

Preventive analgesia: Effect of small dose of ketamine on morphine requirement after renal surgery

Beena Parikh, Jyotsna Maliwad, Veena R Shah

Department of Anaesthesia and Critical Care, Institute of Kidney Diseases and Research Centre, Ahmedabad, Gujarat, India

Abstract

Background: N-methyl D-Aspartate (NMDA) receptors seem to be responsible for pain memory and their blockade can contribute significantly in prevention of pain. This study was conducted to evaluate the preventive effect of small dose of ketamine, a NMDA receptor blocker, given before skin incision in renal surgery, with the aim to compare analgesic efficacy, intra operative and post-operative side effects.

Materials and Methods: In a prospective double-blind study, 60 American Society of Anesthesiologists (ASA) risk I and II adult patients scheduled for elective open renal surgeries by flank incision were randomly divided in two groups. Ketamine group (group K) received ketamine 0.15 mg/kg intravenously, 30 minute before start of surgery followed by infusion of ketamine 2 µg/kg/min till start of skin closure. Control group (group C) received normal saline in place of ketamine. Both groups received morphine 0.15 mg/kg i.v. at the time of skin closure. The analgesic efficacy was judged by visual analogue scale (VAS) at rest and on movement, time to first analgesic and morphine consumption in 24 hours. Opioid or ketamine related side effects were also recorded.

Results: Patients in ketamine group had significantly lower VAS score, longer time to first analgesic (21.6 ± 0.12 Vs 3.8 ± 0.7 hrs), and lower morphine consumption (5.8 ± 1.48 Vs 18.1 ± 1.6 mg) in 24 hours. There were no demonstrable side effects related to ketamine in group K whereas incidence of nausea and vomiting was higher in group C.

Conclusion: Our results demonstrate that small dose of ketamine decreases post-operative pain, reduces morphine consumption, and delays patients request for analgesia beyond the clinical duration of action of ketamine after open renal surgery.

Key words: Analgesia-preventive, drugs-ketamine, morphine

Introduction

Central nervous system plasticity that occurs in response to tissue injury may contribute to the development of persistent post-operative pain. Many researches have focused on methods to prevent central neuroplastic changes from occurring through the utilization of pre-emptive or preventive multimodal analgesia technique.^[1]

The original concept of preemptive analgesia put forward

Address for correspondence: Dr. Beena Kandarp Parikh,
Department of Anaesthesia and Critical Care, Institute of
Kidney Diseases and Research Centre, Civil Hospital Campus,
Ahmedabad - 380 016, Gujarat, India.
E-mail: bina_parikh@yahoo.co.in

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by Crile suggested that administration of an analgesic before surgical incision might reduce the intensity of post-operative pain by reducing central sensitization.^[2] This definition of preemptive analgesia was thought to be too restrictive because central sensitization triggered by surgical incision continues in the intraoperative and postoperative period by noxious stimuli. Hence, analgesic regimen covering this entire duration of stimuli may provide an effective postoperative analgesia. The term, preventive analgesia, was introduced to emphasize the fact that administration of a drug at any point in perioperative period may reduce post-operative pain intensity, analgesic use or both beyond the clinical duration of action of the target preventive drug.^[3]

Although many drugs have demonstrated evidence of preventive analgesic effect, drugs that prevent development of central sensitization have the greatest benefit. Ketamine, nociceptive N-methyl D-aspartate (NMDA) antagonist has a potential for altering central sensitization,^[4] hence we decided to use small bolus dose of ketamine followed by continuous infusion to examine preventive effect on post-operative pain and opioid consumption after open renal surgery.

Materials and Methods

After institutional ethical committee approval and written informed consent, 60 adult patients of American Society of Anesthesiologists (ASA) I and II, 18-70 years of age, scheduled for open renal surgery under general anesthesia were included in this study. Patients with chronic pain on regular medication with analgesics, psychiatric disorder and alcohol or drug abuse were excluded from the study. On the day before surgery, all the patients were made familiar with the use of 100 cm a visual analog scale (VAS) identifying 0 as no pain and 100 the worst imaginable pain.

Patients were randomly selected by picking up a closed envelope for group C or group K. Study solutions were prepared before surgery by an investigator who did not subsequently take part in the study. For bolus dose, 10 ml of normal saline was used in group C and 10 ml ketamine (1 mg/ml) in group K. For infusion during maintenance, 50 ml of normal saline was prepared in group C and 50 ml of ketamine (1 mg/ml) in group K.

After premedication with glycopyrrolate 0.004 mg/kg, ranitidine 50 mg, metoclopramide 10 mg, and fentanyl 2 µg/kg were administered intravenous (IV), anesthesia was induced with thiopental sodium 5 mg/kg and tracheal intubation was facilitated with succinylcholine 1.5 mg/kg. Patients were maintained with O₂, N₂O, halothane, and vecuronium. This was followed by a bolus dose of study solution 0.15 ml/kg (ketamine 0.15 mg/kg in group K and normal saline in group C) and continuous infusion of 0.12 ml/kg/hour (ketamine 2 µg/kg/min in group K and normal saline for group C) till start of skin closure. Morphine 0.15 mg/kg IV was given at the time of skin closure. Intraoperative vital parameters like heart rate (HR), noninvasive blood pressure (NIBP), and oxygen saturation (SpO₂) were monitored and any variations due to surgical stimulus (>20% increase in systolic blood pressure [SBP] and/or HR) were controlled with change in the concentration of halothane. No top-up doses of fentanyl were given. At the end of the surgery, residual paralysis was reversed with atropine 20 µg/kg and neostigmine 50 µg/kg IV and trachea extubated when patients responded to verbal commands and head lift test was positive. Recovery time from completion of reversal to extubation was noted.

