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KETAMINE INFUSION FOR MANAGEMENT OF EARLY POSTOPERATIVE PAIN FOLLOWING ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY: ASSESSMENT OF OPTIMUM DOSE

Anaesthesiology

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ABSTRACT

Background: This study is aimed to assess an optimal dose of ketamine infusion for management of early postoperative pain in elective laparoscopic cholecystectomy. Intensity of pain, requirement of rescue analgesics and fitness to discharge were assessed during immediate postoperative period.

Methodology: Randomised controlled prospective clinical trial was conducted in 140 patients of laparoscopic cholecystectomy and, allocated in four groups of 35 each. Standard anaesthetic regimen was used in all patients, using propofol for induction, atracurium for muscle relaxation and isoflurane for maintenance of anaesthesia. Continuous infusion of the test drug was administered by intravenous cannula placed in alternate hand from start of port placement till wound closure. Group K1, K2 and K3 received an infusion of ketamine hydrochloride at a rate of 20 $\mu g\ kg^{-1} min^{-1}$, 30 $\mu g\ kg^{-1}\ min^{-1}$ and, 40 $\mu g\ kg^{-1}\ min^{-1}$ respectively, while Group N received normal saline. Postoperative pain score, requirement of rescue analgesia, degrees of sedation and postoperative cognitive function were examined postoperatively.

Results: Visual analog scale score ≥ 4 was considered significant pain and, rescue analgesic injection diclofenac sodium 75mg kg^{-1} was administered. Duration of analgesia was 130.71 ± 82.41, 457.14 ± 150.373, 520.97 ± 189.338 and, 524.83 ± 141.436 minutes in group N, K1, K2 and K3 respectively. Out of 35 patients 28, 4, 0 and, 0 patients required three doses of diclofenac sodium in 24 hours in N, K1, K2 and K3 group respectively.

Conclusions: Continuous infusion of ketamine hydrochloride at a rate of 30 $\mu g\ kg^{-1} min^{-1}$ during intraoperative period provide effective pain relief during early postoperative period without influencing cognitive function of the patients.

KEYWORDS

Laparoscopic cholecystectomy; postoperative analgesia, low dose ketamine infusion.

INTRODUCTION:

Postoperative pain although less severe and of shorter duration following laparoscopic cholecystectomy than open cholecystectomy, is still a source of marked discomfort and surgical stress. The delay in hospital discharge happens mainly due to the severity of postoperative pain and the occurrence of nausea or vomiting. Characteristically, overall pain after laparoscopic cholecystectomy carries a high inter-individual variability in terms of intensity as well as duration and is largely unpredictable.[1] The fact that acute pain after laparoscopic cholecystectomy is complex in nature, does not resemble pain after other laparoscopic procedures and, suggests that effective analgesic treatment should be multimodal.[1] Postoperative pain control with multimodal analgesia is important not only to relieve pain but also to reduce post-operative side effects, such as nausea, vomiting, need for sedation, and length of hospital stay.

Ketamine, an NMDA (N-methyl-D-Aspartate) receptor antagonist, a versatile drug successfully used as analgesic drug in lower doses. Ketamine plays an important role in reducing postoperative pain. Singh H et al[2] reported that ketamine reduces analgesic requirement in patients undergoing laparoscopic cholecystectomy and also lower dosage is found to be devoid of the adverse effects pertaining to ketamine. Karcioglu et al[3] also opined that consumption of analgesic was significantly lower in the patients, received ketamine infusion.

The aim of the study was to assess effectiveness of different doses of intraoperative ketamine infusions for reduction of post-operative pain and the requirement for a rescue analgesic agent.

MATERIALS AND METHODS:

Randomised, controlled prospective, single center blind clinical trial was done on patients suffering from calculous of gall bladder without cholecystitis, planned for elective laparoscopic cholecystectomy surgery.

