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Pre-Emptive Analgesic Efficacy of Preincisional I.V. Low Dose Ketamine (0.15mg/kg) in Patients Posted for L.S.C.S. Under Spinal Anaesthesia

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Abstract

Introduction: Inadequate pain relief after caesarean section delivery impairs mother's ability to optimally care for her infant and to breastfeed in the immediate postoperative period. Pre-emptive analgesia is an antinociceptive treatment that prevents the establishment of altered processing of afferent input which amplifies postoperative pain. The lower dose of ketamine is not associated with neonatal depression and complication is minimal with high patient acceptance. *Aim and Objectives:* To assess the pre-emptive analgesic efficacy of pre-incisional i.v. low dose ketamine in patients posted for L.S.C.S under spinal anaesthesia. *Material and Methods*: The present clinical prospective study was carried out in Department of Anesthesiology, during Dec. 2011 to Oct. 2013. Sixty parturients of ASA Grade I and II were randomly divided into two groups of 30 each, every even number patient received IV ketamine (group K) and every odd patient received normal saline (group B). *Results*: Highest level of sensory block reached in group B was T_2 in 7% of patients and 10% of patients in group K. All patients had excellent sensory analgesia. Mean time of total duration of sensory block was 234.27±24.23min in group B and 230±28.8min in group K. Mean time of effective analgesia was 126±17.6 min in group B and 161.6±24.2 min in group K. Hypotension was noted in 12 (40%) in group B and in 9 (30%) in group K. Shivering was observed in 3 patients in group B. *Conclusion*: The pre-incisional administration of low dose intravenous ketamine delayed the time to first analgesic request in parturients. The study could not substantially demonstrate the preemptive analgesic property of ketamine.

Keywords: Ketamine; Caesarian; Spinal Anesthesia; Pre-Emptive Analgesia; Low Dose.

Introduction

One of the primary aims of anaesthesia is to render adequate pain relief, thereby permitting the performance of surgical procedures without stress and discomfort. Inadequate pain relief is associated with undesirable physiological and psychological consequences. Inadequate pain relief after caesarean section delivery impairs mother's ability to optimally care for her infant and breast feed in the immediate postoperative period. Hence, it is necessary that pain relief with mother's ability to move around and care for infant with no adverse effect on the neonate.

Pre-emptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input which amplifies postoperative pain. This concept was formulated by Crile [1] on the basis of clinical observation, he advocated the use of regional blocks in addition to general anaesthesia to prevent intraoperative nociception and formation of painful scar caused due to changes in central nervous system during surgery.

Many drugs are used for the study of pre-emptive analgesia but ketamine is a direct blocker at N-methyl-D-Aspartate (NMDA) receptors involved in central sensitisation [2-4]. Blocking NMDA receptors may improve the efficacy of opioid and

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reduce the development of chronic pain syndrome. Low dose ketamine is defined as a bolus dose of ketamine ≤ 2mg/kg when administered intramuscularly and ≤ 1mg/kg when administered via intravenous or epidural route [5]. The lower dose of ketamine (0.2-0.5mg/ kg iv) is not associated with neonatal depression and complication was minimal with high patient acceptance [5,6]. In India, Ketamine is commonly employed anaesthetic because it is cheap and perceived to be safe. In this study, we have selected patient for elective L.S.C.S. under regional anaesthesia rather than in general anaesthesia to study about the Pre-emptive analgesic efficacy of pre-incisional I.V. low dose ketamine.

Aim and Objectives

1. To assess the pre-emptive analgesic efficacy of pre-incisional i.v. low dose ketamine in patients posted for L.S.C.S under spinal anaesthesia
2. Comparison of time to first request for analgesia in the postoperative period.

Material and Methods

After obtaining Institutional Ethical Committee approval the present clinical prospective study was carried out in Department of Anesthesiology, during the period of December 2011 to October 2013. Sixty parturients of ASA Grade I and II undergoing elective LSCS by taking low transverse (modified Pfannenstiel) incision without medical or obstetric complications formed subjects.

Exclusion

Patients having respiratory, cardiovascular disease, bronchial asthma, history of allergic reactions to drug or food, patients with extremes of height (below 140 cm and above 165 cm) and weight (below 45 kg and above 65 kg) , patients with shock and coagulation disturbances ,patients with a local skin infection, any spinal deformity, spinal tenderness or neurological deficit were excluded. These patients were divided into two groups of 30 each by systematic randomization, every even number patient received IV ketamine (group K) and every odd patient received normal saline (group B).

