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Original Research Article

Pre-Emptive Analgesic and Opioid Sparing Effect of Ketamine in Patients Undergoing Total Radical Mastectomy

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ABSTRACT

Background: The present study has been undertaken to evaluate pre-emptive analgesic and opioid sparing effect of intravenous ketamine in patients undergoing total radical mastectomy.
Method: Eighty female patients undergoing breast cancer surgery under general anesthesia, in a double-blinded, placebo controlled study were randomly divided into two groups of 40 patients each. Group K received ketamine 0.3mg/kg IV just before induction. Group C received normal saline as placebo.
Result: Time to first analgesic dose (TFA) required was significantly delayed in ketamine as compared to placebo group. Statistically significant difference was seen in Visual analog score (VAS), Prince Henry score (PHS) and mean morphine consumption between ketamine and control group.
Conclusion: This study proved that ketamine has a definitive role in reducing postoperative pain and has opioid sparing effect in patients undergoing modified radical mastectomy.

Keywords: Pre-emptive analgesia, Ketamine, Post-operative pain

INTRODUCTION

The concept of pre-emptive analgesia is based on the assumption that the administration of analgesic drug before the occurrence of nociceptive input can prevent massive barrage of afferent impulses from reaching the spinal cord causing central sensitization, which results in improved postoperative pain control. [1]

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. Ketamine is a NMDA receptor antagonist. [2] Evidence about the effectiveness of the NMDA antagonist ketamine to reduce postoperative hyperalgesia and acute and long-lasting pain is inconclusive. There is some evidence that a single dose of perioperatively administered ketamine can reduce postoperative analgesic requirement [3-12] whereas other studies have demonstrated no beneficial effect of pre-emptive ketamine. [13-15]

With this consideration, we designed this study to evaluate pre-emptive analgesic and opioid sparing effect of intravenous ketamine in patients undergoing total radical mastectomy.

MATERIALS AND METHODS

After obtaining Institutional Research Ethical Committee approval and informed written consent, eighty adult female patients aged between 25-75 years with ASA physical status I-III scheduled for elective total radical mastectomy for breast cancer under general anaesthesia were recruited in a double blind, placebo-controlled study. The patients with known history of drug or alcohol abuse, hypertension, CAD, severe respiratory insufficiency, chronic pain syndrome, psychological disorders, long term use of opioids medication and patients who received analgesics within 12 hrs before the surgery were excluded from the study.

During preoperative assessment, information was given to the patient about Visual analog scale (VAS) and Prince Henry scoring (PHS) system for pain assessment. VAS (0= No pain, to, 10 = worst imaginable pain and PHS (0 = no pain, 1 = pain on cough, 2 = pain on deep respiration, 3 = moderate resting pain, 4 = severe resting pain). The postoperative staff was educated about the sedation score which was assessed on 3 point scale (1 = conscious, well oriented, 2 = sedated but responding to verbal commands, 3 = sedated, responding to verbal command with difficulty). Two identical syringes were prepared for each patient marked A and B by an anesthesiologist not involved with the study. Syringe A contain 0.3 mg/Kg Ketamine diluted with normal saline to make total volume 5 ml. Syringe B contain 5 ml 0.9% NS. The patients were randomly assigned to two groups of 40 patients each. In Group K- patients received 0.3 mg/kg ketamine I/V 90secs before surgical incision. In Group C- Patients received 5 ml normal saline 90 sec before incision.

The patients were premedicated with tab diazepam 5 mg, ranitidine 150 mg night before surgery and tab diazepam 5 mg, tab ranitidine 150 mg and tab ondansetron 8 mg two hrs before surgery. Patient was induced with injection midazolam I mg IV, propofol 1-2mg/kg over 30 seconds and intubation was facilitated with non-depolarizing muscle relaxant (NDMR). Injection fentanyl 1μg/kg was given just before the intubation and anesthesia was maintained with nitrous oxide 60% in oxygen, isoflurane, and divided doses of fentanyl with total dose of 2 μg/kg. Muscle relaxation was maintained with divided doses of NDMR after checking relaxation with peripheral nerve stimulator. At the end of the surgery, residual neuromuscular blockade was antagonized with neostigmine and glycopyrrolate.