Sample size for the study was calculated with time to first rescue analgesic as the primary outcome variable. It is calculated that 35 subjects should be required per group in order to detect difference of 30 minute in this time parameter between any two groups with 80% power & 5% probability of Type 1 error.

The study was initiated following the Institutional Ethical Committee approval and a written informed consent. Clinical drug trial registration was done. Patients between 16 to 65 years of age of ASA I and II were counseled to take part in the study explaining the outcome of the study and also that it is a part of the anaesthesia technique in the planned surgical intervention. Patients were made to familiarize the subjective test parameters that were evaluated and required the patient cooperation.

By computer generated random number the total 152 samples were selected for this trial. Twelve patients did not participate due to various reasons and finally 140 patients were randomly allocated in four groups to receive one of the following solutions as continuous infusion.

- Group K1 - Ketamine hydrochloride (100 mg ml^{-1}) 1.2 ml is added to 48.8 ml normal saline in a syringe. Each millilitre of solution contains 2400 µg Ketamine hydrochloride.
- Group K2 - Ketamine hydrochloride (100 mg ml^{-1}) 1.8 ml is added to 48.2 ml normal saline in a syringe. Each millilitre of solution contains 3600 µg Ketamine hydrochloride.
- Group K3 - Ketamine hydrochloride (100 mg ml^{-1}) 2.4 ml is added to 47.6 ml normal saline in a syringe. Each millilitre of solution contains 4800 µg Ketamine hydrochloride.
- Control Group N- Syringe contains 50 ml normal saline.

Standard uniform procedure was used to provide general anaesthesia using oxygen, nitrous oxide, isoflurane and atracurium besylate. Propofol was used as inducing agent and fentanyl citrate 2µg kg^{-1} for intraoperative analgesia. Prepared solution as per the assigned group was started at a rate of 0.5 ml $kg^{-1} hour^{-1}$ to deliver 20µg, 30µg, 40µg or, nil ketamine hydrochloride per kg per minute in group K1, K2, K3 and N respectively. Infusion was stopped 5 minutes before the reversal of anaesthesia. Haemodynamic parameters were documented during perioperative period. Specific steps were followed as mentioned to prevent any bias in blinding and to maintain uniformity.

After extubation, degree of sedation was assessed by Ramsay sedation score at 0, 5 and, 15 minutes.

Ramsay Sedation Scale[4]

1. Patient is anxious and agitated or restless or both

2. Patient is co-operative, oriented and tranquil
3. Patient responds to commands only
4. Patient exhibits brisk response to light, glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response

The study parameters Visual Analogue scale (VAS), Aldrete score were assessed in post-anesthesia care unit (PACU) up to 2 hours and then transferred to post-operative unit and followed-up in specific time frames and intervened till 24 hours after surgery. Visual Analogue score ≥4 was considered as significant pain and Inj Diclofenac 75 mg IM was administered as a rescue analgesic and the time of this first dose was noted down as duration of analgesia. Total dosage of rescue analgesic received in 24 hours was also documented.

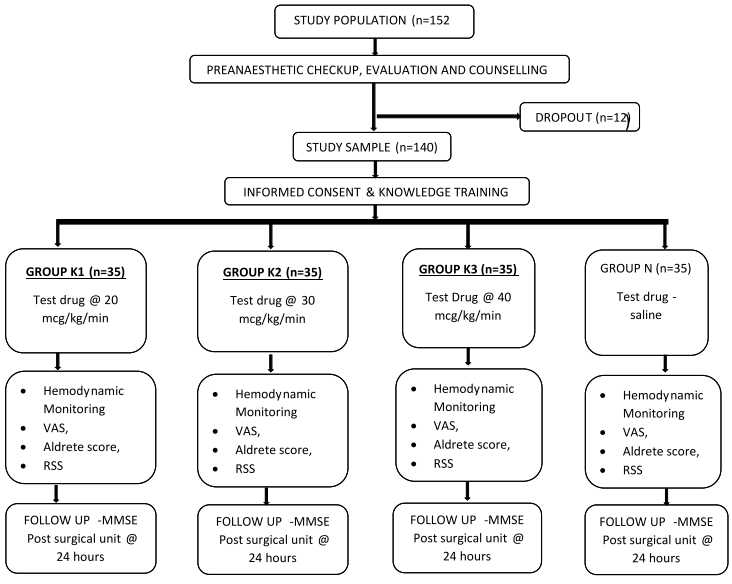
The patients were visited after 24 hours and, were asked to describe about any discomfort or loss of sleep sort of features which points towards the cognitive side effects of ketamine. A Mini Mental Score Examination[5] tool was used to objective evaluation of the state of higher mental functions.

