

## Efficacy of pre-incisional subcutaneous infiltration of low-dose ketamine on postoperative pain after cesarean section

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### ABSTRACT

**Objective:** To evaluate the efficacy of pre-incisional subcutaneous infiltration of low-dose ketamine at the site of incision on the postoperative pain management after cesarean section (C.S).

**Methodology:** In a randomized, double-blind, and placebo-controlled clinical trial, 70 healthy parturients were scheduled for cesarean section under spinal anesthesia. Three minutes before surgical incision, patients received either 30 mg ketamine (study group; n=35) or 0.9% saline (placebo group, n=35) as subcutaneous at the site of incision. The volume of solution was 6 ml. In the placebo group 30 mg ketamine was intramuscularly injected to the control for any related systemic ketamine side effects. Hemodynamic parameters were recorded at regular intervals during operation. The patients were followed up for 24 hours to determine postoperative analgesia and side effects.

**Results:** Incidence of pain-free status (pain score=0) was significantly lower in the study parturients at the post-anesthesia care unit (91.44% vs 0%; p<0.0001) and at three hours after surgery (42.85% vs 25.71%; p< 0.001). The time to first request to analgesic were significantly longer in the study patients (4.16±2.86 hr v.s 0.17±0.51 hr; p<0.0001). Cumulative analgesic (tramadol) consumption during 24h after surgery was significantly lower in the study group (62.00±12.50 mg vs. 31.14±9.82 mg; p< 0.0001). Nausea-vomiting was recorded in the six (17.14%) patients of placebo group (p=0.002).

**Conclusion:** Low-dose ketamine decreased locally postoperative pain scores with a significant decrease of analgesics consumption when it was infiltrated local subcutaneously before surgical incision in patients undergoing cesarean section. This method was associated with no systemic or local side effects.

**KEY WORDS:** Cesarean section, Pre-incisional administration, Subcutaneous infiltration, Ketamine, Postoperative pain.

Pak J Med Sci April - June 2011 Vol. 27 No. 2 344-347

### How to cite this article:

Simin A, Rasool A, Mahzad MS. Efficacy of pre-incisional subcutaneous infiltration of low-dose ketamine on postoperative pain after cesarean section. Pak J Med Sci 2011;27(2):344-347

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- \* Received for Publication: December 13, 2009
- \* Revision Received: September 14, 2010
- \* Revision Accepted: December 20, 2010

### INTRODUCTION

Surgical trauma and nerve injury induce N-methyl-D-aspartate (NMDA) receptors activation which facilitates nitric oxide production, resulting to dorsal horn stimulation. Central sensitization may cause increased postoperative pain.<sup>1-4</sup>

Although opioids remain the strongest analgesics for pain management, one must consider that they may also-paradoxically – facilitate postoperative pain in humans. Opioid-induced hyperalgesia and allodynia have also been observed in human

volunteers after analgesia produced by various opioid injections.<sup>5,6</sup>

A variety of substances and modalities are currently in use for the management of postoperative pain. To optimize pain management and outcome, there is a continuous search for new analgesics and alternative routes of delivery.<sup>7</sup> Some experimental data have shown that preoperative pain treatment before surgical incision (pre-emptive analgesia) could prevent spinal cord neuronal hyperexcitability secondary to peripheral stimulation, which is related to hyperalgesia.<sup>1-4</sup>

Ketamine is a well known short acting general anesthetic in use for almost three decades. Experimental pain research of the NMDA receptor revealed that ketamine is a potential anti-hyperalgesic agent that may inhibit C fiber activity and its actions are as a non-competitive NMDA-receptor antagonist.<sup>4,7,8</sup> There has also been increased interest in the routine use of ketamine in small-dose for pre-emptive analgesia, possibly to prevent opiate tolerance and hyperalgesia.<sup>9</sup>

There are various routes of ketamine administration in the treatment of postoperative pain: topical, intramuscular, intravenous, intra-theal, and recently subcutaneous administration.<sup>1,2,6-14</sup> Continuous subcutaneous infusion (CSI) of analgesics may be an alternative for pain control in patients without an epidural catheter, or in patients undergoing anti-coagulant therapy. Studies have shown the reduction of postoperative opioid consumption, prevention of the adverse effects of opioids, and improvement in analgesic quality via subcutaneous ketamine alone or by combining ketamine and opioids.<sup>12-15</sup>

Therefore, it seems reasonable that peripheral pretreatment with ketamine can be an ideal approach for inhibiting postoperative pain. Tan et al<sup>1</sup> demonstrated that pre incisional subcutaneous infiltration of ketamine suppresses postoperative pain after circumcision surgery.

The aim of this study was to investigate the efficacy of pre-incisional small-dose of ketamine at the site of incision on the postoperative pain after cesarean section.

