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Original Research Article

Intravenous low-dose ketamine in addition to systemic analgesia versus systemic analgesia alone for post-operative pain management in laparotomies: A double-blind randomised controlled study

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ABSTRACT

Background and Objectives: The use of Ketamine, an NMDA receptor antagonist, in sub-anesthetic doses for analgesia is increasingly being administered in inpatient settings with acute pain service guidance and in outpatient settings under a variety of models. At sub-anesthetic doses, ketamine possesses centrally mediated analgesic properties with minimal effects on consciousness and cognition.In this study we have compared the efficacy of IV low-dose Ketamine as an adjunct to conventional systemic analgesia to examine preventive effect on post-operative pain and opioid consumption in patients undergoing laparotomies.

Materials and Methods: The study was carried out on 50 patients, 25 patients received a pre-incisional IV bolus of 0.15 mg/kg of Ketamine,10 mins before the incision followed by IV infusion of 2mcg/kg/min continued for 24 hours postoperatively in addition to systemic analgesia (Group K) and 25 Patients received IV bolus of Normal Saline 10 min before the incision, followed by an IV infusion of normal saline (Group C) till 24 hours post-op and systemic analgesia alone. Saline bolus and infusion were given at equivalent volume/rate of the study group. The analgesic efficacy was judged by NRS (Numeric Pain Rating Scale), Time to first rescue analgesia (TFA) and Total opioid consumption (Tramadol in mg) in 24 hours. Ketamine related side effects were also recorded.

Result: Patients in the Ketamine group had significantly lower Mean total opioid consumption (88.04 ± 29.07 mg vs. 210 ± 23.93 mg) and Numerical pain Rating Scale (NRS) (3.13 +0.34 vs. 4.44+ 0.77). Time to first rescue analgesia was significantly delayed in Ketamine group as compared to Control group (20.65 ± 9.2 mins vs. 5.4 ± 5.38 mins). Ramsay Sedation scores (RSS) were significantly higher in the Ketamine group (2.4 +0.76 vs. 1.52 +0.51) in the immediate post-operative period. There were no demonstrable side-effects related to Ketamine in Group K.

Conclusion: Pre-emptive IV low-dose Ketamine is an effective adjunct to systemic analgesia in abdominal surgeries as it significantly prolongs the time to first rescue analgesia (TFA), reduces mean total analgesic requirement and lowers pain scores (NRS) in the post-operative period with negligible side effects.

1. Introduction

Major abdominal surgeries with upper abdominal incisions lead to severe abdominal pain, which if treated inadequately can cause shallow breathing, atelectasis, retention of

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secretions and lack of co-operation in physiotherapy. This increases the incidence of post-operative morbidity and leads to delayed recovery.[1] A detailed understanding of the mechanisms of pain and analgesia is crux in the practice of anesthesiology. Pain is a multidimensional and subjective experience dependent on social, psychological and environmental factors; and is not entirely due to activation of nociceptors and pain pathways by noxious stimuli.[2]

Age-old drugs such as COX inhibitors, NSAIDS and opioids have been viewed as the standard of care for treating postoperative pain for most surgeries, including abdominal surgery. Although opioids are the mainstay for acute postoperative pain, their many adverse effects such as respiratory depression, nausea, vomiting, and bowel dysfunction, limit their use.[3] This creates a challenging scenario as administration of too much opioid can lead to severe adverse effects, whereas insufficient analgesia can lead to physiologic and psychological manifestations, including the increased risk for the pain to progress to a chronic state.[3] Neuraxial blocks are not applicable to all patients, as they may mask complications after certain types of surgeries, such as spine surgery and patients on anticoagulant therapy may also limit their use.[4]

Since the 1980s, investigations have revealed a critical role of the NMDA receptor in pain processing and Ketamine has received considerable interest as an analgesic.At sub-anesthetic doses (≤0.3mg/kg IV), ketamine possesses centrally mediated analgesic properties with minimal effects on consciousness and cognition.[5]

The variability in patient selection, drug dosing, monitoring, and management protocols requires further studies for forming guidelines. Hence, we planned to study the effectiveness of IV low-dose Ketamine in addition to systemic analgesia for management of post-operative pain in patients undergoing laparotomies.

