Effect of intraoperative low dose ketamine infusion on postoperative analgesia: A randomized controlled trial.

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ABSTRACT

OBJECTIVE: To evaluate the effect of subanesthetic dose of ketamine on postoperative pain scores and narcotic consumption in patients undergoing abdominal surgery under general anesthesia.

STUDY DESIGN: Randomized, double blinded controlled trial.

PLACE AND DURATION: At the Department of Anesthesia, Combined Military Hospital, Khuzdar from 1st February 2018 to 31st January 2019.

METHODOLOGY: Adult patients were randomly allocated into two groups of equal size to receive either IV ketamine bolus, 0.25mg/kg followed by IV infusion, 0.15mg/kg/h (group A) or the same volume/kg of saline (group B). A visual analogue scale (VAS) was used to measure each patient's level of pain on arrival in post anesthesia care unit, at 1, 3, 6, 12, and 24 hours after surgery. Total postoperative morphine consumption and the incidence of side effects were also recorded.

RESULTS: Intraoperative low dose ketamine resulted in effective analgesia in first 12 h postoperatively, seen by low pain scores (P=<0.05). The total morphine consumption was also reduced in the ketamine group (P=<0.05). No serious psychomimetic side effects were noted in both the groups.

CONCLUSION: Intraoperative low dose ketamine infusion should be considered as an adjunct to opioids for postoperative pain management.

KEYWORDS: Abdominal surgery, Postoperative pain, Postoperative analgesia, Ketamine, Morphine, Narcotic consumption, Psychomimetic side effects.

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INTRODUCTION

Effective pain relief during surgery and postoperatively is very important for providing ideal patient care[1,2]. It is not only a part of balanced anesthesia technique, it also helps in blunting the surgical stress response. Surgical pain can initiate complex metabolic and hormonal response which can have a negative impact on the outcome of the surgery[3,4]. Opioids are commonly used to provide balanced anesthesia and postoperative analgesia. But the use of opioids comes with a certain price. Side effects like sedation, respiratory depression, nausea and vomiting are associated with the use of opioids[5]. The use of high doses can also lead to acute tolerance as well. Considering developing countries like Pakistan availability of narcotics at times may also be an issue.

Ketamine, an N-methyl d-aspartate (NDMA) receptor antagonist, at subanesthetic doses has been studied as an adjunct for perioperative analgesia. Studies have shown that NMDA receptors have a role in processing of pain at the level of central nervous system[6]. Due to its analgesic properties and its unique mechanism of action Ketamine has been used to treat various pain syndromes like cancer, neuropathic, acute and chronic pain. The Subanesthetic doses of ketamine (<0.3 mg/kg IV) has been shown to provide centrally mediated analgesia without significant side effects[7].

A multimodal approach to analgesia is now recommended to counter acute pain. Since by targeting various pain mechanisms, multimodal analgesia has been reported to improve pain relief and reduce the opioid usage[8]. We hypothesized that low dose of ketamine infusion given intraoperatively will reduce the postoperative pain scores and consumption of morphine.

The objective of this study was to evaluate the effect of

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subanesthetic dose of ketamine on postoperative pain scores and narcotic consumption in patients undergoing abdominal surgery under general anesthesia in local population.

METHODOLOGY

This prospective, double blinded, randomized, placebo-controlled trial was conducted after approval from hospital ethical committee from 1st February 2018 to 31st January 2019 at Department of Anesthesia, Combined Military Hospital, Khuzdar. Written informed consent was taken from the patients enrolled in the study. A total of 140 patients belonging to American Society of Anesthesiologists (ASA) physical status I and II, of either sex, aged 18 to 65 years scheduled to undergoing variety of abdominal surgeries (open cholecystectomy, laparotomy, hysterectomy, pyelolithotomy, nephrectomy) under general anesthesia were included in the study. Exclusion criteria was patients with hypertension, elevated intracranial pressure, ischemic heart disease and history of allergies to any of the drugs under study. During preanesthesia assessment, patients were explained about the visual analogue scale (VAS) of 0-10 with 0 being "no pain" and 10 being "worst possible pain".