Mini-mental State Examination test:

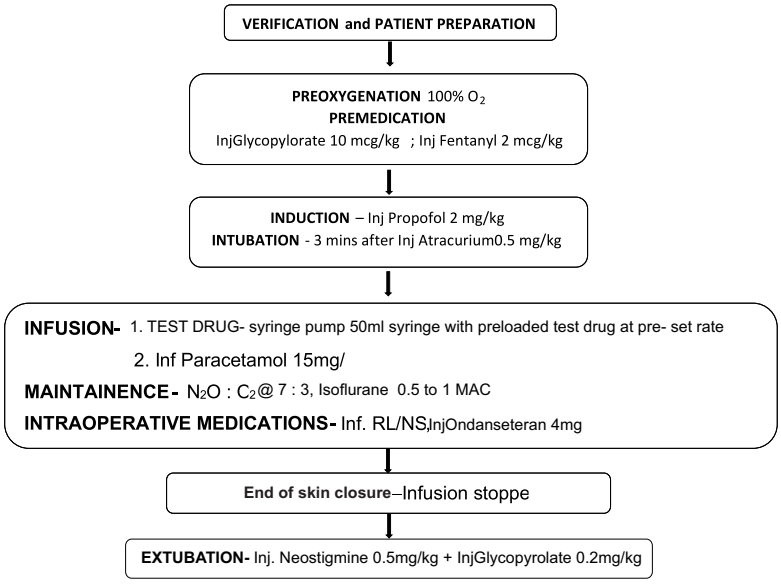
Category	Points	Descriptions
Orientation to time	5	From broadest to narrow
Orientation to place	5	From broadest to narrow
Registration	3	Repetition of name prompt
Attention and calculation	5	Serial seven or spelling backwards
Recall	3	Registration recall
Language	2	Naming a pencil and watch
Repetition	1	Speaking back a phrase
Complex command	6	Involve drawing figure etc

The data collected is charted in a Microsoft Excel spreadsheet by the blinded observer and then analyzed using Statistica version 8 [Tulsa, Oklahoma: Stat Soft Inc., 2007]. The numerical variables are summarized as in a descriptive statistics tables as normally distributed by Kolmogorov-Smirnov goodness-of-ft test. Followed which Comparison of the normally distributed numerical variables between 4 study groups is done by One-way analysis of variance (ANOVA) followed by post hoc Tukey's test for pair wise comparison if ANOVA returns $p < 0.05$ or by post hoc Dunn's test for pair wise comparison if Kruskal-Wallis ANOVA returns $p < 0.05$. Pearson's Chi-square test is employed for intergroup comparison of categorical variables. A p-value of ≤ 0.05 was considered statistically significant.

SCHEMATIC DIAGRAM OF THE PLAN OF STUDY



SCHEMATIC DIAGRAM RELATED TO ANAESTHESIA PROCEDURE



Results:
Based on the inclusion and exclusion criteria, a total of 152 individuals were considered suitable for the study. Seven patients did not participate in this trial. Four cases also excluded from study because operation lasted for more than 2 hour and, one laparoscopic operation was converted to open cholecystectomy. Finally 140 Individuals were participated in this study.

