Section: Anaesthesia

Original Research Article

ANALGESIC EFFECT OF INTRAVENOUS KETAMINE ON POST OPERATIVE PAIN SCORES AFTER SPINE SURGERY: A RANDOMIZED DOUBLE BLIND STUDY

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Abstract

Background: Postoperative pain forms one of the categories of acute pain. Postoperative pain is one of the most undesirable experiences for a patient undergoing surgery. Ketamine is a drug which is effective in perioperative period as well as has shown possibility of preventing or at least reducing incidence and intensity of persistent post-operative pain and hyperalgesia. **Aim and Objectives:** is to evaluate of the analgesic effect of intra venous ketamine given pre emptively and post operatively versus placebo. Seconday outcomes studied were comparison of cumulative post operative fentanyl consumption in patients receiving ketamine at different times versus placebo. **Materials and Methods:** A Sample size of 75 (3 groups of 25) using computer generated random numbers with ASA grade 1 and 2 patients of either sex which were planned to undergo Spine surgeries under general anaesthesia were enrolled in the study and recieved following: Group 1: ketamine I.V. (0.5mg/Kg body weight) during induction and 5cc of normal Saline I.V. after closure of wound, before extubation. Group 2: normal saline I.V. 5cc during induction and ketamine I.V. (0.5mg/Kg body weight) after closure of wound, before extubation. Group 3: normal saline I.V. 5cc during induction and injection normal saline I.V. 5cc after closure of wound, before extubation. **Result:** Pulse rate and mean NRS decreased statistically in both the groups recieving ketamine as compared to placebo group and analgesia is better when ketamine was give pre-emptively. Least consumption of fentanyl was seen in the group which received ketamine preemptively. **Conclusion:** Low dose of 0.5 mg/kg body weight ketamine given preemptively is definitely more effective analgesic as compared to postoperative administration, in patients undergoing surgery on spine, as evidenced by the reduced fentanyl consumption and pain scores and is devoid of any side effects.

INTRODUCTION

The experience of pain is complex, multifaceted, and "an unpleasant sensory and emotional experience" as defined in part by the International Association for the Study of Pain.[1] It is a personal and subjective experience that involves sensory, emotional and behavioral factors associated with actual or potential tissue injury.

Even with advancements in understanding of pathophysiology and pharmacotherapeutics of surgical pain, it still remains under treated and poorly controlled. Spinal surgery has advanced from decompression procedures to complex spinal reconstruction and internal stabilization within the last 25 years and can improve quality of life parameters surgically treated patients.[2-4] Perioperative pain management is crucial for early rehabilitation, improving postoperative quality of life and for decreasing pain-related morbidity. Pre-emptive analgesia has been shown to increase pain thresholds during the perioperative period, which helps patients to better tolerate pain, and reduces postoperative narcotic use[5]. Ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist that has been shown to be useful in the reduction of acute postoperative pain and analgesic consumption in a variety of surgical interventions with variable routes of administration[6]. It has multiple mechanisms of

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action, including but not limited to decreasing central excitability, decreasing acute postoperative opiate tolerance, and a possible modulation of opiate receptors. Furthermore, it has been shown to be effective in the presence and absence of opiates, non steroidal anti-inflammatory medications, and acetaminophen.[7,8]

Evidence about the effectiveness of the NMDA antagonist ketamine to reduce postoperative hyperalgesia and acute and long-lasting pain is inconclusive.[9] Conceivably, a smaller dose may have the benefit of minimal hemodynamic effects without additional psychomimetic adverse effects.[10]

Parikh and co-workers,[11] concluded that small dose of ketamine decreases postoperative pain, reduces morphine consumption and delays patients request for analgesia even beyond the theoretical clinical duration of action of ketamine after open renal surgery, thus implying prevention of pain sensitisation.

S. Bilgen et al,[12] concluded that there was no difference regarding early and late postoperative pain and morphine consumption with ketamine at doses of 0.25, 0.5, and 1 mg /kg in women undergoing caesarean delivery under general anaesthesia, compared with the control group.