2. Material and Methods

The study was carried out in Indian population as a prospective, randomized controlled study after obtaining the Institutional Ethics Committee's approval. Randomization was done using pre-determined computer-generated random allocation plan from RALLOC software version 7.0. 2011 by Minitab corporation. Based on reference study done by Parikh. B et al[6] with primary objective as Time to first rescue analgesia (TFA) sample size of 50 patients, 25 patients in each group is calculated using EPR info. Software. Inclusion criteria were patients between 18-70 years of age undergoing laparotomies under general anaesthesia, ASA grade 1-3, BMI ≤ 30 kg/m^2 and patients willing to participate in the study. The exclusion criteria included patients with high-risk coronary or vascular disease, uncontrolled hypertension, elevated intracranial tension, elevated intra-ocular pressure, globe injuries, history of psychosis and hepatic dysfunction. Newly diagnosed hypertensives not on any medication and persistent side-effects even after administering rescue medications formed the subject withdrawal criteria.

A written informed consent was obtained from each participant after explaining the procedure and the use of NRS to express the intensity of pain. Detailed medical history was obtained, physical examination done, required investigations obtained and ASA physical status was determined. Participants were randomised into 2 groups:

1. **Group K (Study group):** Participants received an IV bolus of 0.15 mg/kg of Ketamine from the syringe labelled —'Bolus', 10 mins before the incision and followed by IV infusion of 2mcg/kg/min (0.12mg/kg/hr) of Ketamine by infusion pump, starting after this bolus and continued for 24 hours postoperatively in addition to systemic analgesia.
2. **Group C (Control group):** Participants received IV bolus of Normal Saline 10 min before the incision, followed by an IV infusion of normal saline till 24 hours after surgery and systemic analgesia alone. Saline bolus and infusion were given at equivalent volume/rate of the study group.

Before the study began, 50 identical opaque envelopes were sealed and coded by a person not involved in the study. Each envelope contained detailed instructions of the preparation of 2 syringes (Ketamine or Saline). On the morning of the surgery, anaesthesia resident prepared 2 syringes, as described in the instructions. The resident had no further involvement in data collection. One 10ml syringe was filled with 1mg/ml Ketamine (for patients in the Ketamine group) or 10ml Saline (for patients in the control group), and the second syringe contained 50 mg of Ketamine (1ml) in 49mL of saline or 50 mL of saline alone. Syringes were labelled as — 'Bolus' and 'Infusion'. After induction of anaesthesia, the resident in charge of the patient brought the syringes into the operating room. Nurses, attending anaesthesiologists and surgeons were unaware of the group assignment until the end of the study.

The patients were taken in the operation theatre, monitors for SPO_2, ECG, $ETCO_2$ and NIBP were attached and all surgeries were carried out under balanced general anaesthesia. All participants were given 1 g of I.V Paracetamol about 30 mins before the end of the surgical procedure. After operation patients were observed in the post-anaesthesia care unit (PACU) for 24 hours and infusions as per group allocation were continued. Paracetamol was given for 24 hours (1g/8hrly) following surgery. When the patient indicated NRS score of >/= 4 a loading dose of I.V Tramadol 50mg bolus was given as rescue medication. If required further additional increments of 25 mg every 10 mins were given to a maximum 100 mg dose of Tramadol. Haemodynamic perturbations,

hallucinations or vivid dreams, nausea and vomiting or any other adverse effects were noted when present and IV Midazolam 1mg was used as a rescue medication for hallucinations and Ondansetron 4 mg for vomiting. Refill of infusion syringe if required was done by the resident who had prepared the syringes and had no involvement in data collection.

After extubation, haemodynamic parameters, time for first rescue analgesia (TFA), total tramadol required in 24 hours, NRS for pain, Ramsay scale for sedation and side effects were noted in the PACU for 24 hours post-operatively.

2.1. Statistical analysis

Data was coded and analysed in a statistical software STATA, version 10.1, 2011. Descriptive statistics includes mean SD for quantitative parameters, haemodynamic parameters such as pulse, blood pressure, frequency and percentages were used to describe categorical or qualitative parameters such as side effects and complications. Information statistics includes test of significance for comparing parameters in 2 groups, two independent sample-T- Test were used to test difference between mean of quantitative parameters in 2 comparison groups. Difference in proportions of qualitative parameters in 2 groups were compared with Chi square test. P value of <0.05 was considered statistically significant for all comparisons.

3. Results

There were 25 patients in each group of total 50 patients and age, gender, weight, BMI and ASA grade data was collected, analysed and the groups were found to be comparable (Table 1).

The study group K had significantly prolonged time for first rescue analgesia (TFA) (20.65 ± 9.2 mins) as compared to Control group (5.4 ± 5.38 mins) with a P value of 0.0001.(Figure 1) Group K had significantly reduced requirement of (p=0.0001) mean total rescue analgesia (88.04 +/- 29.07) of Tramadol (mg) as compared to Group C (210 ± 23.93).(Figure 2) The mean NRS was significantly less in the Ketamine group for most of the time points with p value of 0.0001 as compared to the Control group over 24 hours except at 20, 25, 30 and 45 mins when the difference in NRS was statistically not significant.(Figure 3) The Ramsay Sedation Score (RSS) of Ketamine group at 0, 5, 10 and 60 mins was significantly more (p value> 0.05) as compared to Control group over 24 hours. (Figure 4) Both the groups had comparable RSS at 90 mins till 24 hours in the post-operative period.

