EFFECTS OF PREEMPTIVE KETAMINE ON POST-CESAREAN ANALGESIC REQUIREMENT

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Abstract- ***In a randomized, double blind study, we compared post operative pain and analgesic requirement in patients undergoing cesarean section with two types of general anesthesia: standardized general anesthesia (control group= 26 cases) and preemptive low-dose ketamine (0.2 mg/kg) administered prior to anesthesia induction (ketamine group= 27 cases). Postoperative analgesia was provided for both groups using morphine intravenously based on visual analogue scale (VAS). After the operation we found that the time from the end of surgery to the first request for analgesic was longer in ketamine group (10.22±8 hrs) than in the control group (1.65±1.01 hrs) (P<0.001). Mean dose of morphine consumption over 24 hrs was less in the ketamine group (6.25± 3.45 mg) than in the control group (17.73± 4.08 mg) (P<0.001). VAS of pain scores were lower in ketamine group during 24 hrs (P<0.001). APGAR Scores were similar between the groups. No patient in either group had postoperative hallucination. In conclusion, ketamine in low dose has a preemptive analgesia effect that reduces central sensitization in cesarean section and reduces postoperative analgesic requirement.***
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Key Words: ***Cesarean, postoperative pain, ketamine, preemptive analgesia.***

INTRODUCTION

Over the past decade, research on the management of postoperative pain has led to the recommendation of multimodal approach commonly called "balanced analgesia". Improved outcomes are much more likely to be demonstrated when preemptive analgesia is one of the several components of balanced analgesia for postoperative pain control (1). Peripheral tissue injury causes both central and peripheral sensitization, manifesting as an increase in response to noxious stimuli, and decrease in pain threshold, both at the site of injury and surrounding tissue (2). When this state has been induced, very large doses of opioids are needed to suppress it (3). This large dose of opioids is not free of side effects to the mother.

The standard general anesthetics for cesarean section include induction with thiopental and omission of opioids until after delivery of the fetus (4-6). This may increase the potential for central hypersensitivity states, with a consequent increase in postoperative pain and analgesic requirement (7). Ketamine is an antagonist at N-Methyl-D-Aspartate (NMDA) receptors, which are considerd important in the mechanism of central hypersensitivity (8). Low dose ketamine (0.15 mg/kg) given before surgical incision reduced the post operative morphine requirement by 40% in first 24 hrs after cholecystectomy (3). Although induction of anesthesia in elective cesareans with ketamine (1 mg/kg) resulted in 35% decrease in morphine consumption during first 24 hrs postoperatively compared to patients induced with thiopental, this dose of ketamine may not be applicable to many cesarean candidates as pointed out by the same investigators. However low-dose ketamine may be used almost in all groups of cesareans. Since effects of low-dose ketamine (preemptively) on post-cesarean pain have not been investigated, therefore, in a randomized, double blind study, we compared postoperative pain and analgesic requirement in cesarean section candidates with two types of general anesthesia: A control group, with standard method and ketamine group receiving preemptive ketamine administered before induction of standard method. Our hypothesis was that postoperative pain and analgesic requirement in first 24 hrs would be less in patients who received low-dose ketamine than in those who did not receive it.

MATERIALS AND METHODS

After obtaining approval from local clinical research ethics committee, we studied 53 ASA physical status I and II women, who were candidates for cesarean section under general anesthesia. We calculated that a sample size of 25 patients per group would be sufficient to detect 40% difference in 24 hrs morphine consumption.