Abrishamkar and co-workers,[13] studied about the analgesic effects of ketamine infusion on post-operative pain after fusion and instrumentation of the lumbar spine. In group A, pain was controlled by IV infusion of ketamine (0.5 mg/kg/h) whereas in group B, IV infusion of morphine was done every 6 h. They concluded that ketamine is a good alternative analgesic after fusion of lumbar spondylolisthesis.

Adam et al,[14] evaluated the preemptive analgesic effect of a small dose of ketamine given before or immediately after surgery in a randomized, double-blinded study performed in 128 women undergoing total mastectomy. This suggested that a small ketamine dose (0.15 mg/kg IV) failed to provide preemptive analgesia

Singh et al,[15] studied about preemptive analgesia with ketamine for laparoscopic cholecystectomy in four groups of 20 patients each. Group A patients received ketamine in dose of 1 mg/kg, group B patients were given ketamine 0.75 mg/kg, group C was given 0.50 mg/kg ketamine, whereas group D received isotonic saline. They concluded that preemptive ketamine has a definitive role in reducing postoperative pain and analgesic requirement in patients undergoing laparoscopic cholecystectomy.

Considering lacunae in the previous literature regarding dosage and timing of ketamine use, we planned to do a study on effect of intravenous ketamine given at different times in surgery on post-operative pain scores after spine surgeries.

The primary outcome of this study was evaluation and comparison of the analgesic effect of I.V. ketamine given pre emptively and post operatively Vs. placebo. Seconday outcomes studied were comparison of cumulative post-operative fentanyl consumption in patients receiving ketamine at different times versus placebo.and comparison of post-operative side effects in patients receiving ketamine vs placebo.

MATERIALS AND METHODS

Study was conducted in Indira Gandhi Government Medical College and Hospital Shimla (H.P) as a prospective randomised controlled trial. Ethical clearance was obtained from institutional ethical committee.

After written informed consent, ASA I and ASA II patients coming for routine spine surgeries were taken for the study.

A Sample size of 75 (25 in each group) were created using computer generated random numbers. ASA grade 1 and 2 patients of either sex which were planned to undergo Spine surgeries (Transforaminal lumbar interbody fusion, laminectomy, Posterior decompression and stabilization) under general anaesthesia were enrolled in the study. Patients with cervical spine or with concurrent head injury or chest injury or allergy to opioids, ketamine and NSAIDs, with a history of drug abuse or with psychiatric illness or communication difficulties were excluded from the study.

After a thorough pre anaesthetic check-up, study protocol and NRS scale for post-operative pain was explained to all patients during preanaesthetic evaluation in their vernacular language.

On arrival in operation theatre a standard monitoring was done. Patients were randomly allocated to group 1, 2, or 3 by computer generated random numbers. Both, patient and investigator performing the study and observing the result were blinded to the test drug by giving serial numbers to the patients and serial numbers were decoded in the end. All the observations were made by same observer to eliminate subjective error. The study drug was drawn and diluted to a fixed volume of 5 ml by an anaesthesiologist who was not be involved in the collecting and analyzing the data.

Group 1(K1): Patients received injection ketamine I.V. (0.5mg/Kg body weight) during induction of anaesthesia and 5cc of normal Saline I.V. after closure of wound, before extubation.

Group 2(K2): Patients received injection normal saline I.V. 5cc during induction of anaesthesia and ketamine I.V. (0.5mg/Kg body weight) after closure of wound, before extubation.

Group 3(K0): Patients received injection normal saline I.V. 5cc during induction of anaesthesia and injection normal saline I.V. 5cc after closure of wound, before extubation.

Preoxygenation was done via a face mask for 3 minutes. Injection glycopyrrolate 0.2mg I.V., injection ondansetron 0.1mg/Kg body weight and injection morphine 0.1 mg/Kg body weight was administered intravenously slowly. The coded study drug was administered intravenously. General anaesthesia was induced with injection propofol 2mg/ Kg body weight and endotracheal intubation was facilitated

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with atracurium besylate 0.5mg/kg body weight. After induction patient was moved to prone position and endotracheal tube would be attached to ventilator. Anaesthesia was maintained with oxygen and nitrous oxide in ratio of 1:2 along with isoflurane 0.2-2% and intermittent usage of atracurium besylate 0.1mg/kg body weight on controlled mechanical ventilation. Intraoperatively about one hour before closure inj. diclofenac 75mg/kg i.v. slowly after dilution and inj. paracetamol 15mg/kg body weight i.v. was given. Vital parameters, including HR, blood pressure, electrocardiogram, end-tidal CO2 and O2 saturation were monitored throughout the procedure.

