

# Comparison Between two Different Doses of Ketamine as Pre-Emptive Analgesic in Patients of Laparoscopic Cholecystectomy for Postoperative Analgesia

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## Abstract

**Background:** Pre-emptive analgesic can be used as to decrease early pain post-surgery and also prevent the formation of long-term pain by subsiding the CNS sensory pathway. Ketamine is an n-methyl-d-aspartate (NMDA) receptor antagonist, desired for its effectiveness to intercept intraoperative as well as postoperative pain as a pre-emptive analgesic. Ketamine blocks the NMDA receptors and obliterate the peripheral painful stimulation and theory shows it prevents CNS stimulation. Following lap cholecystectomy pain comes from various components like peritoneal stretching, diaphragmatic irritation and insufflation. So, the study was planned to assess pre-emptive analgesic efficacy of ketamine for patients posted for lap cholecystectomy. **Subjects and Methods:** Randomly patients were allocated in 3 groups of thirty patients with ASA grade I and II of either sex, age group between 18 to 55 years admitted for laparoscopic cholecystectomy. After preoxygenation patient induced and intubated with proper size endotracheal tube. Post intubation the study drug was diluted upto 10ml with saline and administered i.v by an anaesthesiologist 10 minutes before skin incision. Group A patients received Inj.Ketamine 0.5mg/kg i.v, Group B patients received Inj.Ketamine 1.0mg/kg i.v, Group C patients received Normal Saline i.v. This study was carried out to compare and evaluate the efficacy of different doses of ketamine (0.5 and 1.0 mg/kg IV) for pre-emptive analgesia in patients of laparoscopic cholecystectomy with reference to Intraoperative hemodynamic changes, VAS score, time for first top-up analgesic, total number of doses of analgesic used within first 12 hours, postoperative hemodynamic changes, adverse effects. **Results:** The demographic profile and the period of sedation/operation was found to be comparable in groups. Pulse rate and systolic Bp was slightly high in ketamine Group (1.0mg/kg) as compared to ketamine Group (0.5mg/kg) and Group C in first 20 mins which was statistically significant. After 20 minutes pulse rate and systolic Bp higher in saline Group compared to ketamine Groups which was statistically significant. The mean VAS score on deep breathing, at rest and on movement was significantly higher in saline group as compared to ketamine groups postoperatively. The average time for initial rescue analgesic was significantly higher in ketamine groups (1mg/kg & 0.5mg/kg) on average 3 hours as compared to saline group less than hour. Adverse effects related to ketamine was found to be higher with 1.0mg/kg as compared to 0.5mg/kg and saline. **Conclusion:** Hence, ketamine has a conclusive role as a pre-emptive analgesic in minimizing postoperative pain. It also decreases requirement of analgesic in patients undergoing laparoscopic cholecystectomy. Lower dose of ketamine with 0.5mg/kg having fewer side effects and with less vital parameter changes is an ideal dose as pre-emptive analgesia.

**Keywords:** Ketamine, Pre-emptive analgesia, laparoscopic cholecystectomy, VAS score

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## Introduction

Pre-emptive analgesia is interpreted as a therapy which is commenced pre skin incision to intercept the development of CNS response by the injuries occurring during surgery and useful for the initial postoperative period.<sup>[1,2]</sup> Having this effect on the nociceptive pathway, pre-emptive analgesia is better than a traditional analgesic technique which usually initiated after surgery. Pre-emptive analgesia helps to diminish early postoperative pain so the development of chronic pain can be prevented by subsiding the altered CNS response.<sup>[1,3]</sup>

The proposal of pain inhibition was commencement into

history by Crile in 1913 and further it was modified by Wall and Woolf, insisted that time change of analgesic supplement have tremendous effects on postoperative pain'.<sup>[1,4,5,6]</sup> To reduce the dimensions and duration of postoperative pain, the concept of pre-emptive analgesia was introduced by Woolf in 1983 by proving the fact of central component post operation pain sensitivity in experimental studies.<sup>[1,7,8]</sup>

In vast list of analgesic, ketamine is an n-methyl-d-aspartate (NMDA) receptor antagonist, is becoming popular for its effectiveness to intercept intra as well as postoperative pain as a pre-emptive analgesic. Ketamine have gained popularity because receptors have a role in central response blunting and neural desensitization. Subanaesthetic quantity of

NMDA antagonist, by blocking receptors diminished the peripheral painful stimulation and also intercept CNS sensitization.<sup>[9]</sup>

Lap cholecystectomy is related with minor pain and lesser post operative morbidity as compared to open procedure, even though many patients confront extreme pain post operation and hence change in traditional analgesia is needed. Pain related to post laparoscopic cholecystectomy have lots of factors which can be by peritoneal stretching due to insufflation and by irritating diaphragm.<sup>[10,11]</sup>

After all these considerations, the above-mentioned study was planned to assess pre-emptive efficacy of ketamine in patients posted for lap cholecystectomy by injecting bolus dose just pre incision. This investigation also planned to know the different doses of pre-emptive ketamine doses.