Postoperatively, VAS, PHS and Sedation Score were measured immediately on arrival to recovery room by the staff nurse. Patient having VAS > 3 was given morphine 1.5mg iv bolus as a rescue medication till the desired effect is obtained. Pain score, heart rate, arterial systolic blood pressure, diastolic blood pressure, respiratory rate and sedation score was recorded at the time when first analgesic dose is given and also at 2, 4,6,9,12,18 and 24 hrs. The total dose of morphine administered via bolus injection was recorded at 24 hrs after first dose of study medication. The adverse events such as nausea, vomiting, hallucination, respiratory depression and the need for supplement medication were recorded throughout 24 hrs periods.

Demographic data and clinical variables were analysed by using unpaired two-tailed Student's *t*-tests. VAS & PHS pain intensity scores were analysed by using two-way (group 3 time) repeated-measures analysis of variance. Because morphine consumption did not follow a normal distribution, we used the Mann- Whitney *U*-test to compare the doses consumed by the two groups. The x2 test was used to compare the incidence of side effects. A value of *P*, 0.05 was considered significant. The results are expressed as mean ± SD.

RESULTS

Demographic profile was comparable in both the groups in terms of age, weight, height. There was no significant difference in blood loss, the

mean duration of time from induction to incision, incision to closure and closure to recovery between the two groups (table1).

Table-1: Demographic Profile

	Group K	Group C	P value
Age(Yrs.)	43.5±6.6	45.2±7.9	≥0.05
Weight(Kg)	61.40±7.58	64.30±8.69	≥0.05
Induction to incision(Hrs)	24.85±7.05	24.65±4.22	≥0.75
Incision to closure(Hrs)	86.95±19.18	84.00±20.76	≥0.65
Closure to recovery room(Hrs)	15.35±4.57	15.15±5.30	≥0.85
Blood loss(ml)	150.75±53.71	150.50±73.04	≥0.99

Table-2: Comparison of TFA, VAS, PHN, sedation and Morphine consumption

	Group K	Group C	P value
Mean TFA(Hrs.)	32.20±42.68	6.60±2.56	≤ 0.015
Mean VAS	2.43±0.96	3.10±0.76	≤0.001
Mean PHS	0.71±0.56	1.24±0.44	≤0.001
Mean Sedation	1.21±0.21	151±0.15	≤0.001
Mean morphine consumption (mg)	5.40±6.37	10.91±7.30	≤0.001