After closure of wound coded study drug was administered. At the end of surgical procedure, residual neuromuscular blockade was antagonized with injection neostigmine 0.05mg/kg body weight and glycopyrrolate 0.01mg/kg body weight i.v. was administered slowly.

Patient was extubated once he/she was awake after establishment of adequate spontaneous respiration and was shifted to post anaesthesia care unit

All enrolled patients were observed for vitals (HR and Mean BP) pain intensity and relief in postoperative recovery room using numeric rating scale (NRS) along with monitoring for sedation using Modified observer's assessment of alertness scale. The first dose of rescue analgesic i.v. fentanyl 1 mcg/kg. was given when the NRS at rest reached ≥5.

Data was analyzed with the SPSS statistical program (SPSS Inc, Chicago, IL, USA) using Student's t-test, and analysis of variance (ANOVA) test. Data of the different groups was compared by Student's t test for unpaired comparisons for normally distributed data, Kruskal-Wallis test for non-normally distributed data or Chi-square test for qualitative data. Differences among group means were compared using ANOVA. Incidence of side effects and number of patients receiving rescue analgesia were analyzed using Fisher's exact test. Significance levels throughout this study were considered at $P < 0.05$. The following observations were made.

RESULTS

Demographic data: All three groups were comparable (p-value >0.05) in age, weight, sex distribution and American society of Anesthesiologists status(ASA). [Table 1]

Comparison of baseline parameters: The pre-operative baseline parameters, heart rate and mean blood pressure were found to be comparable and the differences were statistically insignificant (p-value >0.05). [Figure 1] (Intergroup comparison of pulse rate)

Post operative observations:

Intergroup comparison of pulse rate and mean blood pressure:

Pulse rate decreased in all three groups from the value at 5 minutes of shifting the patient to PACU. The inter group difference in pulse rate was significant during 60 M, 90 M, 2H, 2H30M, 3H and at 5H (p-value <0.05). At rest of time intervals the pulse rate was statistically comparable (p-value >0.05).

A lower pulse rate was observed during time interval of 30M, 1H, 1H30M, 2H, 2H30M, 3H and 5H(p-value <0.05) in group K1. Comparison of pulse rate in group K0 vs. K2, difference was statistically significant during time interval of 1H30 M, 2 H, 2 H30M, 3Hand 5H (p-value <0.05). During these intervals lower pulse rate was found in group K2. While comparing pulse rate in group K1 vs. K2, difference was not significant statistically at any time (p-value>0.05). [Figure 1]

Mean blood pressure decreased in all three groups but difference was not statistically significant at any time [Figure 2]

Comparison of mean NRS

The difference in NRS values in three groups at all the times of observation was found to be highly significant with a p- value < 0.001, with lowest being in group K1. [Figure 3]

NRS values were less in group K1 than K2, difference was statistically significant. The mean value in group K0 was 8.2±1.44 initially which regressed to 3.36±0.64, while in group K1 it was 4.52±2.26 initially which approached 2.6 ±0.71 at end of 12 hours. While comparing NRS in group K0 to group K1 and K2, the difference was statistically significant at all times (p-value < 0.05) .

Intergroup comparison of OAA/S scores: The difference in sedation level as signified from Modified Observer's Assessment of Alertness/Sedation Scale (OAA/S) was statistically significant at 5 minutes and at 30 minutes while comparing group K0, K1 and group K2.