In the post anesthesia recovery room, another blinded observer assessed VAS pain score at 15 min interval for 1st hour, then at 4, 8, 12, 16, and 24 hours after surgery. When VAS was >40 morphine was given as 1 mg increments until VAS score was <40. Time to first analgesic (TFA-time from end of surgery to first request for morphine), number of patients requiring morphine and total amount of morphine given in 24 hours were recorded in both groups.

Post-operatively, the incidence of side effects like nausea, vomiting, pruritus, diplopia, sedation, emergence reaction (dysphoria or hallucination), and respiratory depression (RR < 10 breaths/min) were noted.

Before the study, sample size was determined. Based on an earlier study, we anticipated the mean morphine consumption over 24 hours to be 50 mg. To detect a difference of 30% in morphine consumption, estimated sample size was 28 patients per group to get a power of 90% and $\alpha=0.05$.

All data were represented as mean \pm SD. Statistical significance was tested with the use of student's 't' test. P value < 0.05 was considered significant.

Results

Both study groups were comparable with respect to age, sex, type and duration of surgery, and recovery time [Table 1]. During the first 12 hrs after surgery, the VAS pain score was significantly low in group K as compared to group C ($P<0.05$) [Figure 1]. In group-K, only five patients required one dose of supplemental analgesic while in group C all patients required additional dose of analgesic which was statistically significant ($P<0.05$) [Table 2]. Total morphine consumption in 24 hours was significantly low in group K

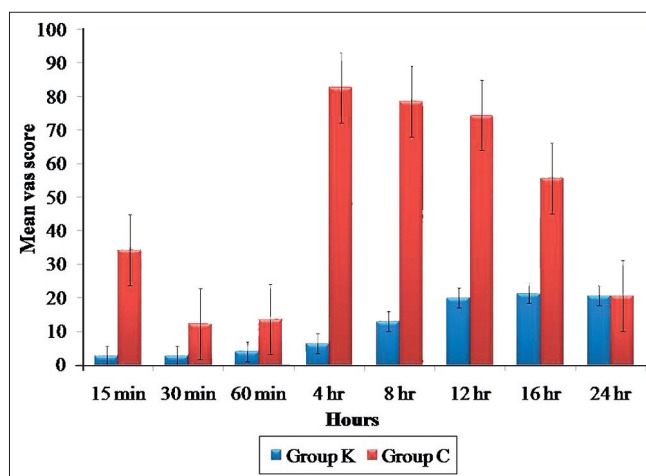


Figure 1: Mean VAS pain scores

Table 1: Demographic data

Variable	Group C (n=30)	Group K (n=30)
Age (yr)	42.2 \pm 10.53	39.2 \pm 12.2
Sex (M/F)	10/20	17/13
Duration of surgery (hrs)	3.4 \pm 0.06	3.5 \pm 0.33
Recovery time (min)	7.5 \pm 0.6	8.3 \pm 1.6
Type of surgery	30 nephrectomy	27 nephrectomy 2 pyelolithotomy 1 pyeloplasty

Table 2: Postoperative analgesic requirement during 24 hours

	Group K	Group C	P value
TFA in hours (mean \pm SD)	21.6 \pm 0.12	3.8 \pm 0.7	<0.05
Total morphine consumption in 24hrs (mean \pm SD) in mg	5.8 \pm 1.48	18.1 \pm 1.6	<0.05
Number of patients requiring additional doses of morphine	5	30	<0.05

(5.8 \pm 1.46 mg) compared to group C (18.1 \pm 1.6 mg) [Table 2]. The first analgesic demand time was long in patients of group K as compared to group C [Table 2] which was statistically significant. Nausea and vomiting was observed in four patients of group C and all of them were treated with Ondansetron 4 mg IV. No side effects like sedation respiratory depression, hemodynamic disturbances, pruritus, emergence reaction, and hyperalgesia were observed in post-operative period in both the groups [Table 3].