Patients allocated in different groups had normal distribution in respect to age, weight, body mass index, duration of surgery, duration of anaesthesia and duration of infusion of ketamine hydrochloride (table 1 and 2).

Table 1: Demographric profile of different groups of patients

S No	Demograp hic Profile	Group N Mean (SD)	Group K1 Mean (SD)	Group K2 Mean (SD)	Group K3 Mean(SD)	P value
1	Age (yrs)	42.71 (12.03)	42.14 (13.54)	39.8 (12.5)	41.03 (13.0)	0.785
2	Sex M/F	42.86/ 57.14	45.71/ 54.29	45.71/ 54.29	44.29/ 55.71	0.99
3	Weight (kg)	52.83 (6.239)	53.31 (6.885)	53.77 (9.114)	50.43 (5.922)	0.213
4	BMI (kg/m^2)	23.35 (1.582)	23.24 (1.98)	23.35 (2.316)	22.51 (1.267)	0.17

Table 2: Duration of anaesthesia, surgery and trial drug administration in different group

S No	Duration in minute	Group Nmean (SD)	Group K1 Mean(SD)	Group K2 Mean(SD)	Group K3 Mean(SD)	P value
1	Duration of Surgery	75.0 (13.339)	77.43 (12.09)	69.71 (14.75)	71.43 (12.75)	0.17
2	Duration of Anaesthesia	79.0 (13.34)	81.43 (12.09)	74.73 (14.75)	75.41 (12.49)	0.07
3	Duration of drug administration	70.0 (13.339)	72.43 (12.09)	64.71 (14.75)	66.43 (12.75)	0.07

Patients remained haemodynamically stable throughout the study period. Changes in heart rate and blood pressure were comparable in different group and statistically insignificant.

Table 3: Duration of postoperative analgesia in minutes

S No	Duration of Analgesia	Group N	Group K1	Group K2	Group K3	p value
1	Mean(SD) (min)	130.71 (82.41)	457.14 (150.37)	520.97 (189.34)	524.83 (141.43)	<0.001
2	Minimun (min)	60	180	240	310	
3	Maximum (min)	350	800	905	905	

Severity of postoperative pain was assessed by visual analog scale. Score ≥ 4 was considered significant pain and, rescue analgesic injection diclofenac sodium 75mg kg^{-1} was administered. Duration of analgesia was 130.71 ± 82.41, 457.14 ± 150.373, 520.97 ± 189.338 and, 524.83 ± 141.436 minutes in group N, K1, K2 and K3 respectively.

It is to be noted that in Groups N and, K1 all 35 patients have received rescue analgesics while in Group K2, 31 have received rescue analgesic and in Group K3, 30 have received rescue analgesic dose. In Kruskal-Wallis ANOVA test followed by post hoc, Dunn's multiple comparisons test showed that the distribution is statistically significant (p value < 0.001).

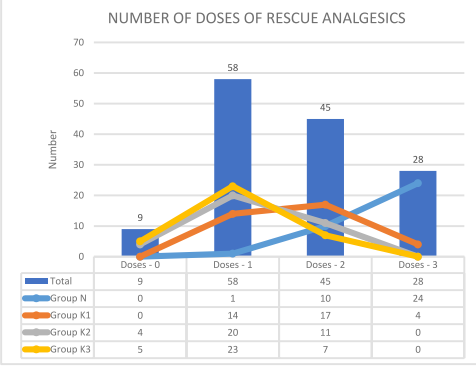


Table 4: Ramsay sedation score of different group of patients immediately after extubation

Postoperati veperiod	Ramsay sedation score	Group N	Group K1	Group K2	Group K3	P value
At 0 min	Mean (SD)	2.83 (0.38)	3.03 (0.17)	3.63 (0.49)	3.89 (0.32)	0.000
	Range	2-3	3-4	3-4	3-4	
At 5 min	Mean (SD)	1.80 (0.47)	1.6(0.55)	2.0(0.43)	2.00 (0.0)	0.0001
	Range	1-3	1-3	1-3	2-3	
At 15 min	Mean (SD)	1.23 (0.43)	1.11 (0.32)	1.34 (0.54)	1.51 (0.51)	0.0027
	Range	1-2	1-2	1-2	1-2	

