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Ketamine as a pre-emptive analgesia in patients undergoing caesarean delivery under spinal anesthesia

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ABSTRACT

BACKGROUND & OBJECTIVES: Lower segment caesarean section (LSCS) leads to moderate to severe pain in the patient. Pain severity is directly proportional to the functional limitations and depression in the postpartum period, making it essential to provide good pain relief after surgery. Maternal wellbeing and better nursing care of newborn requires good postoperative analgesia with minimal side effects. The main objective of the study was to evaluate the analgesic effect of intravenous low-dose ketamine, when administered pre-emptively, in patients undergoing caesarean delivery under spinal anesthesia.

METHODOLOGY: Two groups were made, each with 50 full-term pregnant females with a plan of caesarean section under spinal anesthesia. Group-A received spinal anesthesia with bupivacaine 0.5% along with intravenous placebo of 2cc normal saline, whereas group-B received 0.5mg/kg ketamine intravenously after administration of spinal anesthesia but before the start of surgical incision. Pain intensity was monitored using a visual rating pain scale (VRS), till the need for the first analgesic dose postoperatively.

RESULTS: Both groups were comparable in terms of age and weight. Analgesia was markedly prolonged, and postoperative pain scores were significantly less in Group-B (ketamine group) as compared to Group-A; with p-value< 0.001, demonstrating analgesic properties of ketamine when administered pre-emptively as an intravenous dose.

CONCLUSION: Our study concluded that pre-emptive analgesic dose of ketamine (administered before surgical incision), leads to prolong analgesia in post-operative period in patients who underwent LSCS under spinal anesthesia.

KEYWORDS: LSCS, Analgesia, VRS, Spinal anesthesia, Ketamine.

INTRODUCTION

There has been an increase in the rate of caesarean deliveries, in recent years, all over the world. The causes are multifactorial and include both maternal and fetal factors [1]. Caesarean section is a procedure that can be performed under general or neuraxial anesthesia. It is a major surgery, and the severity of pain ranges from moderate to severe [2]. Infliction of surgical wounds results in the generation of sensitization of pain pathway centrally, leading to amplification of pain [3]. Postoperative good pain control is a challenging entity in patients undergoing caesarean delivery [4].

Various analgesia techniques can be used in patients undergoing Caesarean section and include regional or systemic analgesia; systemic drugs can be given either before the start of surgery or at the end. Preemptive techniques have been found to be more effective as compared to preventive strategies [5].

Preemptive analgesia significantly reduces the development of hyperalgesia and allodynia in patients post-surgery. It is the analgesia that must be administered prior to the surgical

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wound infliction, and it results in lesser dose consumption for analgesics in post-operative period [6]. Opioids and nonsteroidal anti-inflammatory drugs are commonly used as preemptive analgesic agents [7]. Oral and intravenous opioids are associated with nausea, vomiting, gastrointestinal symptoms, and there is risk of respiratory depression and over-sedation as well. None of these is desired by a mother in the immediate postpartum period [8].

Ketamine is an NDMA receptor antagonist with wide range of effects. Use of ketamine has been associated with good analgesic effect with minimal side effects, when given in sub anesthetic dose to patients undergoing Caesarean section. Moreover, a sub-anesthetic dose does not have an effect on the neonatal APGAR score [9].

Since the provision of adequate analgesia is a cornerstone of anesthetic management and patient wellbeing, the objective of this study is to find out degree of pain relief and duration up till the requirement for the first analgesic dose in post-operative period in patients underwent caesarean delivery under spinal anesthesia and received injection ketamine as a preemptive analgesic, as compared to those who received placebo.

METHODOLOGY

This observational study was conducted at a teaching hospital after taking approval from the Institutional Ethical review committee (ABWA MC/HR/1022/21). It was conducted over a period of five months; 31-12-2021 to 30-05-2022. Full-term pregnant patients were distributed among two groups (Group-A and Group-B) 50 in each, using non-probability consecutive sampling.

Patients willing to be part of the study, admitted for elective caesarean section, normotensive, or with controlled chronic hypertension, ASA class I & II were included in the study.

Patients with emergency caesarean section, pregnancy induced hypertension, psychological disorders, ASA III & IV, contraindication for administration of intravenous ketamine and subarachnoid block, not willing to participate, were excluded. Those receiving rescue analgesic pre or intraoperatively were eliminated from the study.

Informed consent was taken from all the patients included in study. Patients were made aware of Verbal Rating Pain Scale (VRS) [10], and any query was addressed properly.