Patients were randomly divided into two groups of 70 each by a sealed envelope technique. Patients in group A were administered a bolus of intravenous ketamine of 0.25 mg/kg followed by an infusion of ketamine at a rate of 0.15 mg/kg/h. Whereas patients in group B were given a normal saline bolus and infusion at the same volume and rate. The administration of bolus dose followed by infusion of both ketamine or saline was started before the skin incision. The infusion (Mindray SK-500, Germany) was continued intraoperatively and was stopped after the skin closure but before the extubation of the patient.

In order to avoid bias the medical staff who was not involved in anesthetizing the patients prepared the study drugs. The drugs were prepared in 20 mL syringe (concentration of ketamine was 10 mg/ml), the saline syringes were also labelled like ketamine syringes. Preoperatively the patients were kept nil per oral for 6 hours before the surgery. Continuous monitoring of pulse, oxygen saturation, electrocardiogram, noninvasive blood pressure and end tidal carbon dioxide was done perioperatively (Operon OM-12, Germany). The anesthesiologist administering anesthesia was not aware of the group to which the patients belonged. The blood pressure was monitored every 3 minutes. An 18 G IV line was secured for drug administration and IV fluid management. IV glycopyrrolate 200 µg and IV metaclopramide 10 mg were given to all the patients as a premedication. IV induction was performed with propofol 2mg/kg and morphine 0.1mg/kg. IV atracurium 0.5mg/kg was used for endotracheal intubation. Maintenance of anesthesia was done with sevoflurane and 100% oxygen. Fluid management was done with IV ringer lactate. The reversal of the residual neuromuscular blockade was done with IV neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/kg. Endotracheal tube was removed on complete recovery of the airway reflexes. The individual involved in data collection of pain scores was not aware of the group to which the patient belonged. Similarly, the staff who provided the postoperative care in the hospital were unaware of the patient group.

The patients were transferred to the post anesthesia care unit (PACU) and pain scores were noted on arrival, 1 h, 3h, 6h, 12h and 24 h postoperatively using VAS. The patients were kept in post anesthesia care unit for 3 h. Patients were shifted to the ward and were given IV ketorolac 30 mg 12 hourly. All the patients who complained of pain score of VAS 4 or above were provided rescue analgesia of IV morphine bolus 0.07 mg/kg. The total amount of morphine given in 24 h were noted for both the groups. Side effects of ketamine and morphine such as hallucination, sedation, nausea, vomiting and respiratory depression were recorded. For hallucination IV haloperidol 5mg, for nausea and vomiting IV metoclopramide 10 mg and for respiratory depression (respiratory rate <9/min) IV naloxone 0.1 mg were kept in hand.

Data Analysis: The results were analyzed using SPSS version 23.0.0 software (IBM). A sample size of 30 patients per group were needed to detect a change of 30 % in morphine consumption between groups with power 80% and $\alpha = 0.05$. Results are presented as mean ± standard deviation or as number of patients. Statistical significance of comparison of gender between two groups was analyzed with Chi-square test. Statistical significance of age, weight, duration of surgery, VAS and morphine consumption between two groups was tested with independent sample t-test. A $P<0.05$ was considered as statistically significant.

RESULTS

A total of 140 patients were included in the study. These patients were randomized into two groups of 70 each. There were no dropouts. The demographics and duration of surgery were comparable between the two groups (Table-I). We did not find statistically significant difference among age, gender and weight of the patients and in the duration of surgery between the two groups.

Table-I: Comparison of Demographics and duration of surgery between two groups (N=140).

Variables	Groups A (N=70)	Group B (N=70)	P
Age	31.1±13.4	31.7±14.6	0.81
Sex (Male/Female)	38/32	39/31	0.87
Weight (Kg)	72.3 (11.34)	73.8 (9.6)	0.6
Duration of surgery (min)	97±21.6	92±22.3	0.31

Data presented as mean ± standard deviation.

n: number of patients, Group A: ketamine group, Group B: saline/placebo group

The comparison of VAS pain scores between group A and group B was statistically significant ($P <0.05$) at arrival in PACU, 1 h, 3 h, 6 h and 12 h intervals. However, the difference of pain score at 24 h between two groups was not significant ($P = 0.17$) as shown in Table-II.