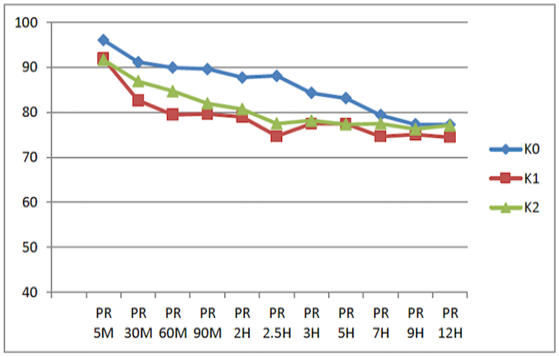

Figure 1: Intergroup comparison of pulse rate during different time intervals

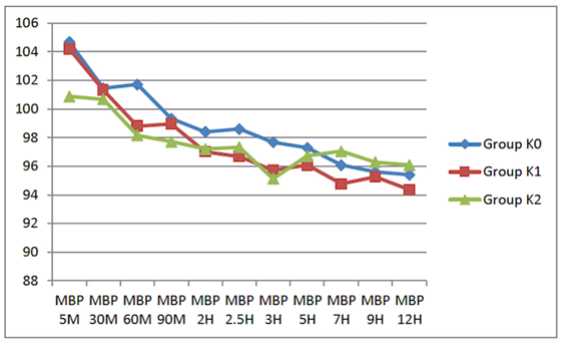

Figure 2: Intergroup comparison of mean blood pressure

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Rescue analgesia: Patients in group K0 were first to demand rescue analgesia with mean time of 7±6.92 minutes while group K1 patients demanded at 39.70±72.51minutes an group K2 patients demanded at 21.136±15.11minutes. This difference was statistically significant.

Number of patients who needed rescue analgesia. Among 25 participants from each group all 25 from groupK0, 17 from group K1 and 22 from group K2 needed rescue analgesia. The difference was statistically significant with p value of 0.006. [Figure 4]

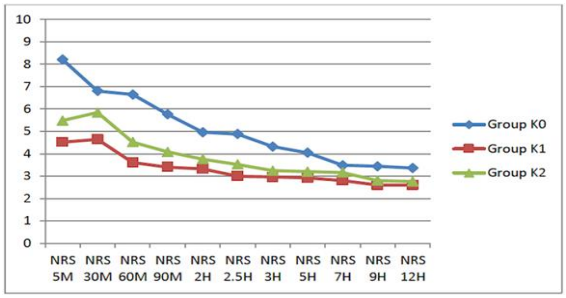

Figure 3: Comparison of mean NRS

6. Hallucination: None of the patients in any group had hallucinations at any point of time.

7. Nausea and vomiting: None of the patient in all three groups had vomiting. Nausea was experienced by 9 patients in group K0 while 4 and 6 patients had nausea in group K1 and K2 respectively. The difference was statistically non significant (p-value > 0.05)

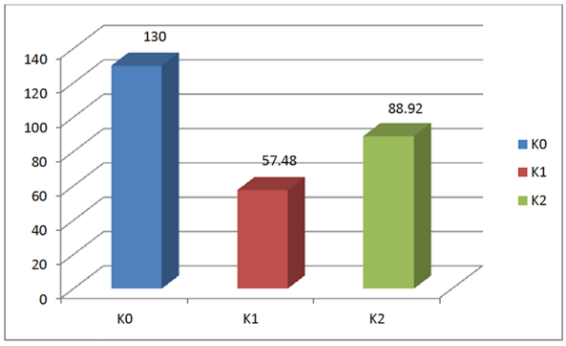

Figure 4: Total intravenous fentanyl in micrograms administered in three groups

Table 1: Demographic data

Parameter		Group K0	Group K1	Group K2	p-value
Age(years)	Mean±S.D.	46.32±10.26	42.88±9.57	41.88±13.40	.345
Weight(kg)	Mean±S.D.	65 ± 10.17	65.8 ± 8.6	64.84 ± 10	.931
Sex	Male	17	17	19	.773
	Female	8	8	6	
ASA grade	1	22	22	22	1
	2	3	3	3	

DISCUSSION

Ketamine administered IV in low dose, is reported to produce analgesic effects by its action as a non-competitive NMDA-receptor antagonist. It is mandatory to make a distinction between the high dose ketamine as an anaesthetic agent and low dose ketamine as an antihyperalgesic agent. Low dose ketamine is defined as a bolus dose of <2 mg/kg, when given intramuscularly or <1 mg/kg, when administered via the IV or epidural route. In continuous IV administration, low dose ketamine is defined as a rate of ≤20 μg/kg/min.[9]

Hemodynamic parameters and Pain:

Studies in literature clearly support the theory that low dose ketamine (at doses ≤0.5 mg/kg) have no significant effect on the hemodynamic parameters15.

