

## Preemptive Use of Ketamine in Postoperative Pain in Breast Cancer Surgery

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### Abstract :

**Background:** There is a widespread belief among clinician that Ketamine is effective as a preemptive analgesic. Modified radical mastectomy (MRM) is one of the most common cancer surgeries in females and commonly followed by acute postoperative pain. In our study we evaluated whether the preemptive use of ketamine controls postoperative pain in female patients undergoing breast cancer surgery. **Materials & Methods:** 60 adult female patients undergoing modified radical mastectomy were randomized into two groups of 30 patients each. Ketamine (K) group received 0.5 mg/kg Ketamine intravenously with induction of anesthesia. In the control(C) group 0.5 mg/kg normal saline was injected. All patients received general anesthesia. Postoperatively, complain of pain at rest and on shoulder movement using visual analogue score (VAS), time of request for first analgesic, total number of analgesic injection & postoperative any complications of drugs were recorded in post anesthetic care unit for 24 hours. **Result:** For all of the evaluated times, the VAS score was significantly lower in the Ketamine group when compared to control group. The interval time for the first Diclofenac inj. was 33.1±4.7 minute for the Ketamine group and 20.3±5.2 for the control group (P=0.0001). Postoperatively, in the first 24 hours, the total number of Diclofenac inj. was 0.6±0.6 for the Ketamine group and 1.0±0.8 for the control group. (P=0.05) No patients had ketamine related side effects. **Conclusion:** A subanaesthetic dose of intravenously administered Ketamine had a preemptive analgesic effect in control of pain after modified radical mastectomy.

**Key words :** Ketamine, MRM, Preemptive analgesia.

### Introduction :

Postoperative pain results from the incision and manipulation of tissue during surgery leading to suffering of patients. Undermanaged postoperative pain increases postoperative morbidity and mortality and decreases patient satisfaction.<sup>(1)</sup> The goal of the postoperative pain management is to decrease or eliminate pain and discomfort with minimum side effects. N-methyl D-aspartate (NMDA) receptors have an important role in the pathogenesis of pain because of their central sensitization effect and wind-up phenomenon. Mechanism of action of Ketamine may be related to its ability to inhibit NMDA receptors.<sup>(2)</sup>

Several studies demonstrated use of ketamine as NMDA receptor antagonist for control of postoperative pain with some contradictory results. Some studies proved the preemptive analgesic effect of subanesthetic dose of

ketamine<sup>(3, 4, 5, 6)</sup> while the others could not confirm this effect.<sup>(7, 8, 9, 10)</sup>

With this consideration, we designed this study to evaluate preemptive analgesic efficacy of intravenous ketamine for postoperative pain control in patients undergoing breast cancer surgery.

### Materials and Methods:

After obtaining approval from the local ethical committee and written informed consent from all patients, 60 adult female patients with cancer breast undergoing elective modified radical mastectomy (MRM) were included in this study. All patients were classified as American Society of Anesthesiologist physical status I & II and aged 18 to 60 years. Patients were excluded if they had a history of cardiac, hepatic and renal disease, high blood pressure, increase intracranial pressure, epilepsy, cerebrovascular accident, psychiatric disorders, communications difficulties and drug abuse.

All patients were premedicated with tablet diazepam 5 mg and tablet ranitidine 150 mg the night before

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surgery. They were instructed about VAS used for measuring postoperative pain.

The study drug was drawn and diluted with fixed volume of 5 ml by an anesthesiologist not related to the management of patient and study and patients were randomly assigned into study & control group.

Anesthetic protocol was similar to all patients. Before induction of anesthesia mean arterial pressure and heart rate were recorded as baseline measurements, intravenous line was established and patients were premedicated with 0.05 mg/kg of midazolam intravenously to avoid probable side effects of ketamine.

