

ORIGINAL RESEARCH

Comparison of combination between ketamine and parecoxib as multimodal preemptive analgesia with ketamine alone for elective laparotomy**¹Dr Vibhor Rai, ²Dr. Gyanender Dutt, ³Dr Vivek Tyagi**¹Assistant Professor, Department of Anaesthesia, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India²Assistant Professor, ³Associate Professor, Department of Anaesthesia, Nation Capital Region Medical Collage, Nalpur, Meerut, Uttar Pradesh, India**Correspondence:**

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Email: raivibhor79@gmail.com**Abstract****Aim:** The aim of this study was to compare the efficacy of preemptive analgesia with IV ketamine alone and multimodal preemptive analgesia that combines low-dose IV ketamine and IV parecoxib.**Methods:** In this prospective study, 60 patients scheduled for elective laparotomy were randomized to two groups of preemptive analgesia, namely, group K-P, in which anesthesiologists administered a combination of 0.3 mg/kg IV ketamine and 40.0 mg IV parecoxib, or group K, in which ones gave 0.3 mg/kg IV ketamine alone. Patients from both groups underwent surgery under general anesthesia, and total intraoperative opioid requirement was recorded. After surgery, morphine administered by automated patient-controlled analgesia (PCA) infusion device was initiated in all patients. Pain score was assessed using the visual analogue scale (VAS), and postoperative opioid requirement was recorded at 1 and 4 hours, and subsequently from 4-hour intervals up to 24 hours after surgery.**Results:** There were no significant differences in demographic characteristics between the two groups. In terms of pain intensity, compared to group K, patients in group K-P showed significantly lower VAS values at all time points tested during 24 hours after surgery.**Conclusion:** Among laparotomy patients, multimodal preemptive analgesia by the use of a combination of low-dose IV ketamine and IV parecoxib was more effective than IV ketamine alone in reducing pain scores and postoperative analgesia requirement.**Keywords:** Ketamine, pain relief laparoscopic surgery, preemptive analgesia, multimodal**Introduction**

Pain control is pertinent for optimal care in surgical patients. Various treatment modalities and their combinations have been used; however, adequate pain control is still not achieved in a majority of patients. Preemptive analgesia has been proposed to result in better pain management, reduced analgesic consumption, and improved patient satisfaction.¹

Laparoscopic cholecystectomy is associated with less pain and disability, nonetheless many patients experience considerable pain in the postoperative period and improvement in

analgesia is desirable. Pain after laparoscopic cholecystectomy involves several components and may be due to peritoneal stretching due to insufflation and diaphragmatic irritation.^{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.⁴ Although many drugs have demonstrated the evidence of preemptive analgesic benefit, N-methyl D-aspartate (NMDA) receptor antagonists have received greatest attention because NMDA receptors have a role in central sensitization and neural modulation.⁵

Ketamine is an N-methyl-D-aspartate receptor antagonist that is commonly used either as an IV induction agent, sedative agent, or as part of multimodal analgesia, and its use as preemptive analgesia has been described in a few studies. A meta-analysis based on data from 5 randomised controlled trials (RCTs) involving the use of ketamine for preemptive analgesia concluded that ketamine was effective in reducing postoperative morphine consumption and prolonging time to first analgesia request. Importantly, it was reported to be as safe as physiological saline with respect to side effects such as nausea and vomiting.⁶

Parecoxib is the only IV cyclooxygenase-2 inhibitor that can be a beneficial analgesic for moderate- to-severe acute postoperative pain, and its use in preemptive analgesia has been described in a few studies. A combination of parecoxib and ultrasound-guided paravertebral block as preemptive analgesia during video-assisted thoracoscopic surgery brings about better pain relief, lower sufentanil and ketorolac consumption, greater haemodynamic stability, and lower surgery-related stress response.⁷

Therefore, the aim of this study was to compare the efficacy of preemptive analgesia with IV ketamine alone and multimodal preemptive analgesia that combines low-dose IV ketamine and IV parecoxib.

Methods

The study was double blinded randomized control trial. It was started after obtaining ethical clearance from Ethical Approval board of the institution and consents from the participants. The written informed consent from patients were obtained and we recruited 60 patients scheduled for elective laparotomy under general anesthesia who met the inclusion and exclusion criteria during pre-operative assessment. The inclusion criteria were American Society of Anesthesiologists classifications I and II, ages 20–60 years, and a plan for postoperative PCA. The exclusion criteria were a known history of allergy to either ketamine, parecoxib or morphine for treatment of chronic pain, gastrectomy surgery because of peptic ulcer disease, liver and renal impairment, pregnancy, or morbid obesity. Patients were withdrawn from the study if unanticipated adverse events occurred intraoperatively, or if they were admitted to intensive care unit postoperatively. The sample size was calculated by using power and sample size software 3.0. The participants were randomized into two groups of preemptive analgesia by using the computer-generated randomisation. In group K-P (n = 30) a combination of IV ketamine 0.3 mg/kg and IV parecoxib 40.0 mg was given, while, in group K (n = 30), IV ketamine 0.3 mg/kg as placebo was given.