Haemodynamic parameters such as heart rate, systolic and diastolic blood pressure, Mean arterial pressure, respiratory rate and SPO_2 in both the groups were comparable. Complications included delayed arousal time

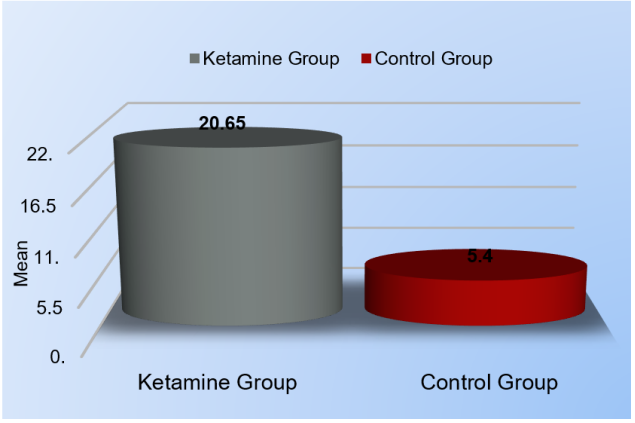

Figure 1: Mean time for first rescue analgesia in two groups

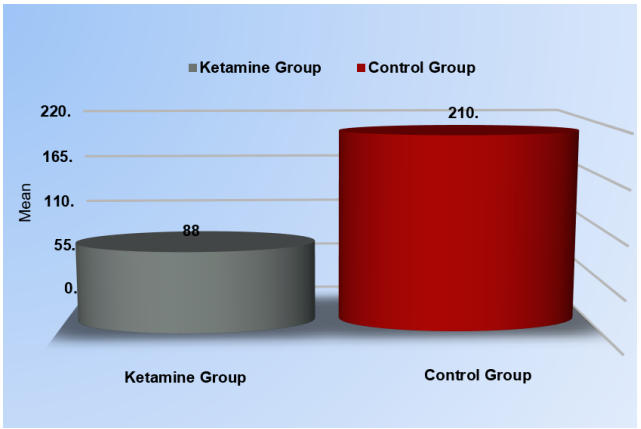

Figure 2: Mean total rescue analgesia of TRAMADOL in two groups

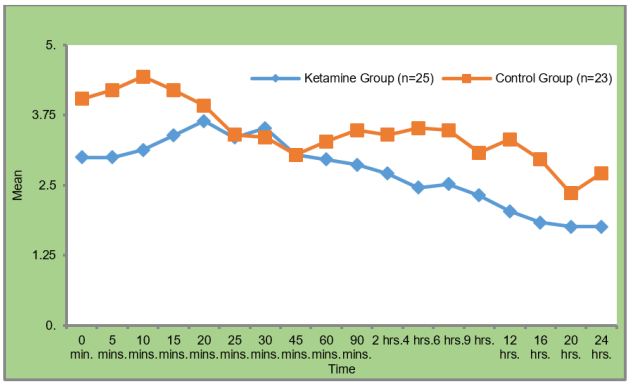

Figure 3: Mean NRS comparison in two groups at interval of time

Table 1: Comparison of baseline demographic characteristics of two groups

Baseline characteristics			Group K (N=23)	Group C (N=25)	P value
Age		Mean ± SD	41.68 ± 14.49	42.36 ±11.82	0.8565
Gender	Male	Number (Percentage)	17 (68)	19 (76)	0.529
	Female		8 (32)	6 (24)	
Weight		Mean ± SD	52.84 ± 11.27	57.04 ± 8.42	0.1422
BMI			19.07±3.18	19.52 ± 3.17	0.5849
ASA	Grade 1	Number (Percentage)	16 (64)	17 (68)	0.597
	Grade 2		8 (32)	8 (32)	
	Grade 3		1 (4)	0 (0)	

Table 2: Comparison of relevant indices of two groups

Parameters	Group K (N=23) (Mean ± SD)	Group C (N=25) (Mean ± SD)	P value
Time for first rescue	(20.65 ± 9.2 mins)	(5.4 ± 5.38 mins)	0.0001
Mean total analgesia	(88.04 ± 29.07) mg	(210 ± 23.93) mg	0.0001
NRS	(3.13 + 0.34)	(4.44+ 0.77)	0.0001
Ramsay sedation scores	(2.4 +0.76)	(1.52 +0.51)	0.0001
Complications			
Delayed extubation time	2 due to excessive sedation	0	8%