In another study done by Kwok et al.16 concluded that low dose of ketamine is devoid of any hemodynamic adverse effect in undergoing gynaecologic laparoscopic surgeries. This same scenario we found in our observation.

In our study also we found that HR progression was along the lines of NRS scores. There was no influence, probably of ketamine in any group at any time except at 5 minutes and 30 minutes postoperatively in group K2 where ketamine was given at extubation.

In our study pain assessment was done with Numeric rating scale with points 0 to 10. Mean NRS scores were significantly lower in groups receiving ketamine (group K1 and K2) as compared to those in control group at all times. When comparing group K1 vs. K2 it was observed that group K1 which received ketamine during induction had better pain relief and NRS scores were significantly higher in group K2 at 30 minutes and at 60 minutes postoperatively while there was no significant difference in pulse rate among these groups.

Patients in group K0 had more pain and could account for the higher pulse rate in this group.

Mean blood pressure decreased in all three groups but difference was not statistically significant at any time.

In a study done by Singh and coworkers15, they studied ketamine in three different doses of 1 mg/kg body weight (group A), 0.75 mg/kg body weight (group B) and 0.5 mg/kg body weight (group C) as compared to placebo (group D), given before incision, in patients undergoing laproscopic cholecystectomy. The VAS score in groups A, B, and C at 0, 0.5, 1, 1.5, and 2 h was comparable with no significant intergroup variation in between them. The difference was not statistically comparable before three hours in control group was due to earlier administration of fentanyl. This

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supports our observation that ketamine groups had lower pain as compared to control till 12 h.

Also supporting our result of ketamine preventing excessive analgesic requirements is a study done by Fu et al,[17] who studied the effect of ketamine given before surgical incision in patients undergoing abdominal surgery. Patients in the preemptive group (n = 20) were given 0.5 mg/ kg ketamine at induction followed by a ketamine infusion of 10 mcg/kg/min, which was discontinued at abdominal closure. The patients in the postwound closure (n = 20) group were given 0.5 mg/ kg of ketamine immediately after abdominal closure. Postoperatively, all patients received intravenous (IV) morphine in the PACU and were started on IV morphine PCA after discharge from the PACU. Postoperative pain was assessed by measuring morphine consumption and visual analog scale (O-100 mm) pain scores at rest. They observed that patients in the preemptive group had significantly lower morphine consumption in postoperative period which is similar to the findings in our study where preemptive drug group

The result of our study which show that ketamine given before surgical insult is better than that given at closure time can be supported by review study of Woolf et al6 upon preemptive use of ketamine in patients undergoing various major surgeries under general anaesthesia, which concluded that preemptive analgesia is better in treating postoperative pain by preventing the establishment of central sensitization.

Parikh et al,[11] while comparing preemptive administration with postoperative administration they found that small dose of ketamine given before skin incision is better than postoperative administration which further supports our findings.

Bilgin and co-workers 18 suggested that a single preoperative dose of ketamine provided less analgesia compared with other dosing regimens that included intraoperative infusions or postoperative administration. This also showed good analgesic effect of preemptive use of ketamine.

In another study by Behaeen et al,[19] comparing effects of timing of administration of ketamine no difference in pain scores was found when compared to placebo. They studied analgesic effect of low dose subcutaneous ketamine administered before and after caesarean section under spinal anaesthesia.

Adam et al,[14] studied analgesic effect of ketamine given at two different timings, as given in our study, in patients undergoing total mastectomy under general anaesthesia. They gave low dose ketamine at induction in one group and at closure in other group. Postoperatively in the PACU, the VAS score was measured immediately on arrival, and patients were connected to a PCA pump system. PCA was still in use in the surgical ward for 24 h, during which no other analgesics were administered. There were no statistically significant differences between the groups in VAS scores throughout the study period. Pain intensity was maximal at the first evaluation in the PACU (Group 1; 33 +/- 22 mm, Group 2; 37 +/- 22 mm; P = 0.21). Their study showed that there were no significant intergroup differences in pain scores while morphine consumption was lower in group receiving ketamine at closure. This conflicting result could be due to the choice of the surgical procedure. All surgeries probably do not induce the same central sensitization. After a total mastectomy, pain intensity is moderate and may not generate enough difference between the preemptive and closure groups.