In the OT, an 18 G or 20 G IV cannula was inserted at the hand and non-invasive monitoring devices, such as electrocardiogram, pulse oximetry (SpO₂), capnography, and non-invasive blood pressure, were put in place. During pre-oxygenation and within 10 minutes before the induction of anesthesia, patients in group K-P received preemptive analgesia of IV ketamine 0.3 mg/kg and IV parecoxib 40.0 mg in 2 mL of normal saline, while those in group K received IV ketamine 0.3 mg/kg and 2 mL of IV normal saline as placebo. Anesthesia was induced with IV fentanyl 2.0 µg/kg and IV propofol 2.0 mg/kg in all patients, and after successful induction, IV rocuronium 0.6 mg/kg was given as muscle relaxant for endotracheal intubation.

After successful intubation, anesthesia was maintained by using sevoflurane, oxygen, and air. All patients were mechanically ventilated to maintain normocapnia with an end-tidal carbon dioxide of 35–40 mmHg.

Postoperative analgesia was initiated at the recovery bay for all patients identically. The first rescue analgesia with IV fentanyl 0.5 µg/kg bolus was considered at the recovery bay if patients experienced severe pain. An automated PCA infusion device that delivered a 1.0 mg bolus of morphine for every demand with a lock-up time of 5 minutes without background infusion was also initiated in the recovery bay for postoperative analgesia within the next 24 hours. Pain severity was assessed postoperatively by using the VAS at 1 hour, and subsequently at 4, 8, 12, 16, 20, and 24 hours. Time-to-first morphine request recorded by PCA device and total morphine requirement delivered by PCA device over 24 hours were documented.

Data were analyzed by using the Statistical Package for the Social Sciences (SPSS) software, ver. 24.0 (IBM SPSS Inc., Armonk, NY, USA). Categorical data were analyzed by using the chi-square test, while numerical data were analyzed by the independent t-test. P-value < 0.05 was considered statistically significant.

Results

Table 1: Demographic Data

Parameter	Group K-P (n=30)	Group K (n=30)	P value
Age	36.4 ± 11.8	40.4 ± 12.5	0.880
Gender			0.500
Male	5	2	
Female	25	28	
Height	152.0 ± 10.0	152.5 ± 10.0	0.850
Weight	58.4 ± 8.6	58.3 ± 12.0	0.876
BMI	25.3 ± 3.0	25.5 ± 4.8	0.650
ASA			0.545
I	24	25	
II	6	5	
Duration of surgery	2.6 ± 0.9	2.8 ± 0.8	0.450

Table 2: The Trend of Pain Intensity Based on VAS

VAS			
Time interval	Group K-P (n=30)	Group K (n=30)	P value
1 hour	3.0 ± 1.5	3.6 ± 0.6	0.002
4 hours	3.2 ± 0.8	4.0 ± 0.5	0.005
8 hours	3.3 ± 1.0	4.0 ± 0.6	0.002
12 hours	2.8 ± 0.7	3.4 ± 0.6	0.001
16 hours	2.6 ± 0.7	3.2 ± 0.7	0.002
20 hours	2.4 ± 1.0	3.2 ± 0.7	0.004
24 hours	1.6 ± 0.9	2.5 ± 0.7	0.003

There were no significant differences in demographic characteristics between the two groups (Table1). In terms of pain intensity, compared to group K, patients in group K-P showed significantly lower VAS values at all time points tested during 24 hours after surgery (Table 2).

Discussion

Intraoperative and postoperative noxious inputs cause prolonged firing of C- fiber nociceptors resulting in the release of glutamate. Glutamate is a major excitatory transmitter in the central nervous system, which activates postsynaptic NMDA receptors. NMDA receptor activation contributes to pain processing and pain phenomena such as wind up, spinal neural plasticity. NMDA receptor activation plays a role in inflammatory and neuropathic pain states and results in the activation and exacerbation of secondary hyperalgesia. This also initiates translational changes of the second- order neurones, which might be a crucial link in the pathogenesis of chronic pain.⁸ Analgesic intervention before the noxious stimulus, that is, preemptive analgesia may attenuate or block sensitization and hence reduce acute pain.⁹

Although many drugs have demonstrated the evidence of preemptive analgesic benefit,¹⁰ treatments that are likely to prevent the development of central excitability may have the greatest benefit. Ketamine, an NMDA receptor antagonist, is an interesting option for this purpose.