Group (B) - Patients receiving hyperbaric bupivacaine (0.5%) 10mg (2ml) and normal saline for injection 10cc IV

Group (K) -Patients receiving hyperbaric bupivacaine (0.5%) 10 mg (2 ml) and 0.15mg/kg ketamine diluted upto 10cc IV. Routine investigations like Hemoglobin, urine examination for sugar and albumin, blood grouping and Rh typing were carried out in all patients. The procedure was explained to the patient, written informed consent for anaesthesia, surgery and blood transfusion was obtained. Baseline pulse rate, respiratory rate, blood pressure [systolic/ diastolic], oxygen saturation [SpO2], were recorded after placing the patient in 15^0 left lateral tilt. Preloading was done with 10 ml/kg body weight with ringer lactate solution in operation theatre before administration of spinal anaesthesia. The position of the table was kept horizontal. The patient was given left the lateral position and under all aseptic precautions, lumbar puncture was performed with lumbar puncture needle of 23 gauge at L_3 - L_4 space. After ensuring the free flow of clear cerebrospinal fluid the desired drug was injected. The patient was immediately turned supine and the wedge was given below right flank for left uterine displacement.

Hypotension was defined as a decrease in systolic blood pressure of more than 30% of baseline value. Hypotension was treated with leg elevation, O_2 supplementation, pushing IV fluids (200 ml bolus), Inj. Mephenteramine 3 mg IV and repeated every 3 min until hypotension was corrected.

Bradycardia was defined as a fall in pulse rate below 50 beats per minute. Atropine was kept ready for bradycardia. Inj. Ondansetran 4 mg IV was given for nausea and vomiting.

Sensory characteristics such as onset of sensory block, maximum level of sensory block, time required to achieve maximum sensory block, time required for two segment dermatome regression, total duration of sensory block and request for first dose of rescue analgesics were studied.

Analysis of data was performed using student's unpaired t-test (for finding the significance of difference between means of two independent samples. Chi -Square test (a test of association between two events in binominal samples). P value less than 0.05 was considered to be significant.

Results

In the present study 60 parturients ASA I and II those underwent caesarean section under subarachnoid block for LSCS were studied. The mean age of patients in group K was 25±3.5 years

Table 1: Showing demographic data and surgical duration

Variable	Group B (mean ± SD)	Group K (mean ± SD)	P value
Age (yrs)	24.8±3.57	25±3	0.80
Weight (kg)	54.3±4.57	53±6	0.99
Height (cm)	151±3.87	151±4.9	0.99
Duration of surgery (min)	52.6±7.2	52.5±5.3	0.91

Table 2: Showing maximum level of sensory block.

Maximum Sensory Level	Group B	Group K
T2	02	03
T3	00	0
T4	08	10
T5	05	02
T6	15	17
Total	**30**	**30**

Table 3: Degree of sensory block (quality of sensory analgesia)

Degree of Analgesia	Group B	Group K
I	0	0
II	0	0
III	0	0
IV	30	30
Total	30	30

Table 4: Showing Time Required For regression of block to S_1 in min

Total duration of sensory block(min)	Group B	Group K
121-180	02	03
181-240	23	20
241-300	07	07
Total	30	30
Mean ± SD(min)	234.27±24.23	230±28.8

Table 5: Showing Duration of Effective Analgesia in min

Duration of Effective Analgesia (Min)	Group B	Group K
90-120	15	00
121-150	15	13
151-180	00	14
181-210	00	03
Total	30	30
Mean ± SD(min)	126±17.6	161.6±24.2

Table 6: Comparison of side effects in both groups

Side effects	Group B	Group K
Nausea/ vomiting	0	0
Hypotension	12	09
Bradycardia	2	0
Pruritis	0	0
Respiratory depression	0	0
Shivering	3	0

Table 7: Showing blood pressure variations

Systolic BP	Group B Mean ± SD	Group K Mean ± SD	P Value
Preoperative	122±8.4	120±8.8	0.37
After 15 Min	89±13	88±9.8	0.57
After 90 Min	114±10.2	113±15	0.76
After 180 Min	118±10	118±7.1	0.99

and in group B was 24.8±3.3 years. The mean height of patients in group K was 151±4.9 cms and in group B was 151±3.87 cms. The mean weight of patients in group K was 53±6 kg and in group B was 54.3±4.5 kg. The mean time of duration of surgery was 52.5±5.34 min in group K and 52.6±7.2 min in group B. Highest level of block reached in group B was T_2 in 7% of patients and 10% of patients in group K. these findings were comparable in both groups (p=0.8, p>0.05).