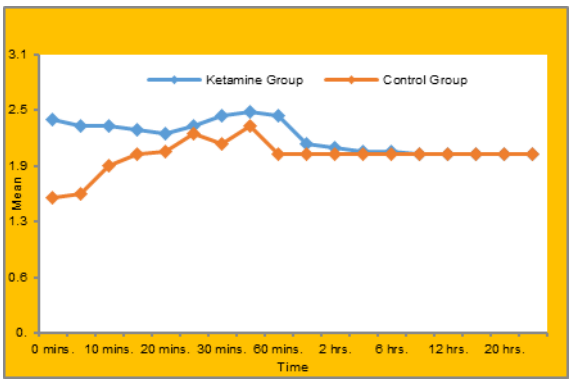

Figure 4: Mean comparison of RSS in two groups at interval of time

in 2 participants in the Ketamine group (8%). There were no other side-effects like hemodynamic perturbations, hallucinations or vivid dreams, nausea and vomiting over a period of 24 hours post-operatively in both the groups (Table 2).

4. Discussion

The etiology of acute postoperative pain is multifactorial. The surgical injury triggers a multitude of responses, from sensitization of peripheral and central pain pathways to feelings of fear, anxiety and frustration. Ideally, treatment of pain should begin pre-emptively. Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period.[7]

Although many drugs have demonstrated the evidence of pre-emptive analgesic benefit, 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. The various studies[8–15] as per the site of surgery, duration and dosing regimen of low-dose ketamine warrants its promising profile in management of post-op pain.

Sadove et al. were among the first who emphasized the analgesic effect of ketamine at low doses and suggested the possibility of using ketamine as an analgesic in sub-dissociative dose as early as in 1971.[16] Ito and Ichiyanagi in 1974 then used it as a variable intravenous infusion rate of 25mcg/kg/min for post-operative pain relief which offered adequate analgesia but with heavy sedation and dreams posing a problem.Owen et al. proposed that these levels could be achieved with a loading dose of 1 mg/kg followed by an infusion of 4 mcg/kg/min.[17] Clements and Nimmo showed that the analgesic effect of Ketamine occurs at much lower plasma concentrations (100 ng/ml) than the anesthetic effects (700 ng/ml).[18] Hence in the present study we planned for a bolus of 0.15 mg/kg pre-incision followed by an infusion of 2 mcg/kg/min.

In our study Time to first rescue analgesia showed a considerable delay in the Ketamine group (20.65 ±9.2) vs. (5.4 ± 5.38) mins in the control group which was statistically significant (Figure 1) and was consistent with the observations of Guignard et al[8] and Parikh B et al.[6]

This delay in demand for first rescue analgesic in the Ketamine group for the initial 15-20 mins post-extubation must have been due to the higher sedation scores. Nitrous oxide may have attributed to the enhanced NMDA receptor inhibition by Ketamine as it too has been reported to exert

NMDA antagonist properties.

The mean total rescue analgesic requirement over 24 hours is the most widely studied parameter. In our study mean total dose of Tramadol required for rescue analgesia in Ketamine group was (88.04 ± 29.07) and Control group (210 ± 23.93) mg (Figure 2) with the p value of <0.0001. Our study is in congruence with previous studies by Zakine J et al,[11] Parikh et al.[6] with a highly significant difference in the 24 hours requirement of mean total analgesia.

It is interesting to note that the reduction in mean analgesic consumption was observed only when Ketamine was given perioperatively, explained by the theory of central sensitization which is induced not only during surgery but also post-operatively by other mechanisms of pain such as inflammation and acute neuropathic pain due to nerve injury etc. Ketamine administration limited to the intraoperative period may be insufficient to control pain during the prolonged inflammatory process due to the short half-life of ketamine, as also seconded by Zakine J et al.[11]

Ketamine reduced opioid consumption most profoundly in upper abdominal and thoracic procedures as compared to orthopedic (limb and spine) and lower abdominal surgery. Opioid-sparing in ENT and oral surgical procedures was not significant suggesting that opioid-sparing was greatest in patients with high VAS scores. Thus, Ketamine analgesia giving an edge over the more painful surgeries.[19]

(Figure 3) shows the distribution of the patients according to the mean NRS between the Ketamine and Control group at different time intervals. At extubation, the NRS scores were 3 for the Ketamine group and (4.04 ± 1.23) in the Control group, this difference is statistically significant (p= 0.0002). Only for the duration of 20 – 45 mins postoperatively, the NRS scores for both the groups were comparable (p=0.1348). This may be due to the peak effect of the rescue medication given IV in control group attained by that time, but whose effect was short-lived. Subsequently, the NRS scores continued to be statistically significantly low (p=0.0001) in the Ketamine group when compared to the Control group at all time intervals over 24 hours since Ketamine administered as a continuous infusion provided better pain relief.