## METHODOLOGY

After the Medical Ethics Committee approval and patient's written consent, 70 ASA class I or II, pregnant women ages between 18 and 36 years, scheduled for elective cesarean section under spinal anesthesia were included into randomized, double-blind, and placebo-controlled study. Patients with a known history of respiratory, cardiovascular, metabolic, and

psychiatric disorders, allergy to local anesthetics or counter-indication for spinal anesthesia were excluded. Several surgeons and two anesthesiologists managed the study subjects.

No patient received sedation or opioid medication before arrival to the operating room. Spinal puncture was performed at the L<sub>3-4</sub> or L<sub>4-5</sub> inter-space with lidocaine %5, 1 ml (50 mg) plus fentanyl 15 µg in all patients. Volume of intrathecal solution was 2.5 ml. Study medications were prepared in advance and transferred to the anesthesiologist in the operating room who did not know the details about the medication. Patients were enrolled in two groups randomly using a computer-generated randomization. Three minutes before the surgical incision, the study group (n=35) received subcutaneous infiltration of ketamine (30mg) along the incision. Other 35 patients (placebo group) received saline normal. In the placebo group 30mg ketamine was intramuscularly injected to the control for any related systemic ketamine side effects. Volume of the subcutaneous solutions were 6ml.

Monitoring during anesthesia consisted of cardio-scope, pulse oximetry and noninvasive blood pressure. Hydration was achieved with 10-15 ml/kg lactated Ringer's or saline normal before spinal puncture and during surgery. Anesthetic time (spinal puncture until regression of sensory block to below T<sub>10</sub>), and surgical time (first incision to last skin suture) were defined. At the end of surgery, patients were transferred to post anesthesia care unit (PACU) and then referred to the ward, when sensory levels had receded to below T<sub>10</sub>.

Pain was evaluated by numerical rating scale (NRS, 0-3) in the PACU, and at 3, 6, 12 and 24 hours after the end of surgery. The time of first analgesic request and total analgesic consumption during 24 hours was recorded. Patients in two groups were treated for pain in exactly the same way in the postoperative period. Tramadol (1mg/kg) was administered to the patients on request or whenever NRS >2. If necessary, tramadol administration was repeated 6 hours after the previous injection. Diclofenac SUPP were provided for analgesia to the patient when she had pain score =1. In addition, systemic (nausea-vomiting, drowsiness, dizziness, and hallucination) or local (hematoma, and swelling) side effects (yes, no) were recorded.

Statistical power calculations ( $\alpha = 5\%$ ,  $\beta = 10\%$ ) based on preliminary data suggested that a group size of 35 should detect a difference of at least 33% in postoperative pain comparing the study group with placebo group.<sup>1</sup> The SPSS 16.0 program (SPSS Inc. Chicago, IL) was used to analyze the statistical data. Patient's characteristics were compared using student t-test.

The incidence of postoperative pain and side effects were statistically tested with the  $\chi^2$ -test. Repeated measures ANOVA is used for comparing HR and MAP changes inter each group. A  $P < 0.05$  was considered statistically significant.

## RESULTS

There were no significant differences among the two groups with respect to age, weight, and duration of surgery or anesthesia (Table-I). There were significant differences between two groups in the mean arterial pressure (MAP) and heart rate (HR) during anesthesia after injection of ketamine (Fig-1).

Table-II shows postoperative pain variables in two groups. Incidence of complete free-pain conditions (NRS=0) in the PACU ( $p < 0.0001$ ) and at three hours ( $p < 0.001$ ) after surgery was higher for the ketamine group. Time to first analgesic supplementation was longer in the study group ( $p < 0.0001$ ). The dose of tramadol was significantly lower for study group ( $p < 0.0001$ ). Twenty-four (68.57%) patients of study group and 25 (71.42%) patients of placebo group received diclofenac Supp postoperatively ( $p = 0.61$ ).

No patient in the study group suffered systemic or local side effects postoperatively, but six (17.14%) patients of the placebo group had postoperative nausea ( $p = 0.002$ ).

## DISCUSSION

The present study demonstrates that the small dose of preincisional subcutaneous infiltration of the NMDA-receptor antagonist, ketamine, increases incidence of the pain-free status (NRS=0) in the PACU, and at three hours after surgery, prolongs the time to first analgesic request, and decreases the use of analgesics during 24 hours after cesarean section.

Studies have demonstrated that pre treatment with systemic injection of NMDA-receptor antagonists inhibit the hyperalgesia. Ketamine, as NMDA-receptor antagonist, when administered intravenously and epidurally, inhibits long lasting secondary hyperalgesia induced by surgery. This findings, show that ketamine has central effects.<sup>1-5</sup>

In this study, ketamine was administered subcutaneously preincision of surgery. Studies have shown