After extubation all patients were assessed for level of sedation by using Ramsay sedation score. Patients belong to K2 and K3 were more sedated than Group N and K1 at 0 min, 5 min and 15 minutes after extubation. Difference in sedation score is statistical significant (Table 4). After 15 minutes, sedation score ranges from 1 to 2 in patients of all four groups.

Fitness for discharge from post anaesthesia care unit was assessed by Aldrete score. After 2 hours Aldrete score was 9.71(0.458), 9.63(0.49), 9.0(0.02) and 8.97(0.618) in group N, K1, K2 and K3 respectively and the difference is statistically significant (p<0.001).

Postoperative cognitive function was assessed 24 hours after surgery in different group of patients. Mini mental state examination (MMSE) score was more than 25 in all groups. It was 25.80(1.023), 25.54(1.172), 25.31(0.796) and 25.86(1.004) in group N, K1, K2 and K3 respectively (p=0.0512).

DISCUSSION:
The rising concern in the modern era of minimal invasive surgery is the prompt and apt management of early postoperative pain following surgeries such as laparoscopic cholecystectomy. Considerations are to be taken to provide early ambulation, recovery and rapid normalisation of cognitive function following a surgery under general anesthesia, thereby facilitating the decrease in hospital stay, which has a direct impact on the total treatment cost of patients.

The hospital stay generally gets prolonged due to the intensity of postoperative pain and occurrence of nausea and vomiting. Unlike open cholecystectomy, pain following laparoscopic cholecystectomy has a visceral component, a somatic component and shoulder pain secondary to diaphragmatic irritation because of CO2 pneumo-peritoneum. The degree of pain after laparoscopic procedures has multifactorial influence including the volume of residual gas, type of gas used, pressure created by pneumo-peritoneum and insufflated gas temperature.[3]

Experimental and clinical studies suggested that the administration of potent short acting opioid for postoperative pain relief is associated with central sensitization to pain, which is known as opioid induced hyperalgesia. Activation of NMDA (N-methyl-D-Aspartate) receptor has been suggested to be the principal mechanism facilitating the response to sensory stimuli and leading to opioid-induced hyperalgesia.[6-8] Although ketamine has variable action, its analgesic effect results from its NMDA antagonism that prevents central sensitization and inhibits this receptor by reducing mean time and frequency of NMDA receptor channel opening, through an allosteric mechanism.[9,10]

During last one decade ketamine hydrochloride has been used intraoperatively in subanaesthetic dose in different clinical trial with variable outcome. Ithnin FB et al[11] and Ragazzoni et al[12] did not observe any beneficial effect of subanaesthetic dose of ketamine in terms of postoperative pain relief. On other hand Saxena D et al[13] and Kim ME et al [14] reported the lower intensity of postoperative pain in patients received subanaesthetic dose of ketamine hydrochloride.

This study was designed to evaluate the influence of intraoperative infusion of ketamine hydrochloride on postoperative pain, rescue analgesic requirement and, also to detect optimum dose of ketamine hydrochloride for postoperative analgesia with minimum adverse effects.

One hundred and forty patients were randomly allocated in Group K1, K2, K3 and N consisting of 35 individuals to receive 20 μg $kg^{-1}min^{-1}$, 30 μg $kg^{-1}min^{-1}$, 40μg $kg^{-1}min^{-1}$ ketamine infusion or equal volume of normal saline. Patients allocated in different groups had normal distribution in respect to age, weight, body mass index, duration of surgery, duration of anaesthesia and duration of infusion of ketamine hydrochloride (table 1 and 2). The hemodynamic parameters such as heart rate, blood pressure were also normally distributed throughout the intraoperative period in the entire study group irrespective of the dose of infusion and duration of surgery. A similar finding was reported by Saxena D et al[13], Singh H etal[2] and Ozhan et al[10].

