Influence of Difference in Timing of Perioperative Administration of Low-dose Ketamine on Postoperative Analgesia

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Abstract

Background: Preemptive analgesia is a part of multimodal regime for effective postoperative analgesia. Ketamine is said to possess preemptive effects, which has been simultaneously refuted by other studies. Hence, we designed this randomized, double-blinded trial to establish the influence of timing of perioperative ketamine administration for superior postoperative analgesia. Methods: Ninety patients undergoing infraumbilical surgeries under spinal anesthesia were randomized to receive ketamine either preincision (Group KI), preincision and during skin closure (Group KII), or only during skin closure (Group KIII). Outcomes studied were postoperative pain, sedation, and incidence of side effects. Results: Analysis of variance statistics for postoperative visual analog scales (VAS) for pain showed no significant difference in three groups. However, there was a significant difference between Groups KII and KIII in the immediate postoperative period (95% confidence interval [CI] of mean VAS for Group KI = 0.9249–1.4889; 95% CI for Group KII = 1.4406–1.8260; \( P = 0.043 \)). Sedation scores in the immediate, 4 h and 8 h postoperative showed a significant difference between Group KI and Group KII (\( P = 0.007, 0.008, 0.001 \), respectively) and between Group KI and KIII (KI: KIII - \( P = 0.0008, 0.0006, 0.02 \), respectively). Although the incidence of psychotomimetic effect was more in Groups KIII, it was not statistically significant. Conclusion: Ketamine possesses postoperative analgesic effects in the immediate postoperative period only when its preemptive administration is supplemented with repeat administration during closure. Incidences of side effects were comparable in all groups.

Keywords: Ketamine, preemptive analgesia, psychomimetic effects, sedation

Introduction

With an increasing number of patients undergoing surgery for varied reasons, managing pain and especially postoperative pain has put a big challenge to anesthesiologists. Besides the availability of multimodal analgesic regimes, the timing of perioperative administration of analgesic drugs is also important in eliciting their effectiveness.\(^1\) In the big armamentarium of analgesic drugs, ketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist, is gaining popularity for its efficacy in preventing postoperative pain as a preemptive analgesic.\(^2\,3\) Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain. NMDA receptor antagonists have received greatest attention because NMDA receptors have a role in central sensitization and neural modulation.\(^1\,3,4\) Subanesthetic dose of ketamine, by blocking the NMDA receptors abolishes the peripheral afferent nocuous stimulation and also prevents central sensitization of nociceptors.\(^5\) Preemptive analgesia has been proposed to result in better pain management, reduced analgesic consumption, and improved patient satisfaction.\(^5\) However, preemptive analgesia, which aims to prevent the establishment of altered central processing, has proven difficult to study.\(^5\) Various studies have shown conflicting results.\(^2\,5,6\)

We designed this double-blinded randomized trial to compare the efficacy of preemptive ketamine administration with...
ketamine given during completion of surgical procedure for better pain management and minimal side-effects.

**METHODS**

After taking institutional ethical clearance and informed consent, 90 adult American Society of Anesthesiologists Grade I and II patients, aged between 18 and 65 years undergoing lower abdominal surgery under spinal anesthesia were selected to participate in this trial. Patients undergoing emergency surgeries, patients with signs of endocrine, renal, hepatic or psychiatric diseases, and patients who were alcoholic and hypertensive were excluded from the study. Enrolled patients were randomized into three groups using computer-generated random number table. Group KI patients received ketamine 0.25 mg/kg diluted to 2 ml with normal saline (NS) before skin incision and 2 ml NS before skin closure. Group KII patients received ketamine 0.25 mg/kg before skin incision and again 0.15 mg/kg ketamine, both diluted to 2 ml with NS, before skin closure. Group KIII patients received 2 ml of NS before skin incision and ketamine 0.25 mg/kg diluted to 2 ml with NS before skin closure. The study drug was prepared and given by a trained anesthesiologist who was no further involved in the study. Study parameters were collected by another anesthesiologist who was in charge of the case. Both the anesthesiologist collecting data and patient were unaware of the type of drug being administered. Hence, the study proceeded as double-blind, randomized trial.

In the operation theater, baseline hemodynamic parameters and oxygen saturation on the room air were noted. Injection ondansetron 4 mg was given intravenously. Patients were turned to the left lateral position, part painted and draped and spinal anesthesia was given in the 3rd or 4th lumbar space with 15 mg of 0.5% bupivacaine heavy after the free flow of cerebrospinal fluid was demonstrated. After the achievement of adequate block, injection midazolam 0.02 mg/kg was given, followed by the study drug over the period of 30 s. Intraoperative monitoring of blood pressure, heart rate, oxygen saturation, and electrocardiography was done. Fluid administration was done in accordance with preoperative fluid deficit and intraoperative fluid requirements. If blood pressure decreased to <80 mmHg or heart rate <50 beats/min, injection ephedrine 3 mg or injection atropine 0.6 mg respectively was given. Before 30 min skin closure, the second lot of study drug was again given according to the randomization code. After the operation, patients were shifted out of the operation theater to the recovery area. Injection diclofenac 75 mg was given intravenously at the time of skin closure and thereafter at 8 hourly intervals. All the additional analgesic and antiemetic drugs given were recorded along with their doses.