Degree of Analgesia (Bromage PR1964)

I. Required general anaesthesia for completion of surgery.

II. Pain that required addition of analgesic drug.

III. Mild discomfort but did not required systemic analgesic.

IV. No discomfort at all during procedure.

All patients in group B and group K had excellent sensory analgesia. No patients from both the groups required general anaesthesia (Grade I). Time Required For regression of block to S_1(total duration of sensory block) Mean time of total duration of sensory block was 234.27±24.23min in group B and 230±28.8min in group K. it is comparable in both the groups (p=0.57, p>0.05).

Time Required for First Dose of Analgesic (Effective Analgesia)

Mean time of effective analgesia was 126±17.6 min in group B and 161.6±24.2 min in group K. Duration of effective analgesia between both the groups was statistically significant (p=0.0004 P<0.001).

Comparison of Side Effects in Both Groups

Hypotension was noted in 12 (40%) of patients in group B and in 9 (30%) of patients in group K, bradycardia was noted in 2 patients of group B and no bradycardia in group K. Shivering was observed in 3 patients in group B and no episode of shivering in K group. As all patients were catheterized urinary retention could not be monitored. Pruritus was not seen in any patients of both groups. Respiratory depression was not seen in any patient of both groups. There was fall in systolic blood pressure following spinal anaesthesia in both groups. Magnitude of fall was similar in both groups and it was not clinically or statistically significant (p>0.05). Statistical analysis of arterial oxygen saturation values for two groups at preoperative, intraoperative, postoperative shows that there was no statistically significant difference in two groups at these four periods (p>0.05).

Table 8: Showing SpO_2 variations

SpO_2	Group B Mean ± SD	Group K Mean ± SD	P Value
Preoperative	98±0.7	99±0.8	0.9
After 15 Min	98±0.7	99±0.8	0.9
After 90 Min	98±0.8	99±0.8	0.9
After 180 Min	98±0.7	99±0.8	0.9

Discussion

The present study is a prospective, double-blind, randomized study done at a tertiary hospital from December 2011 to September 2013.

Multimodal therapy for postoperative pain control is now widely practiced due to the advantage it provides in blocking multiple pain pathways while minimizing side effects of each individual pain medication [7]. Adverse effects such as nausea and vomiting often limit postoperative pain management. There are a number of reasons for postoperative nausea and vomiting (PONV), and these have been exhaustively discussed in the anaesthetic literature.

One possible factor is the use of opioids and adjuvant treatment with opioid-sparing drugs such as ketamine may be of value in giving better analgesia with fewer adverse effects (Schmid 1999) [8]. This research work studied the effect of low dose intravenous ketamine as a pre-emptive analgesia in patients undergoing caesarean section under spinal anaesthesia.

Demographic Data

In the present study the mean age of patients in group K was 25 years and in group B was 24.8±3.3 years. The mean weight of patients in group K was 53±6 kg and in group B was 54.3±4.5 kg. The mean time of duration of surgery was 52.5±5.34 min in group K and 52.6±7.2 min in group B. The difference observed in above demographic data and duration of surgery was statistically and clinically not significant (P- 0.05).

Sensory Block

The meantime required for the onset of sensory block was comparable in both the groups (p=0.41,p>0.05). The highest level of block reached in both groups was comparable (p=0.8, p>0.05). The mean time required to reach maximum sensory level was both statistically and clinically not significant (p=0.55, p>0.05). While the meantime for two segment dermatome regression was 84.33±4.58 min in group B and 84.9±5.76 min in group K that was comparable in both the groups (p=0.99, p>0.05). The meantime of total duration of sensory block was comparable in both the groups (p=0.57,p>0.05). These results were similar to studies carried out by Sen S et al [9] and Ebong EJ et al [10].