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Reasons for exclusion included the followings (i) allergy to either of thiopental, ketamine, morphine, (ii) gestational age less than 36 weeks (iii) candidates with fetal distress (iv) candidate for classical cesarean incision. All patients gave informed consent and were instructed on the numerical rating scales (NRS) and facial rating scales (FRS) of pain scores for measurement of pain. Patients were randomized by drawing of shuffled colored envelops to be put in either control group or preemptive ketamine group. An anesthetist not involved with patient postoperative assessment, calculated the dose and prepared drugs for induction. He or she covered the syringe containing 5^{cc} either calculated ketamine or distilled water with adhesive tape assigned to each patient. After preoxygenation, the content of covered syringe was administered intravenously over 20-30 s. Then 5% thiopental (5 mg/kg) was administered intravenously over 30 s, followed by succinylcholine 1.5 mg/kg. After tracheal intubation, the patients were ventilated with 50% nitrous oxide in oxygen. Halothan 0.5% was added, to maintain the anesthesia. Further neuro-muscular block was maintained by using atracurium as needed. After delivery of the fetus, 5 IU oxytocin, 0.1 mg / kg morphine and 1 mg midazolam were given as bolus IV, in addition 10 IU oxytocin infused intravenously. Uterine incision to delivery time was measured in seconds and recorded. APGAR scores at 1 and 5 minutes was noted by pediatrician and recorded. At the end of the surgery, neuromuscular blocking was antagonized by neostigmine 2.5 mg and atropine 1.25 mg. In the post-anesthesia care unit, patients were observed for any psychomimetic reaction. On obtaining desirable condition, patients were discharged to postnatal ward. In the ward patients were observed for hourly respiratory rate and level of consciousness. Each patient was visited by resident blinded to the patient group at 1, 2 ,6 ,12 ,18 ,24 hrs after surgery and recorded the patient's NRS or FRS and accordingly, administered morphine for control of pain.The amount of morphine administered was based on the scale of patient's pain score. If the scale was ≤ 3 no morphine was administered. For the scales between 4 and 6, 3 mg and for scales of 7 and above, 5 mg of morphine was administered. This regimen is based on investigation that maintaining scales below 4 is adequate for pain control (10). With the help of SPSS 10, descriptive statistics, Mann-Whitney test, independent test and repeated measurements the data were compared and analysed. $P < 0.05$ was considered statistically signifcant.

RESULTS

Both groups were similar in age and gestational period. P values were 0.195 and 0.486 respectively. Surgical procedures in both the groups were performed in the same fashion. There was significant difference of weight between groups (P=0.026, Table 1). Mean of pain scores (ie, NRS or FRS) during first 24 hrs postoperatively were higher in the control group (Fig. 1, (P <0.00l)). Time to first opioid request was longer in low-dose ketamine group (10.22± 8 hrs) than in control group (1.65± 1.01 hrs). (P<0.001). Cumulative morphine consumption over 24 hrs was less in the ketamine group (6.25±3.42 mg) than in the control group (17.73±4.08 mg) (P<0.001). Mean dose of morphine consumption at each time was less in the ketamine group. (P< 0.001. Fig: 2). No patient in either group had post-operative psychomimetic emergence phenomenon. Uterine to delivery time and APGAR scores in first and 5th minutes were similar in both groups (Table 2). P values respectively were=0.230, 0.267, 0.072.

DISCUSSION

The results of study demonstrate that addition of low-dose ketamine, to general anesthesia before induction (preemptive) in cesarean patients, delays the first request for opioid from about 2 hrs to 10 hrs in immediate postoperative period. It was showed that in the ketamine group, the dose of morphine requirement in the first 24 hrs was about $\frac{1}{3}$ of the dose in control group. This is despite the higher mean weight among patients of ketamine group, consideration of which, would widen the difference. Results of pain scores indicated that patients in the control group had much more pain than in the ketamine group throughout the 24 hrs of assessment. These findings support the findings of Peltz and Sinclair (11), who observed that less number of cesarean patients induced with ketamine, awoke in pain, than those induced with thiopental. Findings of our study best correlates with the findings of Roytblas et al (3), who used low-dose ketamine (0.15 mg/kg) in addition to general anesthesia in cholecystectomy patients, and observed that the cumulative dose of morphine required, was reduced by about 40% in the ketamine group.