After preoxygenation with 100% O<sub>2</sub>, general anesthesia was induced with fentanyl 2 mcg/kg, propofol 2 mg/kg and atracurium 0.5 mg/kg intravenously. Endotracheal intubation was done with appropriate sized endotracheal tube. Maintenance was done with oxygen and nitrous oxide in a ratio of 1:2 along with isoflurane (0.8-2.0%) on controlled mechanical ventilation. Supplemental boluses of atracurium 0.1 mg/kg iv were administered as required to maintain muscle relaxation during surgery. 10 minute before incision, Ketamine group were given 0.5 mg of Ketamine by anesthesiologist who was not aware of the study and nature of the drug being administered. Intraoperatively, ondansetron 0.1 mg/kg iv was given to all patients about 30 minutes before closure.

Vitals parameters including HR, BP, ECG and oxygen saturation were monitored throughout the procedure and during 24 hours postoperatively.

At the end of the surgery, neuromuscular blockade was reversed with inj. neostigmine 0.04 mg/kg and

Postoperatively when VAS >4, injection diclofenac sodium AQ was administered 1 mg/kg intravenously for adequate analgesia. Assessment of pain was done after 30 minutes and 2, 4, 6, 12 and 24 hours postoperatively by anesthesia resident who was not aware of the allocation of the study participants. Every time pain assessment was done using 10 point VAS scale. The interval time for the 1st rescue analgesic and total number of analgesic injections in the first 24 hours were noted. Patients were checked for side effects like hallucination, delirium and visual disturbances etc.

Statistical analysis:

Data were analyzed using computer statistical software system Graph Pad InStat Version 3.05 (Graph Pad software, San Diego, CA). Comparisons between groups were performed by using Fisher's exact test for small sample with a 5% risk or Chi-square test, as appropriate. The results were expressed in mean±SD. P value less than 0.05 was considered statistically significant.

#### Result:

The demographic profile was comparable with no statistically significant difference between the groups (Table-1). VAS score at rest and on movement are presented in graph 1 and 2, respectively. They were significantly lower in ketamine group than that of control group. The interval time for the 1st rescue analgesic was 33.1 ± 4.7 min in Ketamine group and 20.3 ± 5.2 minutes in control group (P=0.0001). 63% patients in ketamine group did not need analgesic postoperatively (Table 2).

**Table 1: Demographic data**

Variable	Group-K	Group-C	P-Value
Age(Years)	50.16±8.01	48.64±7.89	0.5023
Weight(Kg)	50.68±10.09	54.84±6.22	0.0857
Height(Cm)	159.60±4.60	161.53±3.54	0.1029
Duration of Surgery(Minute)	129.17±14.03	128.36±15.27	0.8460

Kg-kilogram, Cm-centimeter

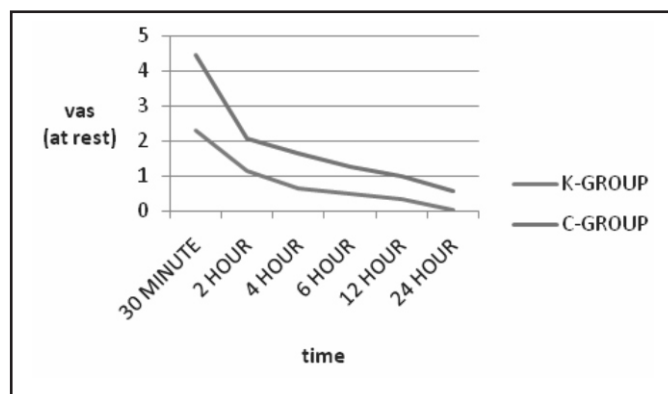
glycopyrolate 0.01 mg/kg. Once the patient was awake and had adequate spontaneous respiration, trachea was extubated.

The total number of Diclofenac injections in the 1<sup>st</sup> 24 hours postoperatively was 0.6 ± 0.6 in ketamine group and 1.0 ± 0.8 in control group (P=0.05) (Table 2). There was no drug related side effects in Ketamine group.