#### Aims of study:

Research was carried out to compare and evaluate the efficacy of two different doses of ketamine (0.5 and 1.0 mg/kg IV) as a pre-emptive analgesic for postoperative analgesia in patients of laparoscopic cholecystectomy with reference to Intraoperative hemodynamic changes, VAS score, time of initial rescue analgesia, total number of doses of analgesic used within first 12 hours, postoperative hemodynamic changes, adverse effects.

#### Subjects and Methods

This prospective study was conducted after obtaining ethical approval from institute and written informed consent were taken from all patients. Total 90 adult patients who satisfied the inclusion criteria, undergoing routine lap cholecystectomy under general anaesthesia were included in the study. Patients were randomly allocated in three groups of 30 patients. Group A patients received Inj.Ketamine 0.5mg/kg i.v, Group B patients received Inj.Ketamine 1.0mg/kg i.v, Group C patients received Normal Saline i.v.

#### Inclusion criteria:

Age group between 18 to 55 years of either sex, ASA grade I and II patients, routine laparoscopic cholecystectomy.

#### Exclusion criteria:

Patients who refuses to enrol in the study, non-laparoscopic cholecystectomy, patients allergic to study drug, unable to understand Visual Analogue Scale (VAS), patients with mental illness or learning difficulties, morbidly obese patients, ASA grade III and IV patients

**Pre-anaesthetic assessment:** All the patients underwent routine anaesthesia fitness which included: History taking, physical examination and all routine lab tests. Informed written consent was taken from each patient with his/her close relative and explained about the study, VAS score as well as all patients were advised nil by mouth as per fasting guidelines.

Once patient was shifted to operation theatre, monitors were attached and baseline vitals such as pulse, systolic/ diastolic blood pressure, respiratory rate, temperature and SpO<sub>2</sub> recorded. An intravenous line was established and all

patients premedicated with Inj. Glycopyrrolate 0.04mg/kg, Inj.Ondansetron 0.15mg/kg and Inj. Fentanyl 2µg/kg intravenously.

Patient were preoxygenation with 100% oxygen for three minutes, induction was done with Inj. Thiopentone sodium (2.5%) 6mg/kg intravenously until loss eyelash reflex. Intubation was done with proper sized, cuffed endotracheal tube facilitated with inj. suxamethonium chloride (Sch) 2.0mg/kg i.v The study drug diluted till 10ml with saline and was administered i.v by an anaesthesiologist 10 minutes before skin incision.

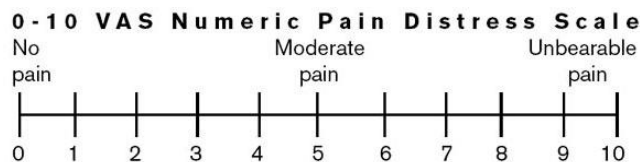
Anaesthesia was maintained with oxygen and nitrous oxide along with sevoflurane on controlled mechanical ventilation. Neuromuscular blockade was achieved with Inj. Atracurium besylate (0.50 mg/kg bolus and 0.10 mg/kg incremental dose).

Vital parameters, heart rate, systolic BP, diastolic BP, SpO<sub>2</sub> were monitored every 5 minutes till 30 mins and then every 15 mins till the completion of surgery.

Once procedure over, the atracurium blockade was reversed with Inj. Neostigmine 0.05mg/kg and Inj. Glycopyrrolate 0.01mg/kg i.v. Extubation was done after adequate muscle tone and power with full respiration and then patients were shifted to recovery.

All patients were evaluated for pain using visual analogue scale (VAS) hourly for initial three hours and then at interval of 6, 9 and 12 hours post operative session. The time zero hour was mentioned when patient shifted to recovery room from operation theatre. On above mention interval each time the pain was assessed on deep breathing, at rest and on movement.