**Data collection**

Pain scores on ten-point visual analog scale (VAS) (0 – no pain; 10 – worst possible pain) were assessed every 4 hourly intervals till 24 h and then 6 hourly till 48 h. Rescue analgesic included injection Tramadol 2 mg/kg intravenous, given when VAS scores were 4 or more than 4.

At the same interval, sedation scores (1 = alert, 2 = asleep, alert after arousal, 3 = asleep, drowsy after arousal, 4 = asleep, difficult to arouse, and 5 = unarousable) were also noted.

The incidence of intra- and post-operative psychomimetic effects was noted till the study duration. Emergence deliriums, hallucinations, vivid dreams, and purposeless involuntary movements were all grouped under psychomimetic effects.

The incidence of nausea and vomiting was also assessed till the study duration of 48 h. Nausea and vomiting will be taken as a single entity and was recorded as a dichotomous variable (yes/no).

**Statistical analysis**

Primary outcome was the postoperative pain. Secondary outcome included the sedation scores, incidences of psychomimmetic effects, nausea and vomiting, and incidence of additional analgesic requirements. Continuous data were presented as mean ± standard deviation. Demographic and VAS scores were compared between the three groups by one-way analysis of variance (ANOVA) test, and if significant, this was followed by comparative analysis between two groups. Categorical data were compared by Chi-square test or Fischer’s exact test. From the previous studies, mean VAS in control group was reported to be 5.2. Assuming 30% reduction in pain scores in our experimental group, i.e., taking mean VAS as 3.5 and standard deviation as 2, we calculated the sample size of 28 patients in each group to achieve the power of 80% with significance at 5%. To compensate for dropouts, we increased the sample size to 30 patients in each group. Statistical analysis was done using Microsoft Excel and Epi-info 7 (Ketamine-Neon Laboratories Ltd, Thane, Maharashtra, India).

**RESULTS**

Of total patients randomized into three groups, two patients had to be dropped from the study. One patient in Group KI (ketamine given preincision and NS given during skin closure) had started complaining of intraoperative pain and had to be supplemented with analgesics according to our institutional protocol. In another patient in Group KII (ketamine given preincision and also during skin closure), spinal anesthesia failed, and general anesthesia (GA) was administered. All the patients in Group KIII (ketamine given during skin closure and NS given preincision) fulfilled the study criteria. Demographic profile of the patients in all the three groups is presented in Table 1.

ANOVA statistics for postoperative VAS showed no significant difference in three groups at all the studied time intervals [Figure 1]. However, when comparing means between the two groups, there was a significant difference between Groups KII and KIII in the immediate postoperative period (95% confidence interval [CI] of mean for Group KI = 0.9249–1.4889; 95% CI for Group KII = 1.4406–1.8260; P = 0.043).

For sedation in the postoperative period, ANOVA statistics revealed a significant difference in three groups in the immediate postoperative period, and at 4 h and 8 h postoperative...
(P = 0.003, 0.002, 0.006, respectively). There was a significant difference between Group KI and Group KII (P = 0.007, 0.008, 0.001, respectively); and between Group KI and KIII (P = 0.0008, 0.0006, 0.02, respectively) at these specific time periods. However, there was no significant difference in the sedation scores between Group KII and KIII at any of the time periods [Figure 2].

Although the incidence of psychomimetic effect was greater in Group KIII, there was no significant difference in the three groups during the duration of the study (P = 0.36). The incidence of rescue analgesia administration also showed no significant difference and so was the incidence of nausea and vomiting [Table 2].

### Table 1: Demographic and surgical characteristics

|                | KI (n=29) | KII (n=29) | KIII (n=30) |
|----------------|-----------|------------|-------------|
| Age (years)    | 43.69±12.84 | 40.83±12.36 | 41.07±15.97 |
| Weight (kg)    | 62.14±7.55 | 60.97±9.31 | 61.67±8.32  |
| Gender (male:female ratio) | 14:15 | 18:11 | 19:11 |
| Duration (h)   | 1.71±0.50 | 1.65±0.46 | 1.72±0.48  |
| Type of surgeries (%) | | | |
| Inguinal hernia | 12 (41) | 13 (45) | 14 (47) |
| Incisional hernia | 4 (14) | 2 (7) | 3 (10) |
| Epigastric hernia | 1 (3) | 2 (7) | 1 (3) |
| Appendicectomy | 4 (14) | 6 (21) | 7 (23) |
| Abdominal hysterectomy | 8 (28) | 6 (21) | 5 (17) |

Values as mean±SD or n (%). Group KI=Ketamine given preincision, Group KII=Ketamine given preincision and during closure, Group KIII=Ketamine given during closure, SD=Standard deviation