Above results show that onset, duration and spread of sensory block is similar in both ketamine and control group. As peripheral human NMDA receptors have been identified and ketamine has local anaesthetic like properties, but the peripheral effect in small dose does not provide sufficient analgesia when used alone [11].

The observed effect of prolonged first dose of analgesic is inhibition of central sensitization and not due to the peripheral action of ketamine. Demonstration of pre-emptive analgesia with systemic but not spinal suggests that supraspinal effect predominates with systemic ketamine administration and has a similar effect as opioid. Antinociceptive effect of systemic ketamine involve activation of the mono aminergic descending inhibitory system, and this effect does not occur after spinal administration [12,13].

First Dose Analgesic Requirement

In the present study, it was noted that time to first request for analgesic was significantly delayed in ketamine group than the control group. This finding is same as in the study of Amanor-Boadu et al in which ketamine prolong the time for the first analgesic [14]. It has been demonstrated in other studies that ketamine delayed the first request for analgesic by approximately 10-30 min compared to control group [15].

Our results are similar to Sen S et al [9] who demonstrated that time for first dose analgesic requirement was significantly longer in ketamine(197min) group than Fentanyl (165min) and control(144 Smin) group. Since in this study 3cc hyperbaric bupivacaine was used hence the time for first dose analgesic requirement was more in all the groups than our study but the difference in control and ketamine group is clinically significant; difference between TFA in both studies is due to different dose of hyperbaric Bupivacaine.

Evidence has shown that postoperative pain is the product of both peripheral and central sensitization [16]. Following stimulation of free nerve ending by incision, cutting, and traction, the chemical mediator of pain such as bradykinin and prostaglandins maintain the pain longer resulting in primary hyperalgesia.

To achieve sustained pre-emptive analgesia, the pain of initial injury must be blocked and since chemical mediators continue to be released for longer than the initial insult, their effect must be prevented for a longer time than the duration of action of a single dose of analgesia administered unfortunately our study cannot demonstrate the sustained pre-emptive effect. But the study demonstrated that first dose requirement was significantly prolonged in the group that has received low dose ketamine.

Studies of Himmelseher S et al [11] show that small dose of ketamine reduced opioid requirement for postoperative pain

Comparison of Side Effect

In the present study, hypotension was noted in 12 (40%) patients in group B and in 9 (30%) of patients in group K. Shivering was observed in 3 patients only in group B. Respiratory depression was not seen in any patient. In our study episode of hypotension in ketamine group was 30% and in control group, it was 40% that difference may be attributed to the sympathomimetic activity of ketamine.

In the present study, only 6.33% of the women in the placebo group developed some bradycardia and none in the ketamine group. Ketamine is well known to cause a rise in blood pressure and heart rate due to its sympathomimetic activity. This could be the reason for the less incidence of bradycardia observed in the group that received low dose ketamine.

Postspinal shivering was a complication that was prominent amongst the placebo group. None of the women in the ketamine group developed shivering. This observation is similar to the study carried out by Ebong EJ et al [10]. Ketamine, a competitive NMDA receptor antagonist, also inhibits postoperative shivering [17]. Psychometric response to a small dose of ketamine is not found troublesome [11]. The absence of characteristic sedation, dreams

and hallucination observed in this study is similar to that observed by Amanor-Boadu SD et al [14]. None of the patients who had ketamine scored more than zero on Ramsay sedation scale. This could be due to the small dose used during the study [12,13].

Haemodynamic

Pulse Rate

In comparison, there was no statistically significant difference found in both groups with respect to pulse rate (P value>0.05). Bradycardia was reported in 2 (6.33%) patients in group B. No statistically significant difference was found between the two groups (p-value 0.6120).

Blood Pressure

In comparison, there was no statistically significant difference found in both groups with respect to mean blood pressure (P value>0.05). Hypotension was reported in 12 (40%) patients in B group and 9 (30%) in ketamine group with no statistically significant difference in both the groups (p-value-1.0000).

Oxygen Saturation (SpO_2)

The SpO_2 monitoring was done with pulse oximetry. None of the patients developed respiratory depression in our study.

Conclusion

The pre-incisional administration of low dose intravenous ketamine delayed the time to first analgesic request in parturients who had caesarean section under bupivacaine spinal anaesthesia. The study could not substantially demonstrate the preemptive analgesic property of ketamine.

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