Discussion

Ketamine has analgesic properties that are mediated by a number of mechanisms. NMDA receptor noncompetitive antagonism accounts for most of its analgesic effects through a use-dependent channel blockade.^[5] The affinity of ketamine for NMDA receptors is several-fold higher than that for μ receptors, non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, and monoaminergic transporter sites.^[3]

Pharmacological studies also suggest that addition of low-dose ketamine to opioids produces synergistic or an additive analgesic effect most likely as a result of the combination of presynaptic opioid inhibition reducing afferent transmission by diminished transmitter release and postsynaptic NMDA blockade which reduces wind up and central sensitization.^[6,7] In recent years, attenuation of the development of acute tolerance to opioids by ketamine has received specific attention. Opioids produce anti-nociception through μ receptor agonist activity and activation of monoaminergic descending pathways at spinal level. They activate NMDA receptors resulting in acute tolerance to opioids and delayed hyperalgesia. Small dose of ketamine given before noxious stimulation has an advantage of attenuating analgesic tolerance to opioids and hyperalgesia by blocking NMDA receptors.^[8]

There are conflicting results in the literature concerning preemptive effect of ketamine. Many studies have documented a preemptive effect,^[9] but others have failed to demonstrate significant preemptive analgesic effects.^[10] In a qualitative systematic review of the role of NMDA receptor antagonists in preventive analgesia, ketamine produced a significant

Table 3: Post-operative side effects

Side effects	Group C	Group K
Respiratory depression	0	0
Hypotension/hypertension	0	0
Tachycardia/bradycardia	0	0
Nausea/vomiting	4	0
Pruritis	0	0
Emergence reaction	0	0
Hyperalgesia	0	0

preventive analgesic benefit in 58% of studies.^[3] Ketamine appears less effective when given after surgical stimulus. Apart from the timing of treatment, route of administration, insufficient afferent blockade, use of opioids during surgery, intensity of noxious stimulus, and outcome measurement problems seem to be important factors responsible for lack of evidence for preemptive effects.^[1]

Optimal dosage is another controversial area. Due to high affinity of ketamine for NMDA receptors, it has been observed that smaller the dose, the more selective the ketamine interaction with NMDA receptors. The low-dose ketamine is defined as a bolus dose of less than 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via IV or epidural route. For continuous IV administration, low-dose ketamine is defined as a rate of $\leq 20 \mu\text{g/kg/min}$ ^[6] or a serum concentration of 30-120 ng/ml. Our dosage scheme for the ketamine infusion was calculated using published pharmacokinetic variables to achieve a plasma concentration of about 60 ng/ml which is in the small range of concentrations known to counteract hyperalgesia while producing minimal side effects.^[11] The initial loading bolus was 0.15 mg/kg and it was followed by a maintenance infusion of $2 \mu\text{g/kg/min}$ until start of skin closure. Patients in the control group were given equal volumes of saline. Similar dose of ketamine has proven to be effective after major abdominal surgery with remifentanyl-based anesthesia.^[6,12]

We observed that the analgesic effect of ketamine evaluated with VAS, time to first analgesic, and postoperative morphine consumption, extended beyond the pharmacological actions of ketamine. The plasma half-life of ketamine is ≤ 17 minutes and analgesia produced by ketamine 125 and 250 $\mu\text{g/kg IV}$ lasts approximately five minutes when the plasma ketamine concentration is $> 100 \text{ ng/ml}$. Ketamine concentration in our study would be expected to be sub-analgesic with the dose used producing analgesia lasting for few minutes, however, the analgesic effect of ketamine, was clearly evident during the postoperative period (i.e., approximately 3.5 plasma half-lives of ketamine). Similar results have been reported in different studies. Stubhaug *et al.*, infused ketamine for three days after nephrectomy and found that ketamine reduced the

area of punctuate mechanical hyperalgesia surrounding the surgical incision for the seven post-operative days.^[13] With preemptive administration of ketamine, a decrease in post-operative morphine consumption was observed for two post-operative days after abdominal surgery.^[13,14] Tucker *et al.*^[15] and Zankine J *et al.*,^[16] showed clinical benefit of ketamine when co-administered with opioid. We believe that this long-lasting post-operative analgesia might be explained with a preventive analgesic effect of ketamine on central sensitization and not due to attenuation of acute tolerance to opioid because intraoperative opioids were not used in our study. Nitrous oxide, used in the present anesthetic technique, may have enhanced NMDA receptor inhibition by ketamine because nitrous oxide too has been reported to exert NMDA antagonist properties.^[17] However, it is unlikely that nitrous oxide confounded our results as it was also present in the control group.

As morphine consumption was lower in group K, the incidence of morphine-associated side effects, such as pruritus, nausea, and vomiting were also decreased. We did not observe any psychomimetic effects related to ketamine. The overall incidence of adverse CNS symptoms in patients receiving low-dose ketamine is approximately 10% and is dose related.^[18] Large doses (>2 mg/kg, i.v.) and rapid administration (>40 mg/min) predispose to this side effect whereas they are minimal at infusion rate less than 2.5 mg/kg/min^[1] or around 200-300 mg/24 hrs.^[19] It is interesting to note that the highest risk is found in sedated patients who do not receive benzodiazepine, whereas in patients undergoing general anesthesia the incidence is really low and independent of benzodiazepine premedication.^[20] We used low dose under general anesthesia without benzodiazepine premedication and did not observe any adverse effects.

Conclusion

Small dose of ketamine given before skin incision and as continuous infusion throughout the surgery decreases the postoperative pain, reduces morphine consumption and delays patients request for analgesia after open renal surgery. This confirms the preventive analgesic effect of ketamine.

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