Visual Analogue Score –VAS was used to assess pain.



**Time for the first rescue analgesic:** Inj.Diclofenac sodium (75mg) i.v were given as a rescue analgesic when VAS exceeded more than three or on demand of patient. Total number of doses of analgesic required within first 12 hours were documented. Adverse effects of ketamine like hallucination, illusion, nystagmus, increased muscle tone(catatonia), Nausea / vomiting were noted.

All data were calculated as mean  $\pm$  standard deviation (SD) for quantitative data. For qualitative data, Chi-square test and for comparison between groups un-paired t-test was used. Difference was considered statistically significant if  $P < 0.05$ . Microsoft Excel was used for mean and SD calculation and open Epi software for calculation of P value.

#### Results

**Table 1: Demographic Data (Mean $\pm$ Sd)**

Variables	Group A	Group B	Group C
Age (years)	36.93 $\pm$ 8.63	36.56 $\pm$ 8.91	36.96 $\pm$ 11.55
Sex (M:F)	7:23	5:25	8:22
Weight(kg)	56.23 $\pm$ 6.77	55.93 $\pm$ 6.85	55.66 $\pm$ 5.60
ASA(I:II)	12:18	17:13	15:15

Demographic data were comparable in all the groups.

**Table 2: Duration of Surgery**

Time	Group A	Group B	Group C
<45 min	0	0	0
45-75 min	18	16	16
≤90 mins	12	14	14

Total period of surgery was found to be comparable in all the groups.

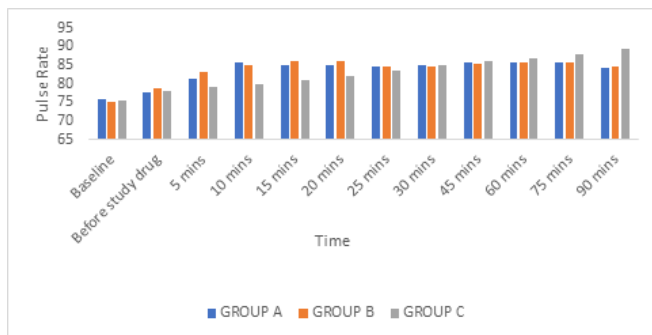
**Discussion**

International Association for the Study of Pain have defined pain as an unpleasant sensory & emotional experience can be associated with potential/actual tissue trauma or described in terms of such damage.<sup>[12,13,14,15,16,17]</sup> Following surgical procedures patient have pain a due to tissue handling/damage which can later on land up in physical, emotional and cognitive morbidity. The ultimate consequence of the surgical management can be influenced by the gravity of post operative pain. Progress of chronic pain post-surgery can greatly affect the long- term aspect of patient’s life. So, better peri and post-operative pain treatment is required.<sup>[18,19,20,21,22,23]</sup> The Pain Society of America have declared pain as the fifth vital sign.

Now a days NMDA receptor antagonist have become popular as it has a role in CNS and neural benumb effect. Many studies showed that pre-emptive analgesia provide better result in pain management, reduced analgesia consumption immediate post op and improve patient satisfaction.<sup>[16,22]</sup>

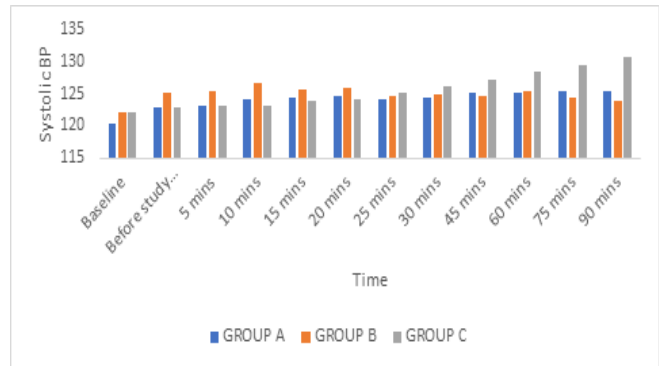
Ketamine is a “unique drug” having amnesic (short-term memory loss), hypnotic (sleep-producing), analgesic (pain-relieving) effects, there are very few medicines in practice to develop these types of effects at the same time.<sup>[18]</sup> Demographic data regarding age, sex, weight and duration of surgery were comparable in all the groups.

By stimulating sympathetic system, ketamine can increase circulating nor-adrenaline lead to momentary hemodynamic changes.