All the patients were monitored by electrocardiogram, non-invasive blood pressure, and pulse oximetry; starting from the pre-anesthesia point. Pre-loading was done by a colloid intravenous solution. Group-A (control group) received spinal anesthesia with 0.5% bupivacaine hyperbaric and 2cc normal saline placebo was given intravenously prior to the start of surgery. Group-B (study group) received 0.5mg/kg injection of ketamine intravenously after administration of spinal anesthesia with 0.5% bupivacaine heavy before the skin incision was given.

Postoperative pain assessment was done hourly for the first six hours using verbal rating pain scale. The time duration post-operatively at which first dose of analgesic was administered in both groups was also recorded. The anesthesiologist, who was unaware of the drug administered to the patients, was responsible for the collection of data on a pre-designed proforma. The 4-point VRS followed was:

- No pain
- Mild pain (tolerable)
- Moderate pain (hurts a lot)/severe
- Severe pain (hurts to die) [10]

Data was entered and analyzed by using SPSS version 20. Mean, and standard deviation were calculated for quantitative variables (like age, and weight). Frequency and percentages were calculated for qualitative variables. Confounders were controlled through stratification. Pearson Chi-Square test was applied by keeping $p \leq 0.05$ as significant.

RESULTS

Mean age of the patients in group-A was 34.62±4.893, with a range of 23 -43 years. Whereas in group B mean age was 34.76±4.838, with a range of 27-45 years (table-I). In group A mean weight was 74.64±10.344, in Group B it was 72.64±10.20 (table-II). Both the groups were comparable in terms of age and weight of the patients.

The severity of pain was assessed for up till six hours in the post-operative period. At 2 hours after caesarean section,11 patients required analgesic top-up in group A, whereas very good analgesic profile was shown by Group B patients (table-III).

Table-I: Age distribution of female patients among groups A & B.

Age in Years	Group A n(%)	Group B n(%)	Total	x^2	p-value
25-30 years	12(24)	10(20)	22	1.955	0.582
30-35 years	22(44)	25(50)	47		
36-40 years	11(22)	7(14)	18		
41-45 years	5(10)	8(16)	13		
Total	50	50	100		

Table-II: Weight of patients in groups A & B.

Age in Years	Group A n(%)	Group B n(%)	Total	x^2	p-value
51-60 kg	7(14)	7(14)	14	1.354	0.716
61-70 kg	10(20)	11(22)	21		
71-80	16(32)	20(40)	36		
81-90	17(34)	12(24)	29		
Total	50	50	100		

At 3rd hour postoperatively 19 patients from group-A had moderate pain as compared to none from group B. Seventeen patients from group-A while 03 patients from group B did not require analgesic supplementation. A significant difference in pain control among both groups was shown at 03-hour post operatively. At 4th hour post-operatively, 31 patients from group A had already received rescue analgesic intravenously, whereas none of the patients in group B had yet required

top-up analgesia. Results were significant with chi-square value=14.918 and p<0.001 (table-III). Assessment at 5 hours was also significant, with 10 patients demanding analgesia in group A as compared to 01 patient from group B (table-IV). Maximum number of patients from group A had received rescue analgesic till 5th post-operative hour. At 6th hour rescue analgesia was administered to 05 patients from ketamine group B. At that time patients experiencing no pain in Group-A had already received analgesic top-up, thus showing significantly better pain control in Group B patients who had received ketamine a preemptive analgesic, along with spinal anesthesia (table-IV).

Table–III: Pain severity at 2, 3 & 4 hours post-operative among Groups A &B.

Time of post-operative pain severity	Pain severity	Patient groups		Total	χ^2	p-value
		Group-A n(%)	Group-B n(%)			
At 02 Hrs	No pain	17(34)	49(98)	66	45.689	≤0.000
	Mild pain	22(44)	01(2)	23		
	Moderate pain	11(22)	0(0)	11		
At 03 Hrs	No pain	14(28)	47(94)	61	46.652	≤0.000
	Mild pain	17(34)	03(6)	20		
	Moderate pain	19(38)	0(0)	19		
At 04 Hrs	No pain	31(62)	47(94)	78	14.918	≤0.000
	Mild pain	19(38)	03(6)	22		
	Total	50	50	100		

Duration of analgesia was markedly prolonged in Group-B with minimum duration being 4-6 hours and maximum being 18 hours post-operatively. Whereas in Group-A postoperative analgesia lasted for 4–6-hour maximum. The patients in Group-B who received intravenous ketamine as pre-emptive analgesia showed longer pain free periods as compared to patients in control group, who received a normal saline placebo.

Table–IV: Pain severity at 5- & 6-hours post-operative among Groups A &B.

Time of post-operative pain severity	Pain severity	Patient groups		Total	χ^2	p-value
		Group-A n(%)	Group-B n(%)			
At 05 Hrs	No pain	27(54)	45(90	72	16.628	≤0.000
	Mild pain	13(26)	04(08)	17		
	Moderate pain	10(20)	01(02)	11		
At 06 Hrs	No pain	28(56)	42(84)	70	9.400	0.009
	Mild pain	07(14)	03(06)	10		
	Moderate pain	15(30)	05(10)	20		
	Total	50	50	100		

Table-V: Duration of analgesia after spinal in patient groups A & B.