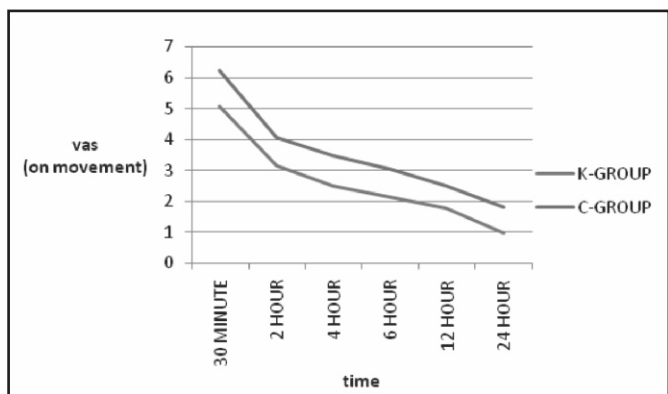
**Table 2: Rescue analgesic requirement**

	<b>Group-K</b>	<b>Group-C</b>	<b>P-Value</b>
Interval time for 1 <sup>st</sup> analgesic need	33.1±4.7	20.3±5.2	0.0001
Total number of Diclofenac required in first 24 hours	0.6±0.6	1.0±0.8	0.0512

**Graph 1: VAS at rest (VAS-Visual Analogue Scale)**



**Graph 2: VAS on movement (VAS-Visual Analogue Scale)**



**Discussion:**

Intraoperatively and postoperatively maximum stimulus results in stimulation of C fibres nociceptor resulting in the release of glutamates and activates postsynaptic NMDA receptors. Increase NMDA receptor activation play role in incisional and neuropathic pain and results in the activation and exacerbation of secondary hyperalgesia.

Analgesic intervention before the noxious stimulus means preemptive analgesia attenuates or eliminates sensitization and so decrease acute pain.<sup>(5)</sup>

Ketamine as NMDA antagonist produces its analgesic effect by inhibiting the hyperexcitability of dorsal horn nucleus resulting from tissue damage. So it can decrease the intensity of acute postoperative pain.<sup>(2)</sup>

In a study done by Adam et al,<sup>(13)</sup> ketamine was used in mastectomy in a small dose of 0.15 mg/kg and it failed to prove preemptive analgesic effect of it. Our results were opposite to their result, which may be due to their use of very low dose of ketamine(0.15 mg/kg). We used ketamine in the dose of 0.5 mg/kg intravenously. S D Amasoph et al used low dose Ketamine (0.5 mg/kg iv) pre-incision and post-incision in major gynecological surgery. They found in their study that 1<sup>st</sup> requirement for analgesic was significantly longer in pre-incision group. This result is in accordance with our study.<sup>(16)</sup>

In another study also, preemptive analgesic effect of ketamine was not found with 0.15 mg/kg dose of ketamine for elective gynecological surgery.<sup>(17)</sup> Some studies showed that low dose of ketamine decreases VAS score and postoperative opioid consumption if given preoperatively.<sup>(3,6,11,12,14,15)</sup> However, when Ketamine is given after incision, it is observed that it did not produce that effect.<sup>(7, 8, 9, 10)</sup> In this study, VAS score results showed good analgesia with ketamine. Moreover some patients in ketamine group did not require rescue analgesic in 1<sup>st</sup> 24 hour postoperatively. There is a statistically significant difference between both groups in the total analgesic dose consumption and in the time interval to request the 1<sup>st</sup> analgesic.

H Singh et al used three different dose of Ketamine for preemptive analgesia for laparoscopic cholecystectomy and found that 0.5 mg/kg dose of Ketamine was effective in terms of analgesic efficacy without any hemodynamic changes and adverse effect.<sup>(5)</sup> One limitation of our study was that the patients were not followed up for chronic pain evaluation with

subanesthetic dose of ketamine. Further research is required to elicit long term effect of Ketamine in reducing the incidence of chronic pain syndrome. We did not find any haemodynamic changes and adverse effect like hallucination, nightmare, and visual disturbances in ketamine group.

### Conclusion:

Preemptive ketamine has got an important role in reducing postoperative pain and analgesic requirement in breast cancer patients undergoing modified radical mastectomy. A subanesthetic dose of 0.5 mg/kg intravenous was not associated with any adverse effect and haemodynamic changes.

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