**Figure 1: Intraoperative Changes In Pulse Rate**

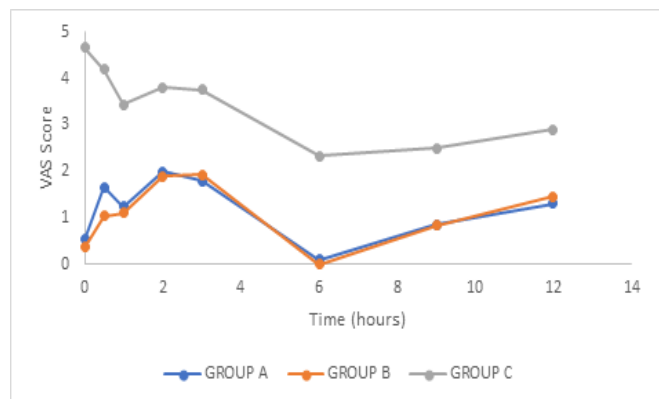
Pulse rate was slightly more in ketamine group(1.0mg/kg) as compared to ketamine group (0.5mg/kg) and saline group C in first 20 mins and was statistically significant (p value <0.05). After 20 mins, pulse rate was comparable in both ketamine groups (p value >0.05). But it was higher in saline Group as compared to both ketamine Groups which was statistically significant.



**Figure 2: Intraoperative Changes in Systolic BP**

Systolic BP was slightly more in ketamine Group(1.0mg/kg) compared to ketamine Group(0.5mg/kg) and saline Group C in first 20 mins which was statistically significant (p value <0.05). After 20 mins, SBP was comparable in both ketamine Groups (p value >0.05). But it was higher in saline Group as compared to both ketamine Groups which was statistically significant. Diastolic BP was comparable in all the groups with no statistical intergroup difference.

**Postoperative Vas Score**



**Figure 3: VAS Score at Rest**

At rest average value of Visual analogue score was remarkably higher (p value 0.0001) in saline Group as compared to both ketamine Groups postoperatively with maximum value of 4.66±0.66 at 0 hour. The average VAS score at rest in both ketamine Groups were comparable with no statistical significance between them.

Harsimransingh et al (2013),<sup>[14]</sup> and Vaijyanti Nitin Gadre et al,<sup>[20]</sup> (2017) conducted study on pre-emptive analgesia with ketamine for laparoscopic cholecystectomy with three different doses of ketamine in Group A, B, C (1, 0.75 and 0.5 mg/kg iv) & D(saline) and of three doses of ketamine in Group 1, 2, 3 (1, 0.75, 0.5 mg/kg iv) & Group 4(saline) respectively. Both of them have observed that the average VAS score at rest was remarkably higher in control saline group and in Group 4(saline) postoperatively with maximum value of 4.75±1.41 and 2.77±01 at 0 hour respectively. They both found no significant intergroup difference among three ketamine doses group.

**Postoperative vas score on movement:**

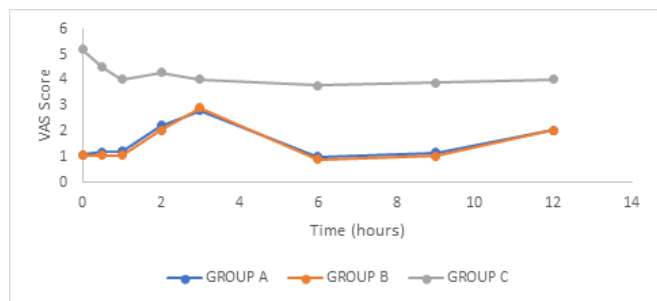


Figure 4: VAS score on movement

The average VAS score on movement was remarkably higher in saline Group compared to both ketamine Groups A and B postoperatively with maximum score  $5.2 \pm 0.610$  at zero hour. The average VAS score on movement in ketamine Groups A and B was comparable with no statistical significance.

S.S Wang et al (2015), [17] conducted study on intravenous ketamine as pre-emptive treatment in patients undergoing lap cholecystectomy with two different doses of ketamine in Group 2, 3 (0.25 and 0.5 mg/kg iv) and Group 1 (placebo). They observed that VAS values at 0 hour was significantly lower in Group 3 (0.5mg/kg) as compared to Group 1 and 2.