### Table 2: Incidence of adverse effects and rescue analgesia

|                  | KI (%) | KII (%) | KIII (%) | P      |
|------------------|--------|---------|----------|--------|
| Psychomimetic effects | 5 (17.2) | 7 (24.1) | 10 (33.3) | 0.36   |
| Rescue analgesia  | 4 (13.8) | 8 (27.6) | 6 (20.0)  | 0.44   |
| Nausea and vomiting | 4 (13.8) | 5 (17.2) | 4 (13.3)  | 0.90   |

Values as n (%). Group KI=Ketamine given preincision, Group KII=Ketamine given preincision and during closure, Group KIII=Ketamine given during closure

### Discussion

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[8] Pain from the surgical procedures occurs as a consequence of tissue trauma and may further result in physical, cognitive, and emotional discomfort. The outcome of the surgical procedures can be affected as a result of changes arising from pain.[9] Because the intensity of early postoperative pain correlates with the development of residual pain after some type of surgery, perioperative pain management can greatly influence the long-term quality of life in patients.[10] Due to the excessive importance of pain, the Pain Society of America declared pain as the fifth vital sign.[11]

ANOVA statistics in this study revealed no significant difference in VAS pain scores in the three groups. However, there was a significant difference in score between Group KII (ketamine given preincision and during skin closure) and Group KIII (ketamine given during skin closure) in the immediate postoperative period. Our results demonstrated that preemptive analgesic effects are evident only when preincision ketamine is supplemented by similar injection during the last stages of surgery. When given solely as preemptive drug as in Group KI or during the skin closure as in Group KIII, it did not show any difference in analgesic effects.

Our study results are consistent with those shown by Dahl et al. in abdominal hysterectomy, where ketamine failed to produce preemptive analgesic effects.[5] Infect, authors, found that ketamine given after the skin closure resulted in significantly lower VAS score in the early postoperative period as compared to the ketamine given before skin incision or the control group. The mean dosage of rescue analgesic drug was same in preincision as well as ketamine given after skin closure groups. Although this study confirms the intrinsic analgesic effect of a small dose of ketamine, it did not demonstrate its preemptive effects.[5]

Similarly, another study again demonstrated no effect of preemptive ketamine in postoperative pain, nausea and vomiting, and perioperative additional analgesic requirements...
in ophthalmic surgery, although it improved extubation time.[6] Bauchat et al. in their study performed in cesarean sections under spinal anesthesia failed to demonstrate analgesic effects of ketamine when it was administered following delivery.[12]

In contrast to our study, Kwok et al. found that preincision ketamine resulted in lower pain scores as compared to postincision ketamine or placebo in first 6 h postoperatively in patients undergoing gynecological surgeries under GA. Mean morphine consumption was less in the preincision group.[2] Similar preemptive effects of ketamine were also shown by Sen et al. in cesarean section patients.[13] Another study in laparoscopic cholecystectomy also showed preemptive ketamine to be effective in reducing postoperative pain scores.[1]

The analgesic effects of ketamine do not end with NMDA receptors. It has been shown to interact with opioid receptors μ. Hence, ketamine has diverse mechanisms of actions for eliciting its analgesic effects.[7,18,15] Whereas timing of treatment is an integral part of the concept of pain management, the interaction between drug dosage and stimulus intensity must also not be overlooked.[2] Thus, an insufficient dose of ketamine or an intense noxious stimulus may stimulate NMDA-receptor activation and subsequent hyperalgesia. The insufficient afferent block may account for the many studies that have found a lack of evidence for preemptive analgesia.[2] These could be the reason for lack of preemptive analgesic effects of ketamine in our study.

Kapfer et al. demonstrated postoperative ketamine administration was associated with sedation, the results of which are consistent with our findings that ketamine produced sedation in both the groups (Groups KII and KIII) where it was administered during wound closure.[16]

The incidence of psychomimetic effects was more when ketamine was administered just before the skin closure (Group KIII) in our study. This could be because effect of midazolam, which was administered early during the surgery, was decreased by the time skin closure was started and hence not effective in suppressing psychomimetic effects of ketamine that was administered towards the end of the surgery. We had 17.2%, 24.1%, and 33.3% incidence of ketamine in Groups KI, KII, and KIII, respectively. Perumal et al. observed delirium in the range of 13%–20%, while dreams had the incidence of 10%–20% in short surgical procedures when used along with midazolam premedication.[17] Similar incidence of psychomimetic effects was shown by Somashekara et al.[18]

Needless to say, effects of ketamine in the human body, both within the realm of analgesia and without, are incredibly complex.[8] However, as is evident, ketamine does possess analgesic effects, which mitigates postoperative pain. One deficiency our study had was the absence of control group. However, including a control group in a study is debatable and ethically questionable.[19] Furthermore, the effect of ketamine on chronic pain was not studied, due to poor patient compliance in our setup.

**Conclusion**

Administration of ketamine before skin incision and again repeated during the closure is associated with postoperative analgesia in the initial hours following surgery. Our study failed to demonstrate any significant difference with either preemptive administration or administering it during last stages of surgical procedure, to be associated with reduction in pain scores.

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**Conflicts of interest**

There are no conflicts of interest.

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