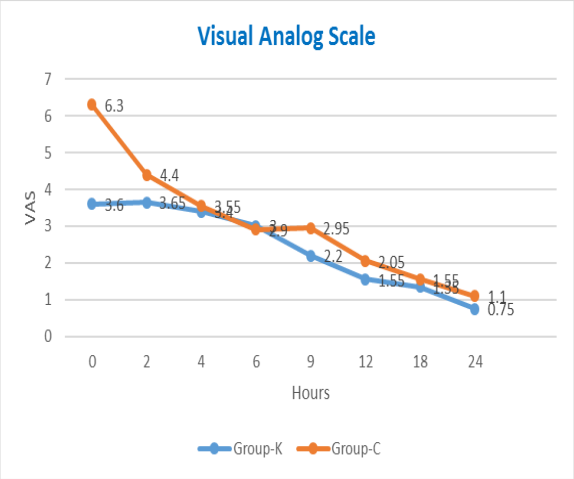

Fig: 1: Visual Analog scale

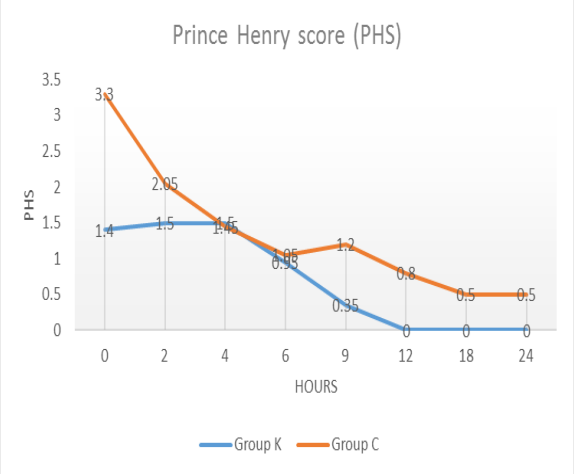

Fig: 2: Prince Henry score

The time to first analgesic (TFA) dose required was significantly delayed in group-K as compared to control group(p≤0.015) (table 2). Patients in control group had statistically significant higher pain score than ketamine group (p≤0.001). Statistically significant difference was seen in VAS & PHS score between control and ketamine groups (table 2, Fig 1 &2). Mean morphine requirement was significantly higher in placebo group as compared ketamine group (p≤0.001) (table2). The incidences of adverse effects were recorded throughout the postoperative period between the two groups. Three patients in ketamine and four patients in placebo group had complained of nausea and vomiting. None of the patients in either of the groups had respiratory depression. In both the groups every patients was asked in detail about hallucinations or having observed dreams of any kind. Not a single patient in any of the group was found to have hallucinations or dreams.

DISCUSSION

Surgical procedures almost invariably cause tissue damage resulting in pain. The impact of inadequate pain relief is well known and it can result in delayed mobilization and related complications as well as psychological distress and anxiety. [5]

Ketamine is an I.V anaesthetic and has marked analgesic effect even when used in small doses. Various mechanisms have been suggested for antinociceptive effects of ketamine: NMDA receptor antagonism, interaction with spinal μ receptors and activation of descending pain inhibitory monoaminergic pathways, which is expressed by α2 adrenoceptors at spinal level. [15]

The main finding of this study shows that pre-emptive intravenous low dose

ketamine decreased postoperative pain and opioid requirement in patients undergoing total mastectomy. As measured by time to rescue medication (TFA), pain intensity ketamine was statistically superior to control group in consistent manner.

In our study, the time to first rescue analgesic (morphine) required was 32.20 min in ketamine group as compared to 6.60 min in control group which was statistically significant ($p \leq 0.015$) (table 2).

Pain intensity score was also significantly low in ketamine group as compared to control group throughout the study period which proves that when ketamine used before skin injection has definite pre-emptive analgesic effect for postoperative pain relief. The VAS and PHS score in ketamine group was 2.43±0.96 & 0.71±0.56 respectively as compared to control group 3.10±0.76 &1.24±0.44 ($p \leq 0.001$) (table-2). Our findings are comparable to various studies which show that administration of low dose of ketamine before skin incision increase time to first analgesic requirement, decrease VAS score and postoperative opioid consumption. [3-12] Our results, however, are at a variance with the finding of Adam et al, who failed to prove pre-emptive analgesic effect ketamine in patients undergoing total mastectomy which may be due very low dose of ketamine (0.15 mg/kg) used in their study. [1,13-15] We used ketamine in the dose of 0.3 mg/kg intravenously.

Solanki et al also used low dose Ketamine (0.5 mg/kg iv) before skin incision in patients undergoing modified radical mastectomy. They found in their study that time for first analgesic requirement was significantly longer in ketamine group. This result is in accordance with our study. [3]

Use of ketamine hydrochloride for pre-emptive analgesia did not associated with any side effect. None of our patients in any of the group had psychotomimetic effects and patients were found to be more alert instead of drowsy. It may be, because ketamine was used in small dose and that too in the beginning of the surgery.

CONCLUSION

Pre-emptive ketamine has a definitive role in reducing postoperative pain and has opioid sparing effect in patients undergoing modified radical mastectomy. A low dose of 0.3 mg/kg was devoid of any adverse effects and hemodynamic changes.

Conflict of Interest: None

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