Time of post-operative pain severity	Patient groups		Total	χ^2	p-value
	Group-A n(%)	Group-B n(%)			
1-3 hours	21(42)	0(0)	21	65.635	≤0.000
4-6	27(54)	09(18)	36		
7-9	01(02)	16(32)	17		
10-12	01(02)	09(18)	10		
13-15	0(0)	16(32)	16		
Total	50	50	100		

DISCUSSION

Acute post-surgical pain if treated inadequately can lead to the development of chronic pain and patients have tendency to develop post-traumatic stress disorder. Moreover, in obstetric patient it is not only important for the parturient, but for the newborn as the mother has to take care of the baby and she can be able to do so only if her pain has been well managed [11]. Postoperative pain management can be achieved by a variety of techniques and drugs, ranging from intravenous analgesics to nerve blocks and patient-controlled analgesia. But a consensus over a single best technique has not been achieved [12].

Though Opioids have been used widely for pain management, there is a greater risk of neonatal depression associated with intravenous administration in antenatal period. Recently intravenous ketamine in subanesthetic dose has gained much popularity as a pre-emptive analgesic agent [13]. Role of ketamine as an anesthetic agent has been well established, it can be used as an adjunct as well as sole anesthetic agent for a variety of procedures. Low dose of ketamine, that is, a sub-dissociative dose can be safely used alone or in combination with other analgesics to provide good quality analgesia. It mediates its effects via NDMA, glutamate, Mu and sigma receptors [14].

Our study shows that the patients (Group-B) who received injection ketamine after receiving spinal anesthesia with 0.5% hyperbaric bupivacaine before the start of the surgery experienced longer pain free period postoperatively, ranging from 7 to 18 hours, p-value=0.000 as compared to the control group (Group-A), who received 2 ml normal saline placebo intravenously. Up till 6 hours in post-operative period, there was a marked difference in pain score between both groups. Group A showed significantly higher pain scores as compared to Group B, it shows superiority of the technique involving the use of ketamine. Sen S et al also identified that patients in whom ketamine was given preemptively, had markedly prolonged pain free interval in post operative period, showing outcomes similar to our study [15]. Hesen M et al, also described a better post operative analgesic profile in patients in whom ketamine was used as a pre-emptive analgesia along with spinal anesthesia. Moreover, no significant side effects were noted. Their study supports pre-emptive analgesic role of ketamine with both general

and spinal anesthesia techniques. Neonatal outcome was not affected by ketamine administration in these patients [16].

Adhikari P et al conducted a randomized control trial in patients undergoing emergency caesarean section under spinal anesthesia. He concluded that administration of ketamine in analgesic dose before giving surgical incision in the patients not only improved postoperative pain scores but also reduced opioid requirement in the first 24 hours [17].

Wang J et al, analyzed 20 randomized controlled trials. He reached the conclusion that ketamine supplementation along with spinal anesthesia provides good pain relief for longer duration. Opioid consumption was also decreased in post operative period in these patients. In our study Group-B patient had prolonged analgesia and thus required a minimal dose of opioid in first 24 hours [18]. Another study conducted in African parturient identified a marked increase in mean time for postoperative analgesia and significantly lower pain score at 120 minutes in ketamine group as compared to control group. At early stage there was a lower need for analgesic drugs as compared to control group. In our study parturient showed a significant difference in pain score at 2 and 3 hours post operatively with p-value<0.001 [19].

A randomized control trial conducted by Behzad S identified that ketamine administration caused a significant decrease in mean pain scores as well as statically significant prolongation in the length of post-operative analgesia, in patients who underwent Caesarean delivery under spinal anesthesia. These patients received a low dose of ketamine intravenously before the start of surgery [20].

CONCLUSION

Our study concludes that administration of sub-anesthetic dose of ketamine prior to the surgical incision, results in better and prolong pain control in patients receiving spinal anesthesia for caesarean section, thus reduces need for opioids in postoperative period. Pre-emptive analgesia provides maternal benefit and allows for better nursing care of newborn. The limiting factor in our study was a small sample size, we would recommend further research should be done on a larger number of patients to allow for the wider acceptance of the technique.

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Humaira Ahmad: Substantial contributions to the conception, design, data analysis, drafting.
Samina Aslam: Conception and acquisition of data for the work.
Sahir Shafiq: Design and drafting of the work.
Asif Sagheer: Interpretation and final approval of the version to be published.
Sarwat Bibi: Critical review for important intellectual content.

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