Another study which substantiates the findings of our study was done by Kwok et al,[16] who evaluated the preemptive effect of a small dose of ketamine on postoperative wound pain. They compared the analgesic requirement in patients receiving preincision ketamine with ketamine administration after skin closure or placebo after gynaecologic laparoscopic surgery. Patients received preincision or postoperative ketamine or saline IV Patients receiving preincision ketamine had a lower pain score in the first 6 hours after operation compared with the postoperative (P = 0.001) or placebo groups (P < 0.001). This showed that even low dose of preemptive ketamine is effective in surgeries.

Sedation levels: In our study sedation levels were high in group K2 at time of first and second observation postoperatively i.e. at 5 minutes and at half hour from both the groups, which might be due to influence of administration of ketamine at extubation.

At rest of times patients in all groups had equal sedation levels till end of observations. The plasma half-life of ketamine is ≤ 17 minutes, this could attribute to more sedation in group K2 for first half hour.

In support of our this observation is a study done by Wason et al20 who studied effect of 0.5 mg/kg body weight ketamine given IV on control of shivering in patients undergoing surgery in neuraxial anaesthesia and found that this dose causes sedation.

Rescue analgesia

Patients in group K0 required first rescue analgesic at 7±6.92 minutes postoperatively while in group K1 and K2 demand was at 39.70±72.51 and at 21.136±15.11 minutes respectively. In group K0 all 25 patients needed rescue analgesia while 22 patients needed rescue analgesia in group K2 and only 17 patients needed rescue analgesia in group K1 which was least among all three groups.

Same results were found by Kwok and coworkers16 while comparing time of demand of first rescue analgesic in their three groups. The mean time to first request for analgesia in the preincision group was longer than the postoperative group or the placebo group. Placebo group was earliest to demand analgesic as in our study. Menigaux et al,[21] demonstrated that low dose ketamine have beneficial effects on pain scores.

Results of our study show that the total quantity of fentanyl used within 12 hours post surgery was significantly lower in the groups who received ketamine.

This is in support of the evidence that ketamine has long term analgesic effects. This has been shown in our study with reference to NRS scores. The findings

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are in support of various other studies which also showed that ketamine administration decreases requirements of rescue analgesics.

Bilgin and co workers18 suggested that a single preoperative dose of ketamine provided less analgesia compared with other dosing regimens that included intraoperative infusions. This also showed good analgesic effect of preemptive use of ketamine along with infusion of ketamine. Lower pain scores and morphine consumption in their group which received bolus of IV ketamine followed by infusion of ketamine as compared to other groups may be related to higher plasma ketamine concentrations caused by the higher doses.

Hallucinations

None of the patient in our study experienced hallucinations. Ketamine-related adverse effects are rare when the surgery is performed under general anaesthesia. In our study, all the surgeries were performed under general anaesthesia and hence none of the patient complained of hallucination. Large doses (>2 mg/kg, IV) and rapid administration of ketamine (>40 mg/min) predispose to this side effect whereas they are minimal at low dose.[22]

Nausea and vomiting: No patient had vomiting in all three groups while 36% had feeling of nausea in group K0, 16% had nausea in group K1 and 24% patients had nausea in group K2. This incidence of nausea among all three groups was not significant. Maximum patients who experienced nausea were females and PONV is common among them.

The results of our study match with those of Parikh et al,[11] who also concluded that low dose ketamine decrease post-operative opioids requirement leading to less nausea and vomiting.

CONCLUSION

Ketamine given through intravenous route is an effective analgesic agent. More over low dose ketamine given preemptively is definitely more effective analgesic as compared to postoperative administration, in patients undergoing surgery on spine, as evidenced by the reduced fentanyl consumption and pain scores. A low dose of 0.5 mg/kg body weight is devoid of any adverse effects and hemodynamic changes. Hence, it is an optimal dose for preemptive analgesia in patients undergoing spine surgery. Further studies should be undertaken at large level to study appropriate timings and dose of ketamine in various surgeries to give effective analgesia to patients and reduce opioids related side effects due to postoperative use.

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