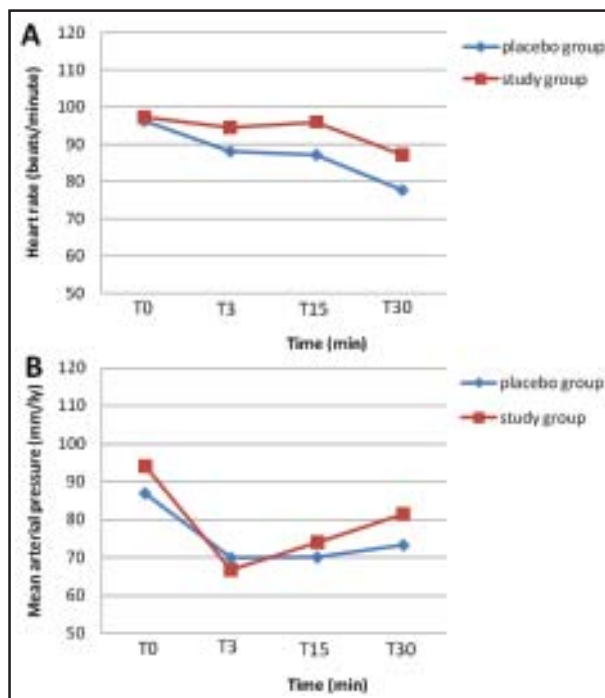


Figure-1. (A) Heart rate changes; before and after injection of study solutions. (B) Mean arterial pressure changes; before and after injection of study solutions. T0= Base line; before the injection of study solutions. T3= 3 minutes after injection of study solutions. T15= 15 minutes after injection of study solutions. T30= 30 minutes after injection of study solutions.  $P < 0.0001$  at 30 min after injection of study solutions.

that the NMDA-receptors in the skin may contribute to the induction of postoperative hyperalgesia. It is also observed that an analgesic effect of subcutaneous infiltration of ketamine is not likely from central but most likely peripheral in origin.<sup>4-9</sup> Tan<sup>1</sup> et al demonstrated that ketamine prevented glutamate-induced activation of NMDA-receptor on primary afferents in the skin, which subsequently reduces peripheral nociceptive input into spinal cord. The decrease in wound pain scores postoperatively after pre-incisional infiltration of ketamine, with high incidence of free-pain status in the PACU and at three hours after surgery, and decreased need to analgesics could be explained by its pre-emptive effect on the inflammatory response to surgery. The local anesthetic properties of

Table-I: Patient's characteristics and duration of surgery and anesthesia in two groups.

	Study group (n=35)	Placebo group (n=35)	p
Age (yr)	30.26±4.94	30.46±4.97	0.86
Weight (kg)	69.68±8.78	67.37±6.84	0.26
Duration of anesthesia	75.52±8.65	73.24±8.42	0.19
Duration of surgery	54.46±6.61	51.71±6.85	0.28

Values are mean (SD)

Table-II: Post-operative pain variables in two groups.

	Study group (N=35)	Placebo group (N=35)	P
Incidence of free-pain at (%)			
PACU	32 (91.44)	0(0)	<0.0001
3 hr	15 (42.85)	9 (25.71)	<0.001
6 hr	2 (5.71)	3(8.57)	0.20
12 hr	24 (68.57)	25 (80.071.42)	0.22
24 hr	30 (85.71)	31 (88.57)	0.64
Time to first analgesic request (hr)	4.162±2.86	0.17±0.51	<0.0001
Incidence of need to tramadol (%)	14 (40.00)	30 (85.71)	<0.0001
Incidence of need to diclofenac (%)	24 (68.57)	25 (71.42)	0.61
Total dose of tramadol (mg)	31.14±9.82	62.00±12.50	<0.0001

Values are mean (SD)

ketamine have been demonstrated in previous studies.<sup>1-9</sup> A transient increase of the hemodynamic variables (HR, MAP) in the study group was due to sympathomimetic effect of ketamine.<sup>9</sup>

In this study, no patient of the study group and six patients of placebo group had postoperative nausea. Postoperative analgesia with opioids may result in nausea and respiratory depression. Ketamine is an effective and safe alternative and safe.<sup>10-15</sup> There were no psychomimetic effects of systemic use of ketamine, such as delirium or hallucination. In this study, we used a small dose of ketamine (30mg). This dosage induces very low plasma ketamine concentrations with no significant signs of accumulation. Emergence phenomena occur at certain plasma levels (blood concentration > 150 ng/ml), even if the level is only transient.<sup>6-8,12</sup>

Although subcutaneous infiltration of analgesics have advantages, skin swelling due to excessive volume of solution and hematoma induced oozing from wound may be seen.<sup>1,10-15</sup> In this study, a volume of 6ml ketamine was chosen to minimize tissue swelling, and no patients in two groups experienced tissue edema. In Tan's report, only two cases from all patients had minor hematoma due to nature of surgery (circumcision surgery).<sup>1</sup> In the present study no patient experienced local hematoma.

This is the second study that demonstrates pre-incisional subcutaneous infiltration of ketamine. The first study performed by Tan et al<sup>1</sup> showed that pre-incisional subcutaneous ketamine was used as subcutaneous in minor surgery. Our study has demonstrated that, the use of pre-incisional subcutaneous ketamine 30mg, before cesarean section is quite effective in Post Operative pain management. Further studies by large doses of ketamine for various surgeries are needed.

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