Our study demonstrated that low- dose i.v. ketamine administered before surgical incision has preemptive effect on postoperative pain and reduced analgesic requirements during the first 24 h after laparoscopic surgery. We assessed VAS at rest, on slight movement, and on deep breathing as the VAS assessment at slight movement and at deep breathing is more reproducible than the VAS at rest. The VAS scale was used as it is easier for the patient to use.⁵

The role of preemptive analgesia with ketamine has been previously reported in laparoscopic gynecological surgery.¹¹ Preemptive ketamine also had an opioid sparing effect in opioid abusers undergoing lithotripsy.¹²

One previous study that compared preemptive IV ketamine 0.5 mg/kg, IV parecoxib 40 mg, and placebo in 81 patients undergoing laparoscopic uterine surgery who also received postoperative sufentanil-based PCA showed that a single injection of short-acting ketamine before surgery had the same efficacy as long-acting parecoxib with respect to an opioid-sparing effect in the first 24 hours after surgery. However, it is known that parecoxib has better analgesic effect in the early postoperative period,¹³ and based on this fact, we show that a combination of IV ketamine and IV parecoxib led to better postoperative analgesia compared to single therapy. Importantly, we used a lower dose of IV ketamine at 0.3 mg/kg while the study on uterine surgery used 0.5 mg/kg.

Another study compared the effectiveness of a combination of IV ketamine 0.15 mg/kg and the non-steroidal anti-inflammatory drug diclofenac at 1.00 mg/kg with that of placebo, ketamine, or diclofenac alone in 80 consecutive patients undergoing laparoscopic cholecystectomy and reported that, at one hour after surgery, patients who received the combination had significantly lower pain scores compared with those receiving placebo or ketamine alone. Further, even though patients from all the four groups required postoperative analgesia, the time-to diclofenac sodium request was significantly longer in patients given the combination compared to those given placebo, ketamine, or diclofenac alone. This study also stated that ketamine at a dose of 0.15 mg/kg did not elicit a preemptive analgesic effect¹⁴ but supported the concept of multimodal preemptive analgesia. It is possible that the lower dose of IV ketamine (0.15 mg/kg) used in that study did not yield any significant effect.

Singh et al.,¹⁵ in their study on multiple dosing of IV ketamine, at 1.00, 0.75 and 0.50 mg/kg for laparoscopic cholecystectomy, found that preemptive ketamine had a definitive role in reducing postoperative pain and analgesia requirement. Further, among the three tested doses, 0.5 mg/ kg led to no adverse effects or haemodynamic changes while the dose of 1.00 mg/kg resulted in significantly higher heart rate and blood pressure, compared with other groups, at 0.0 and 0.5 hours, apart from a 10% incidence of hallucinations.

The study conducted by Nistal-Nuño et al.¹⁶ used 0.5 mg/kg IV ketamine before surgical incision and did not report a preemptive analgesic effect or a reduction in postoperative opioid requirement for pain in patients given IV morphine after colon surgery. Similarly, two other studies that used low-dose IV ketamine 0.5 mg/kg as preemptive analgesia during elective caesarean sections performed under either spinal anesthesia or general anesthesia showed that low-dose ketamine did not have a preemptive analgesic effect and that it was not effective in reducing postoperative pain scores or opioid requirements.^{17,18}

One study by Heydari et al.¹⁹ compared the effectiveness of three preemptive analgesic agents, namely, IV ketamine 0.25 mg/kg, IV paracetamol 15 mg/kg, IV magnesium sulphate 7.5 mg/kg, and placebo. The drugs were administered immediately after the induction of anesthesia in patients scheduled for elective lower extremity orthopaedic surgery under general anesthesia and the results showed that mean postoperative pain score during 24 hours after surgery and mean additive analgesic use during 12 hours after surgery were significantly lower in the ketamine group compared to others.

The use of parecoxib as preemptive analgesia has been previously studied in a few types of surgery. Xiao et al.²⁰ studied the effect of preemptive IV parecoxib, 40 mg, given 30 minutes before the first incision for total hip arthroplasty, by comparing it with a placebo. Another study by Bian et al.²¹ on preemptive IV parecoxib for total knee arthroplasty showed that it significantly decreased VAS values in the short term, relieved pain shortly after surgery, and did not increase the incidence of complications.

Conclusion

Multimodal preemptive analgesia using a combination of low-dose IV ketamine 0.3 mg/kg and IV parecoxib 40 mg was more effective than IV ketamine 0.3 mg/kg alone in post-laparotomy patients.

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