Pain intensity as measured by visual analogue scale (VAS) of ≥ 4 was considered as significant pain and noted as duration of analgesia. It is also evident that as the dose of the ketamine gets increased the minimum duration of analgesia also increases exponentially as 60 minutes, 180 minutes, 240 minutes and 310 minutes in Group N, Group K1, Group K2 and Group K3 respectively. It is also reflected statistically significant in the mean period of pre rescue period taken in each group as the dose of ketamine infusion gets increased (p value <0.001) (table 3).

This is similar to the observation made by Ithnin et al[11] who had observed a lower pain score in early postoperative period in comparison with placebo control group. Saxena D et al[13] found an efficacious analgesic effect of ketamine infusion postoperatively, which was also the supported by Lee et al[8]. Kim ME et al[14].Miziara et al[15] and Karcioglu et al[16] also approved of the better pain relief in the observed time frames when comparing with the control group. It is contrary to the findings, Ragazzoni et al[12]did not observe any significance difference in terms of pain relief between the study group. Leal et al[9] has mentioned that ketamine marginally reduces intensity of pain but that is statistically insignificant.

Irrespective of the study groups, intramuscular diclofenac sodium 75 mg was given as rescue analgesic during immediate postoperative period when VAS score ≤4. It was observed that all 35 patients have received rescue analgesics in group N and K1, while in Group K2, 31 patients and in Group K3, only 30 patients have received rescue analgesic during first 24 hours after surgery. The number of doses of rescue analgesic received by patients in each group during the first day following the surgery i.e. within first 24 hours in each group were also recorded and found that maximum of 3 doses were consumed. Out of 35 patients, 24 and 4 patients of group N and K1 required three doses of diclofenac sodium and none in K2 or K3 group.

The difference in the number of rescue analgesic doses required by the patients of different groups was found to be statistically significant (p = < 0.001). Similar observations were made by Miziara et al[15], Ozhan et al[10]and, Singh H et al[2].

After extubation, degree of sedation as assessed by Ramsay Sedation score were statistically significant at 0 minute (p = 0.000), 5 minute (p = 0.001) and 15 minute (p = 0.027). After 15 minutes, sedation score ranges from 1 to 2 in patients of all four groups and fit to transfer to the post anaesthesia care unit. Patients received ketamine are more sedated immediately after extubation and delayed the transfer from operation theatre to post anaesthesia care unit (table 4). This delay in sedation level is similar to the observations that has been made by Ithnin et al.[11] Discharge from post anaesthesia care unit was not delayed due to ketamine infusion. All patients fulfilled Aldrete score criteria and found fit to discharge from PACU after 2 hour.

The difference between the study groups with respect to Mini Mental State Examination tool was not statistically significant (p = 0.0912) and, there was no evidence or history elicitable of any possible cognitive side effects of ketamine at any of the dose administered. Similar observations were made by Ozhan et al[10], Lee et al[8] and, Singh H et al[2]. On contrary, Mendes et al[17] reported presence of cognitive side effects of ketamine.

In our study, we were able to appreciate that the intensity of pain was better controlled by using subanaesthetic doses of ketamine during laparoscopic cholecystectomy surgery even when the lowest dose of infusion (20 μg kg^{-1} min^{-1}) was given. Groups K2 and K3 are superior to group K1 in terms of pain relief. When specifically considering to preserve the benefit and also in getting a less unfavorable outcome, through this study we would like to conclude that continuous infusion of ketamine at a rate of 30 μg kg^{-1} min^{-1} is superior to the groups receiving 20 μg kg^{-1} min^{-1} and 40 μg kg^{-1} min^{-1}ketamine hydrochloride.

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Conflicts of interest:
There are no conflicts of interest

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