Roytblat et al[18] in their study found that the visual analog scale (VAS) was higher in patients in the control group during the first 5 hours after surgery (P<0.021), later between 5 and 24 hours after surgery VAS was not significantly different (P>0.05). This could be because they used IV Ketamine only as a bolus of 0.15mg/Kg after induction of anaesthesia and before surgical incision. The metabolite of Ketamine such as Nor-ketamine also has analgesic effect, that was short-lived due to single bolus dose. Parikh B et al.[6] stated that the lower VAS seen in group K is because of preventive analgesic effect of Ketamine on central sensitization.

Another possible explanation given for reduction of pain with low dose Ketamine might be related to its effect on the thalamo-neocortical projection systems. Ketamine depresses neurons in the cortex and thalamus, while simultaneously increasing activity in the limbic system, a phenomenon termed "Functional Disorganization".[20] Excitation of Limbic functioning combined with depression of thalamic cortical functioning could affect the patient's emotional response or evaluation of pain sensation. Thus, patients receiving Ketamine may be experiencing less suffering or emotional response to a similar level of nociception or somatic pain sensation.[21] Furthermore, when exposed to standardized painful stimuli, ketamine infusions reduce pain response in areas of the brain such as the anterior cingulate cortex that are well-known to modulate the affective components of pain. Figure 4 shows comparison of Ramsay Sedation Score (RSS) between Ketamine and Control group at different time intervals over 24 hours. Both the groups had comparable Ramsay sedation score at 90 mins till 24 hours which is also in accordance with the study conducted by Guignard et al,[8] Saxena et al,[14] they used low dose Ketamine as sole analgesic in patients undergoing laparoscopic gynecological surgeries and observed that in only 3 patients (4.28%) a Ramsay sedation score of 5 was seen just after extubation.

In the present study, 2 participants from the ketamine group were excluded from the analysis owing to heavy sedation and inability to assess pain. The Ketamine infusion was stopped in the post-operative period as the RSS for 1 participant continued to be 5 for 1 hour post extubation, another study subject showed an RSS of 4 for the initial 15 mins post-extubation which gradually reduced to 3 over a period of 1 hour. In a study conducted by Roytblat et al,[18] 1 patient was withdrawn from group 2 (Morphine 1mg/hour + Ketamine 5 mg/hour) after 8 hours because of severe drowsiness.

There was no incidence of side effects like hemodynamic perturbations, hallucinations or vivid dreams, nausea and vomiting with either groups. The risk of psychomimetic effects of Ketamine is dose dependent and clinical experience suggests that a bolus dose of <0.5 mg/kg and Ketamine infusions of 0.12-0.2 mg/kg/hour have no increased incidence of psychomimetic effects or measurable cardiovascular effects.[5] Large doses (>2 mg/kg, IV) and rapid administration of Ketamine (>40 mg/min) predispose to side effects whereas they are minimal at infusion rate of <2.5mg/kg/min.[13]

Even though low-dose Ketamine does have an undisputed analgesic potential, the details of this aspect are still not entirely clear when it was tried in opioid-dependent patients.[22] Also, current scientific literature appears to support the use of Ketamine in Enhanced Recovery Protocols (ERAS) and most recently as a novel therapeutic option for treatment-resistant depression. However, its

applicability in terms of dosing and management guidelines need to be studied further.[23] There are a few limitations of this study- We did not follow up the patients to evaluate whether chronic pain was reduced with the small doses of Ketamine used in the study. As we have not included opioid-tolerant patients or cancer patients on chronic pain medications as a part of this study, we cannot comment on the efficacy of such low-dose Ketamine for post-operative pain management in such populations.

5. Conclusion

We conclude that intravenous low-dose Ketamine in the form of a pre-emptive bolus of 0.15mg/kg followed by continuous infusion of 2mcg/kg/min (0.12mg/kg/hour) is an effective adjunct to systemic analgesia in abdominal surgeries as it significantly prolongs the time to first rescue analgesia (TFA), reduces mean total analgesic requirement and has lower pain scores (NRS) in the post-operative period with negligible side effects. Thus, it holds a promising profile in acute post-operative pain management in laparotomies.

6. Source of Funding

None.

7. Conflict of Interest

None.

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