Original Paper

Preemptive Use of Low Dose Intravenous Ketamine on Post Operative Pain after Laparoscopic Cholecystectomy

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Abstract

Introduction: There is a widespread belief for the efficacy of preemptive analgesia among clinicians. Different drugs and methods are used as preemptive analgesic method for postoperative pain management.

Objective: To evaluate the efficacy of preemptive use of small dose intravenous ketamine on post operative pain on patients undergoing laparoscopic cholecystectomy.

Materials and Methods: Sixty patients of both sexes as per American Society of Anaesthesiologists (ASA) physical status I and II underwent laparoscopic cholecystectomy were randomly allocated into two groups. In the operating room, Group A (n=30) received 0.5 mg/kg body weight of ketamine intravenously 10 minutes before the surgical incision. In Group B (n=30) 0.5 mg/kg body weight of normal saline was injected. Post operative analgesia was maintained with on demand intramuscular pethidine 1.5 mg/kg body weight. The pain intensity was assessed at time 0 (immediately after arousal) and 6, 12, and 24 hours postoperatively using the 10 points visual analogue scale (VAS). Side effects like nausea, vomiting, delirium and hallucination were also recorded.

Results: For all of the evaluated times, the VAS score were significantly lower in Group A with ketamine compared to Group B with normal saline. The interval time for the first analgesic request was 22.9±6.8 (Mean±SD) minutes in Group A and 17.8±7.2 (Mean±SD) minutes in Group B and the difference was statistically significant (P=0.021). The total number of pethidine injections in first 24 hours post-operatively was 0.7±0.6 (Mean±SD) in Group A and 1.9±0.7 (Mean±SD) in Group B and the difference was statistically significant (P=0.037). The mean total cumulative amount of pethidine administered over 24 hrs period following the end of surgery in group A was 97.31±10.12 mg (Mean±SD) and in group B was 151.23±12.02 mg (Mean±SD) and the difference was statistically significant (P=0.008).

Conclusion: A low dose of intravenously administered ketamine had a preemptive effect in reducing pain after laparoscopic cholecystectomy.

Key-words: Preemptive analgesia, ketamine, laparoscopic cholecystectomy, postoperative analgesia.

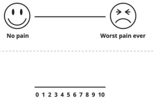
Introduction

Pain after laparoscopic cholecystectomy results from the stretching of the intra abdominal cavity, port incisions, dissection of gall bladder and phrenic nerve irritation by residual carbon dioxide in the peritoneal cavity. Proper postoperative analgesia is essential in facilitating early mobilization and discharge of these patients. As knowledge of the epidemiology and pathophysiology of postoperative pain increases, analgesic concept has been developed and applied for the prevention of pain, preemptive analgesia; whereby analgesic treatment is started prior to trauma and surgical intervention[1]. The underlying assumptions are that a pretreatment strategy reduces acute pain scores and analgesic requirements more than post surgical treatment[2]. The concept was propounded in the early 1980s when experimental studies showed that measures to antagonize the nociceptive signals before injury prevented central hyper sensitization, thereby reducing the intensity of pain following injury[3]. Analgesia is achieved by suppressing, either together or separately, central or peripheral sensitization. Preemptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements and a decline in morbidity, promoting wellness and shortening the length of hospital stays[1,4].

Local anaesthetics, opioids, non steroid anti inflammatory drugs (NSAIDs) and paracetamol group can be used either alone or in combination for preemptive analgesia[5]. Ketamine hydrochloride is a well known general anaesthetic and short acting analgesic in use for almost three decades[6]. The analgesic properties of ketamine are related to its action on a non competitive N-Methyl-D-Aspartate (NMDA) receptors present in nerve cells which cause excitatory function on pain transmission and binding with ketamine seems to prevent or reverse the central sensitization of every kind of pain including post-operative pain[7]. Ketamine demonstrates a potent analgesic effect by central blockage of perception of pain with subanaesthetic doses[8]. Preemptive ketamine may be a useful addition in pain management regimens. This study tried to evaluate whether preemptive use of low dose intravenous ketamine decreases postoperative pain and opioid requirement in patients undergoing laparoscopic cholecystectomy.

Materials and Methods

This prospective clinical study was conducted at department of Anaesthesia and Intensive Care in Border Guard Hospital, Pilkhana, Dhaka from July 2015 to June 2016. Permission was taken from departmental review board before starting the study. Sixty patients of both sexes aged between 18-50 years, ASA physical status I and II scheduled to undergo elective laparoscopic cholecystectomy under general anaesthesia were included in the study. Patients with psychiatric illness, hypertension, ischaemic heart disease, raised intracranial pressure and emergency operation were excluded from the study. Pre-anaesthetic check up was done 24 hours prior to surgery and the procedure was explained to the patient and written consent was obtained from each patient. During the preoperative interview, patients were instructed how to assess postoperative pain by using the Visual Analogue Scale (VAS)[9]. VAS is a straight horizontal line of fixed length, usually 10 cm/100 mm (Figure-1). The ends are defined as the extreme limits of the parameter to be measured orientated from the left to the right; 0-10, 0=no pain, 10=the worst imaginable pain. All patients received oral diazepam (5 mg) at night before surgery. All patients were divided in to two groups. In operating room Group A (n=30) patients, received 0.5 mg/kg body weight of ketamine intravenously 10 minutes before surgical incision and in Group B (n=30) patients received normal saline as placebo. Operation was done under general anaesthesia with controlled ventilation. Pethidine 1 mg/kg body weight was slowly given intravenously before induction of general anaesthesia. Induction was done with thiopentone 5 mg/kg body weight. After intubation with vecuronium 0.1 mg/kg body weight, anaesthesia was maintained with 70% nitrous oxide in oxygen, halothane 0.5-1% and muscle relaxation was maintained with incremental doses of vecuronium. Patient's heart rate, blood pressure, ECG in lead II, respiratory rate, oxygen saturation (SpO_2) and end tidal carbon di oxide ($ETCO_2$) were monitored and recorded in every 5 minutes interval. After completion of operation, the patients were extubated by reversal of muscle relaxant with Inj neostigmine with atropine. After recovery from anaesthesia all patients were observed in the postoperative ward for 24 hours. Postoperative analgesia was assessed in both groups subjectively by VAS. Postoperatively if patients asked for analgesia; were administered intramuscular pethidine 1.5 mg/kg body-weight. VAS Observations were made in postoperative ward at time 0 (immediately after arousal) and at 6, 12 and 24 hours for 24 hours. Other than the VAS score, the interval time for the first request of analgesia, the number of times pethidine was injected and total postoperative pethidine consumption in the first 24 hours were recorded. Side effects like nausea, vomiting, delirium and hallucination were also recorded.