Table-II: Pain assessment (VAS) in postoperative period (N=140)

Time (hours)	Groups A (N=70)	Group B (N=70)	P
0 hour (On arrival in the post anesthesia care unit)	2.03±1.11	3.93±1.46	0.001
1 hour	1.86±0.95	3.87±1.35	0.001
3 hours	2.1±1.32	4.07±1.51	0.001
6 hours	2.61±1.2	4.95±2.12	0.001
12 hours	3.44±2.32	5.16±2.14	0.01
24 hours	4.85±2.6	5.43±2.32	0.17

Data is presented as mean ± standard deviation.
n: number of patients, Group A: ketamine group, Group B: saline/placebo group, VAS: visual analogue scale

The mean consumption of morphine in group A was 4.79 mg (SD 1.24) and in the group B was 13.36 mg (SD 2.76). This difference was statically significant (Table-III).

Table III: Postoperative cumulative Morphine consumption (N=140)

	Groups A (N=70)	Group B (N=70)	P
Cumulative Morphine consumption in 24 h (mg)	4.79±1.24	13.36±2.76	0.001

Data are presented as mean ± standard deviation or number of patients.
n: number of patients in each group, Group A: ketamine group, Group B: saline/placebo group

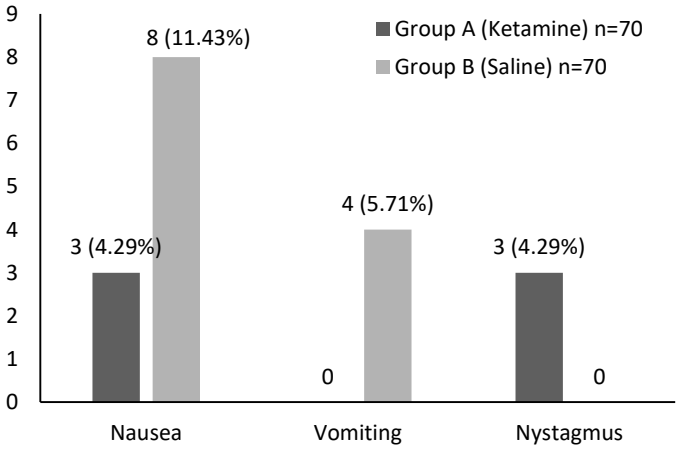

Figure-1: Comparison of side effects of ketamine/morphine between two groups (N=140)

Data presented as number of patients having side effects and the percentage.
n= Total number of patients, Group A: ketamine group, Group B: saline/placebo group.
None of the patients developed respiratory depression in both the groups. There was no incidence of hallucination as well.
The incidence of nausea was 11.43% in group B versus 4.29% in group A and that of vomiting was more in group B (5.71%) while nystagmus was observed in 3 patients (4.29%) in group A as shown in Figure-1.

DISCUSSION

The opioids have remained a conventional choice for treating and managing the postoperative surgical pain. But the concerns regarding the side effects, tolerance, addiction and opioid crisis have focused the strategy of managing the postoperative pain with other options[5,9,10]. Regional anesthesia, multimodal analgesia, ketamine, dexmedetomidine, pregabalin and gabapentin are some of the unique alternative approaches in this regard[11].
Ketamine, a phencyclidine derivative, has analgesic effects because of its NMDA receptor antagonist activity. The anesthetic high doses of ketamine (> 1-2 mg/kg IV) are associated with psychomimetic side effects[12,13]. There has been renewed interest in the beneficial effects of subanesthetic doses (<1mg/kg IV) of ketamine which does not have psychomimetic side effects. Various studies internationally have proven that subanesthetic doses can improve the postoperative pain scores as well as the narcotic consumption[8,14-19]. However, there has been limited research on our local population. Siddiqui et al. observed the effects of low dose ketamine bolus before induction on postoperative morphine consumption in local population undergoing day care procedures[14]. But the prolonged postoperative effects like 24-48 hours postoperative of the low dose ketamine has yet to be studied in the local population. To study the effects of low dose ketamine infusion intraoperatively on postoperative pain in the local population was one of the reasons for performing this study.
Literature review of various clinical trials reveal that a range of subanesthetic doses of IV ketamine has been given as a single bolus only, single bolus followed by continuous IV infusion or only a continuous IV infusion. In some studies, the infusion has been given intraoperatively only, while in some the IV infusion has been continued postoperatively to 2 hours and up to even 48 hours[8,16,20]. In our study we observed the analgesic actions of intraoperative administration of low dose ketamine up to 24 h postoperatively in local population. We gave ketamine bolus followed by a continuous infusion which was continued after skin closure but was stopped before extubation of the patient. The IV infusion was not continued in our study in the postoperative period. Siddiqui et al[14] gave an initial bolus on induction. The postoperative pain score (VAS) was measured at 30 minutes after surgery. We measured the scores up to 24 h postoperatively. Kaur et al[15] and Cengiz et al[17] also gave a bolus dose followed by an intraoperative IV infusion. Pain scores were measured up to 24 h postoperatively. Garg et al[18] administered the IV ketamine infusion in the postoperative period up to 24 h and observed the pain scores for 48 h postoperatively. All these studies have shown significant reduction in postoperative pain scores as well as the postoperative opioid analgesia requirement.
We observed significant reduction in postoperative pain scores till 12 h postoperatively. Kaur et al.[15] observed low pain score (VAS) up to 6 h as compared to our study which revealed lower VAS up to 12 h. This may be due to high ketamine dose we used