### Postoperative Vas Score on Deep Breathing

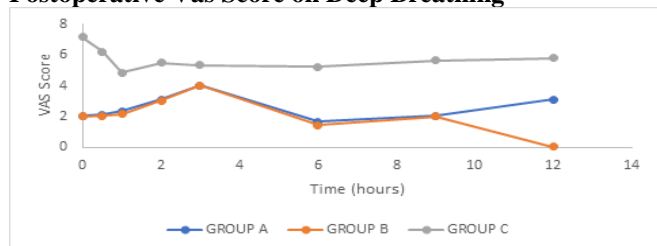


Figure 5: VAS Score on Deep Breathing

As we can see from above graph the average VAS values on breathing was higher than at rest and on movement. Maximum VAS score on deep breathing were observed in saline Group C at 0 hour with a mean of  $7.16 \pm 0.69$  score. The average VAS score on deep breathing in Group A and B were comparable with no statistical significance between them. Harsimrarsingh et al (2013) [14] and Vaijyanti Nitin Gadre et al (2017) [20] studies have observed that the average VAS score on deep breathing was remarkably high in control Group saline & in Group 4 (saline) respectively as already mentioned four groups under vas score at rest. It was maximum of  $7.40 \pm 1.43$  and  $4.5 \pm 0.00$  respectively in non-ketamine groups. In ketamine groups they both have found no significant intergroup difference.

### Postoperative Hemodynamic Changes

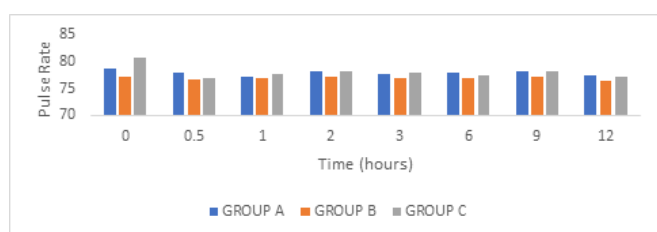


Figure 6: Postoperative Changes in Pulse Rate

At zero-hour, average pulse rate was high in saline Group as compared to both ketamine groups A and B. The average pulse rate at 0 hour in saline Group was  $80.76 \pm 4.22$  per min as compared to  $78.7 \pm 4.31$  per min and  $77.16 \pm 2.88$  per min in Group A and B respectively. This data shows statistically significant difference. After 0 hour there was no significant intergroup difference. Harsimrarsingh et al (2013), [14] have observed that pulse rate was remarkably high in saline Group as compared to ketamine Groups.

Present study shows significantly high Mean arterial pressure in saline Group as compared to both ketamine groups at zero hour. The mean arterial pressure at 0 hour in Group C was  $99.03 \pm 8.15$  as compared to  $95.7 \pm 9.31$  and  $95.46 \pm 10.1$  in Group A and B respectively. It shows statistically significant difference. After 0 hour there was nonremarkable intergroup difference. Rebecca F. K. et al (2004), [12] and S.S Wang et al (2015), [17] conducted a study on preoperative ketamine improves postoperative analgesia after laparoscopic. In their study they found no significant changes in vital parameters among the study groups.

### Time For First Rescue Analgesic

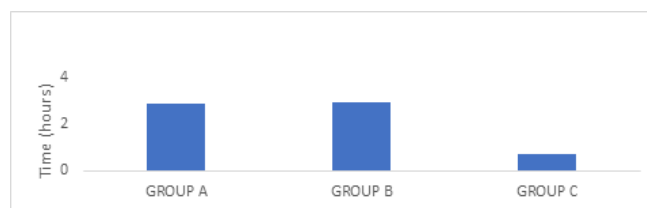


Figure 7: Time for First Rescue Analgesic

The average time for 1st rescue analgesia was remarkably higher in the Group A  $2.9 \pm 0.305$  hours and Group B  $2.966 \pm 0.182$  hours as compared to Group C  $0.733 \pm 0.449$  hours. The mean time to rescue analgesia was similar in both ketamine Groups with no statistically significant difference (p value 0.3133). Yang L et al (2014), [15] conducted a metanalysis of 5 studies on pre-emptive effects of ketamine in patients undergoing surgery. In their metanalysis, the time to first rescue analgesic was significantly longer in ketamine groups compared to control group (p < 0.0001)

In present study, the mean number of doses of rescue analgesic requirement was significantly more in saline Group  $1.833 \pm 0.379$  as compared to ketamine Group A  $1.1 \pm 0.305$  and Group B  $1.033 \pm 0.182$ . There was no significant difference between ketamine Groups (p value 0.3061).