Central sensitization is induced or initiated by stimuli (surgery) that ultimately results in the activation of protein kinase-C (PKC) or tyrosin kinase in the post-synaptic neurons. PKC is highly calcium sensitive, and any stimulus, which increases intracellular calcium in the dorsal horn, which contains this enzyme, will activate it (12). Phosphorylation of NMDA receptor decreases the magnesium block at resting membrane potential and produces long lasting increase in synaptic efficacy. Therefore this activity dependent change in synaptic

efficacy within the dorsal horn, is the ultimate underlying mechanism of central sensitization (13). Among various drug or techniques that prevent central sensitization, only NMDA antagonist reverses the established sensitization (8,14,15). Preemptive analgesia aims to prevent or reduce this sensitization, and thus to reduce post-operative pain (7). Clements and Nimmo (16) showed that the analgesic effect of ketamine occurs at much lower plasma concentration (100 ng/ml) than anesthetic effect (700 ng/ml). In healthy volunteers, IV ketamine in doses of 0.125 to 0.25 mg/kg increased pain threshold, when the plasma concentration of ketamine, was greater than 100 mg/ml, but the duration of analgesia was short with an onset of 30 seconds and a half life of only 10-15 minutes. Thereafter, the levels decrease significantly below the analgesic threshold (<100 mg/ml) (16). Therefore in present study, we used 0.2 mg/kg of ketamine prior to induction of anesthesia, direct analgesic effect of which would have lasted only for about 15 minutes. But what we observed was reduction in the pain for much more prolonged period, and reduction in the cumulative morphine required during first 24 hrs. This result could be explained by prevention of central sensitization prior to tissue injury and probably by the reversal of any established central sensitization in patients who may have arrived with labour pain.

We found that the APGAR scores of neonates were similar in both the groups, as was the uterine incision to delivery time. Our finding is same as that of Kee Warwick et al (7), However they did not record the time interval between the uterine incision to delivery, and their candidates were all elective.

We also found that no patient in either group had signs or symptoms of psychomimetic phenomenon. This finding supports the findings of Roytblat L, et al (3). Several investigators have reported a decrease in the incidence of psychomimetic phenomenon when ketamine is used in conjunction with sedative-hypnotic (thiopental), general anesthetics (halothane, N_20), benzodiazepines (17) and decrease in ketamine dose (18). All factors were observed in this study.

In conclusion, ketamine in analgesic dose (0.2 mg/kg), given before induction of general anesthesia in cesarean patients, has a preemptive analgesia effect that prevents central sensitization. It may also reverse the established central sensitization in patients who have had experienced labour pain. These altogether, cause much reduction in postoperative analgesic requirements.

Table 1. Patients Characteristics prior to anesthesia

	Ketamine group N= 27	**Control group N=26**	**P**
Age (years)	28.66±5.25	27.07 ± 3.28	0.195
Gestational Period (weeks)	39.92	39.72	0.486
Weight (kg)	74. 48 ± 12.49	67.16 ± 10.31	0.026

Table 2. Comparative APGAR score and uterine incision to delivery time.

	Ketamine group N= 27	**Control group N= 26**	**P**
Uterine incision to delivery time (s)	78.51 ± 20.03	70.42 ± 27.99	0.230
Ist minute APGAR: 7	1	7	
8	10	6	0.26
9	16	12	
10	0	1	
5 th minute APGAR: 9	0	3	0.072
10	27	23	

