that prominent analgesic afterwards which is explained and justified by measuring blood levels of ketamine at different intervals done by clinical trials like in Domino et al[11] studies, it can also explained by Low dose IV ketamine used in our study may have reduced pain and delayed the onset of central sensitization. Although this effect of ketamine may be due to antagonism of spinal NMDA receptor sites, it can also act on several opioidergic and cholinergic receptor types but the development of secondary hyperalgesia is induced by peripheral sensitization when facilitation of A-α and A-β nerve fibers occurs which by chemical mediators continue to be released following the initial insult, their effects must be prevented for a longer time than the duration of action of single dose of analgesia administered. Overall ketamine if given in pre incision time, it's analgesia action is more pronounced.

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APGAR score recorded at 1 and 5 mins after delivery of baby in our study APGAR scores at 1 min and 5 mins of group A was 8.20, 1.67 and 9.43, 0.86 while group B was 8.43, 0.87 and 9.00 2.61 for which the p value is >0.05 and hence is statistically non-significant.

This is explained and is obvious because the sub anesthetic dose given is after 5 mins of baby delivered, ketamine crosses the placenta rapidly with mean fetal-maternal ratio of 1.26 following an intravenous induction dose of anaesthesia. As a result, concern has been expressed as to whether ketamine administered in clinical doses at the time of delivery produces neurotoxic effects in newborns. But studies have shown ketamine administered at 1mg/kg intravenous in parturient did not worsen the newborn acid-base status by Maduska AL et al [13] and Nayar R, Sahajanand H.[12] did comparison to either thiopentone anaesthesia or placebo group with ketamine for its effect on fetus by APGAR scores at 1mg/kg ketamine intravenously.

Incidence of adverse effects and complications

In our study group 3 patients had experienced nausea and vomiting separately in group A and 4 patients had nausea and 3 patients had vomiting in group B, they are shown to be statistically non-significant (p value<0.05) while other symptoms such bradycardia, hypotension, tachycardia, shivering were not recorded by any patients in 24 hours.

In Bhiwal AK et al [9] study the incidence of post-operative nausea and vomiting (PONV) was found higher in control group (38%) than the Ka (25%) and Kb (19.4%) group, but the difference was statistically nonsignificant (P = 0.14), there were incidence of 2 patients reporting disturbed dreams in group kb(0.3mg/dl) as because the dose given is more since other group patients didn't complained as such.

While in Adhikari et al[1], Mojgan Rahmanian, et al.[10] had similar results as our study. Mojgan Rahmanian, et al.[10] showed a greater prevalence of hallucination in the ketamine group. Difference

is due to differences in the type of anesthesia, Ramsey sedation scale and Satisfactory level of patients for analgesia In our study in Group A, 3 patients had RSS 1 while 27 patients had RSS 2 with Mean SD of 1.90 0.31 while in group B, 21 patients had RSS 1 and 9 patients had RSS 2 with Mean SD of 1.27 0.45. p value is less than 0.001 and hence highly significant.

RSS 1 scale means patients who are anxious and agitated or restless or both, while RSS 2 means patients who are Co-cooperate, oriented and tranquil, that is ketamine group only 3 patients are either anxious, agitated or restless while rest all are oriented, tranquil which shows patients are adequately satisfied with pain, this can be explained by CNS depression activity by ketamine. In both groups None of the patients had RSS greater than 2, which signifies no significant adverse effects of ketamine.

In Group A all patients have said to be satisfactory for analgesia while in Group B ,4 patients are satisfied while rest 26 patients are not satisfied with adequate analgesia throughout 24 hours.

The similar results are seen in Bhiwal et al [9], Adhikari et al [1], Mojgan Rahmanian, et al.[10]

There are some limitations in our study. We could not assess the efficacy of subanesthetic doses of ketamine for preemptive analgesia. We did not measure central sensitization as we recorded pain scores only in the immediate postoperative period up to 24 h following surgery. We did not find out how ketamine might affect different components of pain as global pain scores. We did not study antidepressant effects in the postpartum period. Mood-altering effect of ketamine and its effect on chronic post CS pain can also be studied in future.

Conclusion

Administration of subanesthetic doses (0.2 mg/kg) of intravenous ketamine after 5 minutes of baby delivery in our study enhanced postoperative analgesia in women undergoing cesarean delivery under spinal anesthesia without any significant side effects following ketamine injection, with an additional benefit offered by in increasing the time to first postoperative rescue analgesic request with excellent satisfaction for postoperative pain.

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