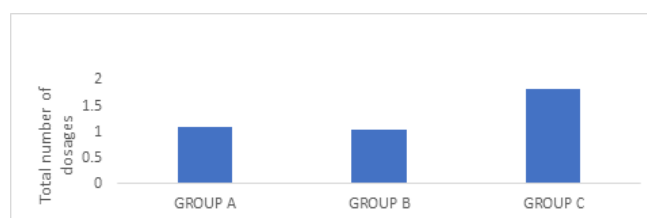


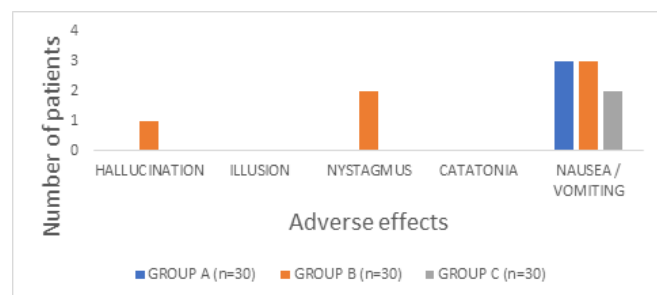
Figure 8: Total Number of Doses of Analgesic In First 12 Hours

Harsimrarsingh et al (2013), [14] have observed fentanyl



consumption was more in saline group (7.35) compared to ketamine Groups A (4.55), B (4.45) and C (4.25). Launo C et al (2004),<sup>[13]</sup> showed that intraoperative administration of 0.7 mg/kg iv ketamine reduced the amount of rescue tramadol dose post operatively. It was consistent with present study. Vaijyanti Nitin Gadre et al in (2017),<sup>[20]</sup> conducted a comparative study of three doses of ketamine in Group 1, 2, 3 (1, 0.75, 0.5 mg/kg iv) and Group 4(saline) in laparoscopic surgeries. They showed that total number of doses of fentanyl up to 12 hours was 32, 30, 21 and 58 in Groups 1, 2, 3 and 4. Khalid M et al (2015),<sup>[19]</sup> conducted study on effect of preinduction low dose ketamine bolus on intraoperative and immediate postoperative analgesia requirement in day care surgery. They found that the mean morphine consumption in ketamine fentanyl group was  $5 \pm 0.82$  mg and in saline fentanyl group it was  $8 \pm 2.46$ mg. This difference was significant (p value 0.02).

In present study adverse effects related to ketamine was found to be more in Group (1.0mg/kg) ketamine dose as compared to ketamine Group(0.5mg/kg) and saline Group C. In Group B (1.0mg/kg) total 6 out of 30 patients found to have an adverse effect.



**Figure 9: Adverse Effects**

Harsimransingh et al (2013),<sup>[14]</sup> have found in Group A(1mg/kg) total 3 out of 30 patients and in Group C(0.5mg/kg) total 2 out of 30 have an adverse effect like Nausea/vomiting. Yang L et al (2014),<sup>[15]</sup> conducted a metaanalysis of 5 studies on pre-emptive effects of ketamine in patients undergoing surgery. In metaanalysis they found that nausea and vomiting as a side effect of a ketamine were present in studies but there was no significant difference between ketamine and control groups. It showed that the safety of ketamine was equal with physiological saline.

## Conclusion

Intraoperatively, pulse rate and systolic BP were slightly higher for initial 20 mins after administration of study drug with ketamine 1mg/kg iv. After 20 mins there was no statistical difference between ketamine groups (1mg/kg & 0.5mg/kg). There was higher pulse rate and systolic BP in saline group as compared to ketamine groups after 20 mins which was statistically significant. There was no statistical difference in diastolic BP in all the three groups. The mean VAS score at rest, on activity and on deep tidal volume breathing was remarkably higher in saline group as compared to ketamine groups postoperatively. The average time for 1st rescue analgesic was significantly higher in ketamine groups (1mg/kg & 0.5mg/kg) on average 3 hours

as compared to saline group less than hour. Adverse effects related to ketamine was found to be higher with 1.0mg/kg as compared to 0.5mg/kg and saline.

Hence, ketamine has a conclusive role as a pre-emptive analgesic in minimizing postoperative pain. It also decreases requirement of analgesic in patients undergoing laparoscopic cholecystectomy. Lower dose of ketamine with 0.5mg/kg having fewer side effects and with less vital parameter changes is an ideal dose for pre-emptive analgesia.

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