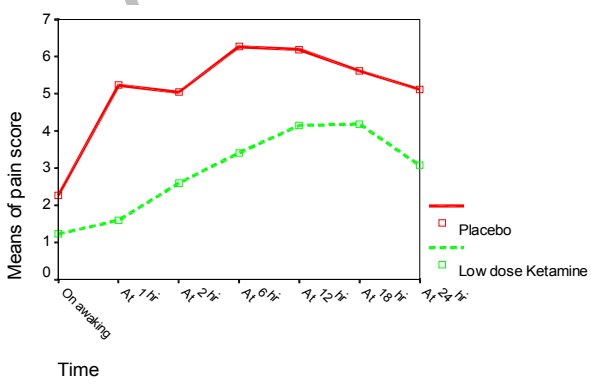

Fig. 1. Comparison of mean of pain scores among study groups

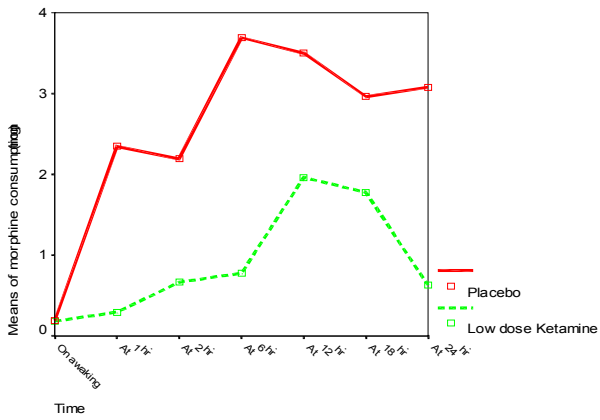

Fig. 2. Comparison of mean dose of morphine among study groups

REFERENCES

1. Mc Caffery M, Portenoy R. Multimodal continous analgesia: balanced analgesia. In: Mc Caffery M, Pasero C. Pain clinical mannual. USA: Mosby; 1999; 119-21.

2. Woolf CJ, chong Ms. Preemptive analgesia: treating postoperative pain by preventing the establishment of central sensitization. Anesthesia Analgesia. 1993; 77: 362-79.

3. Roytblat L, korotkorucko A, katz J, et al. Postoperative Pain: the effect of low dose ketamine in addition to general anesthesia. Anesthesia Analgesia. 1993; 77: 1161- 68.

4. Reisner Ls, Lind D. Anesthesia for Cesarean Section. In: Chestnut DH. Obstetric Anesthesia principles and practice. USA: Mosby; 1999; 480.

5: Golste B. Anesthesia for cesarean section. In: Miller RD. Anesthesia. USA: Churchill Livingston 2000; 2046-52.

6. Shnider SM, Levinson G. Anesthesia for cesarean section. In: Shnider SM, Levinson G, eds. Anesthesia for obstetrics. Baltimore: william and wilkins. 1993; 211-45.

7. k Warwick DN, K kim S, M Marlene L, et al. Postoperative analgesic requirements after cesarean Section. Anesthesia Analgesia. 1997; 85: 1294-98.

8. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on NMDA receptor activation: implication for the treatment of post-injury Pain hypersensitivity states. pain. 1991; 81: 57-62.

9. K Mohammad, H Malekafzali, W Nahapetian. Number of samples required to estimate ratio of mean. In: K Mohammad, H Malekafzali, W Nahaptian. Statistical methods and Health indices. Tehran: Moalleffin' 1999.

10. Mc Caffery M, Pasero C. Pain assessment. In: Mc Caffery M, Pasero C. Pain Clinical mannual. USA: Mosby. 1999; 35-102.

11. Peltz B, Sinclair DM. Induction agents for cesarean section: a comparison of thiopental and ketamine. Anesthesia. 1973; 28: 37-42.

12. Malmbery AB, chen C, Tonegawa, et al. Preserved acute pain and reduced neuropathic pain in mice lacking PKC gamma. Science. 1997; 278: 279-83.

13. Chen L, Huang L- YM. Protein kinase C reduces magnesium block of MMDA receptor channel as a mechanism of modulation. Nature. 1991; 356:521-3.

14. Ma Q-p, Woolf CJ. Involvement of neurokinin receptors in the induction but not the maintenance of mechanical allodynia in the rat flexor motor neuron. J. Physiology. 1995; 486: 769-77.

15. Traub RJ. The spinal contribution of substance P to the generation and maintenance of inflammatory hyperalgesia in the rat. Pain. 1996; 67: 151-61.

16. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effects of ketamine in man. Br. J. Anesthesia. 1981; 53: 27-30.

17. Dundee JW. Pros and cons of ketamine. In: Dundee, eds. Current topics in anesthesia: intravenous anesthetic agents. London: Edward Arnold publishers, 1979; 32-45.

18. Slogoff S, Allen GW, Wessls JV, etal. Clinical experiences with subanesthetic ketamine. Anesthesia Analgesia. 1974; 53: 354-8.