in our study. The cumulative consumption of morphine was also significantly reduced in our study. Our results are comparable with other studies in reduced total opioid consumption for postoperative analgesia and pain scores[8,14-19].

The subanesthetic doses of ketamine are associated with no or very few psychomimetic side effects[14-20]. Other side effects like hypertension and tachyarrhythmias are transient and seen with anesthetic doses only so is hypersalivation which has not been reported with subanesthetic doses, can be treated with antisecretory agents like glycopyrrolate[8,12,21,22]. We did not observe any incidence of hypertension, tachyarrhythmias or hypersalivation in our study. Similarly, serious psychomimetic side effects of ketamine like hallucinations were also not observed in our study. There were 3 patients (4.29%) who had nystagmus in ketamine group in our study. Kaur et al[15] and Garg et al[18] also observed no incidence of hallucinations. However, Siddiqui et al[14] observed 6.6 % and Cengiz et al[17] observed 7% incidence of hallucinations in patients who were administered Ketamine. Opioids use may cause side effects like nausea and vomiting so because of low opioid consumption the subanesthetic doses of ketamine can reduce incidence of nausea and vomiting. The incidence of nausea and vomiting in our study was lower in ketamine group with 4.29% incidence of nausea and no case of vomiting. The incidence of nausea in saline group was 11.43% and vomiting 5.71%. Siddiqui et al[14] observed more incidence of nausea in placebo group. Similarly, Cengiz et al[17] also observed more incidence of nausea and vomiting in the placebo group. Overall intraoperative subanesthetic doses of IV ketamine bolus followed by an IV infusion reduced cumulative postoperative morphine consumption and enhanced the postoperative pain relief in our study. It also did not cause any serious side effects associated with high doses of ketamine.

Ketamine has some very promising recent clinical uses. Recent works include its antidepressant role[23], treatment option for resistant cases of chronic pain, neuropathic pain[24] as an analgesia alternative in Intensive care units, trauma[25] and managing pain in sickle cell crisis[26]. So, in the coming future it may open more frontiers for researchers to explore.

One of the shortcomings of our study is that we didn't continue the IV ketamine infusion postoperatively. The 24-72 h postoperative IV ketamine infusion can be an alternative for opioids analgesia to major surgeries that require longer hospital stays and increased analgesic requirements. Further studies maybe conducted to observe the postoperative effects of IV ketamine subanesthetic doses

CONCLUSION

Intraoperative ketamine infusion should be considered as an adjunct to opioids for postoperative pain management.

CONTRIBUTION OF AUTHORS

Atif M: Designed research methodology, Literature search, Data collection, Manuscript writing.
Khurshid T: Literature review, Data interpretation, Manuscript writing.
Haque IU: Data interpretation.
Yousaf MJ: Data interpretation, Statistical analysis.
Syed FT: Literature search, Data collection.

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REFERENCES

1. Subramanian P, Ramasamy S, Ng KH, Chinna K, Rosli R. Pain experience and satisfaction with postoperative pain control among surgical patients. Int J Nurs Pract 2016;22(3):232-38.
2. Ahmed A, Yasir M. Role of acute pain service in optimizing postoperative pain relief in a tertiary care teaching hospital. J Pak Med Assoc 2015;65(11):1164-68.
3. Fenton BW, Shih E, Zolton J. The neurobiology of pain perception in normal and persistent pain. Pain Manag 2015;5(4):297-317.
4. Timmers I, Kaas AL, Quaedflieg CWEM, Biggs EE, Smeets T, de Jong JR. Fear of pain and cortisol reactivity predict the strength of stress-induced hypoalgesia. Eur J Pain 2018;22(7):1291-303.
5. Ismail S, Siddiqui AS, Rehman A. Postoperative pain management practices and their effectiveness after major gynecological surgery: An observational study in a tertiary care hospital. J Anaesthesiol Clin Pharmacol 2018;34(4):478-84.
6. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol Rev 2018;70(3):621-60.
7. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. J Anaesthesiol Clin Pharmacol 2016;32(2):160-67.
8. Jian W, Rejaei D, Shihab A, Alston TA, Wang J. The role of multimodal analgesia in preventing the development of chronic postsurgical pain and reducing postoperative opioid use. J Opioid Manag 2018;14(6):453-61.
9. Rummans TA, Burton MC, Dawson NL. How Good Intentions Contributed to Bad Outcomes: The Opioid Crisis. Mayo Clin Proc 2018;93(3):344-50.
10. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. Morb Mortal Wkly Rep 2016;65(50-51):1445-52.
11. Dunn LK, Durieux ME, Nemergut EC. Non-opioid analgesics: Novel approaches to perioperative analgesia for major spine surgery. Best Pract Res Clin Anaesthesiol 2016;30(1):79-89.
12. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Clin Pharmacokinet 2016;55(9):1059-77
13. Grathwohl KW. Does ketamine improve postoperative analgesia? More questions than answers. Pain Med 2011;12(8):1135–36.

14. Siddiqui KM, Khan FA. Effect of preinduction low-dose ketamine bolus on intra operative and immediate postoperative analgesia requirement in day care surgery: A randomized controlled trial. Saudi J Anaesth 2015;9(4):422-27.
15. Kaur S, Saroa R, Aggarwal S. Effect of intraoperative infusion of low-dose ketamine on management of postoperative analgesia. J Nat Sci Biol Med 2015;6(2):378-82.
16. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med 2015;16(2):383-403.
17. Cengiz P, Gokcinar D, Karabeyoglu I, Topcu H, Cicek GS, Gogus N. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: a prospective, randomized double-blind placebo-controlled trial. J Coll Physic Surg Pak 2014;24(5):299-303.
18. Garg N, Panda NB, Gandhi KA, Bhagat H, Batra YK, Grover VK et al. Comparison of Small Dose Ketamine and Dexmedetomidine Infusion for Postoperative Analgesia in Spine Surgery-A Prospective Randomized Double-blind Placebo Controlled Study. J Neurosurg Anesthesiol 2016;28(1):27-31.
19. Mitra R, Prabhakar H, Rath GP, Bithal PK, Khandelwal A. A comparative study between intraoperative low-dose ketamine and dexmedetomidine, as an anaesthetic adjuvant in lumbar spine instrumentation surgery for the post-operative analgesic requirement. J Neuroanaesthesiol Crit Care 2017;4:91-98.
20. Zhu J, Xie H, Zhang L, Chang L, Chen P. Efficiency and safety of ketamine for pain relief after laparoscopic cholecystectomy: A meta-analysis from randomized controlled trials. Int J Surg 2018;49:1-9
21. Vadivelu N, Schermer E, Kodumudi V, Belani K, Urman RD, Kaye AD. Role of ketamine for analgesia in adults and children. J Anaesthesiol Clin Pharmacol 2016;32(3):298-306.
22. Allen CA, Ivester JR Jr. Ketamine for Pain Management-Side Effects and Potential Adverse Events. Pain Manag Nurs 2017;18(6):372-77.
23. Strong CE, Kabbaj M. On the safety of repeated ketamine infusions for the treatment of depression: Effects of sex and developmental periods. Neurobiol Stress 2018;9:166-75.
24. Maher DP, Chen L, Mao J. Intravenous Ketamine Infusions for Neuropathic Pain Management: A Promising Therapy in Need of Optimization. Anesth Analg 2017;124(2):661-74.
25. Losing AK, Jones JM, Keric A et al. Ketamine infusion therapy as an alternative pain control strategy in patients with multi-trauma including rib fracture; case report and literature review. Bull Emerg Trauma 2016; 4(3): 165-69.
26. Hagedorn JM, Monico EC. Ketamine Infusion for Pain Control in Acute Pediatric Sickle Cell Painful Crises. Pediatr Emerg Care 2019;35(1):78-79.