Fig–1: The Visual Analogue Scale (VAS)

All statistical analysis were carried out using SPSS (Statistical Package for social sciences) 17.0 for windows. All results are expressed as mean±standard deviation (Mean±SD) or in frequencies as applicable. Results were considered statistically significant if p<0.05.

Results

Patient's demographics and perioperative data were similar and fairly comparable in both groups and differences were statistically not significant (Table-I). Duration of surgical procedure and duration of anaesthetic procedure were similar in both groups and differences were statistically not significant (Table-I). No patient was withdrawn from the study. Operating conditions were pronounced satisfactory by the surgeon concerned in all the cases. The pain intensity was measured by visual analogue scale in both groups in postoperative ward at 0, 6, 12 and 24 hours (Table-II). For all of the evaluated times, the VAS score was

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significantly lower in Group A than that of the Group B and differences were statistically significant. Analgesic requirement related data were analyzed (Table-III). The interval time for the first analgesic request was 22.9±6.8 (Mean±SD) minutes in Group A and 17.8±7.2 (Mean±SD) minutes in Group B and the difference was statistically significant (P=0.021). The total number of pethidine injections in first 24 hours postoperatively was 0.7±0.6 (Mean±SD) in Group A and 1.9±0.7 (Mean±SD) in Group B and the difference was statistically significant (P=0.037). The mean total cumulative amount of pethidine administered over 24 hrs period following the end of surgery was less in group A compared to group B. Mean dose of pethidine in group A was 97.31±10.12 mg (Mean±SD) whereas in group B was 151.23±12.02 mg (Mean±SD) and the difference was statistically significant (P=0.008). Incidences of postoperative side effects like nausea; vomiting, delirium and hallucination were observed and recorded in both groups (Table-IV). Incidences were almost similar in both groups and differences were statistically not significant.

Table-I: Demographic and Perioperative data

Characteristics		Group A (n=30)	Group B (n=30)	P Value	Result
Age(Years)		38.7±6.08	37.1±6.13	0.097	NS(student 't' test, unpaired)
Body weight (Kg)		58.4±6.3	59.2±5.8	0. 318	NS(student 't' test, unpaired)
Sex	Male	10(33.34)	11(36.66%)	0.768	NS(chi square test)
	Female	20(66.66%)	19(63.34%)	0.789	NS(chi square test)
ASA physical status	I	22(73.33%)	23(76.66%)	0.776	NS(chi square test)
	II	08(26.67%)	07(23.34%)	0.784	NS(chi square test)
Duration of Surgery(min)		55.9±10.3	54.2±9.8	0.783	NS(student 't' test , unpaired)
Duration of Anaesthesia(min)		65.6±11.8	66.3±12.1	0.851	NS(student 't' test , unpaired)

Values are expressed in Mean±SD and Percentage, NS–Not significant

Table-II: Mean pain score (VAS) after surgery

Measurement Time	Group A (n=30)	Group B (n=30)	P Value	Result Student 't' test, (unpaired)
At 0 hours	3.8±1.0	5.1±1.1	0.027	Significant
At 6 hours	2.7±0.8	3.6±1.0	0.046	Significant
At 12 hours	2.4±1.1	3.5±0.9	0.041	Significant
At 24 hours	1.4±0.5	1.9±0.7	0.045	Significant

Values are expressed in Mean±SD

Table-III: Analgesic requirement related data

Variable	Group A (n=30)	Group B (n=30)	P Value	Result Student 't' test, (unpaired)
The interval time for 1st analgesic request (minutes)	22.9±6.8	17.8±7.2	0.021	Significant
The total number of pethidine injections in first 24 hours postoperatively	0.7±0.6	1.9±0.7	0.037	Significant
Mean dose of pethidine (mg)	97.31±10.12	151.23±12.02	0.008	Significant

Values are expressed in Mean±SD

Table-IV: Incidence of side effects during postoperative period

Side Effects	Group A (n=30)	Group B (n=30)	P Value	Result (Chi Square test)
Nausea	3(10%)	4(13.33%)	0.717	Not significant
Vomiting	3(10%)	2(6.67%)	0.534	Not significant
Delirium	5(16.67%)	4(13.33%)	0.628	Not significant
Hallucination	3(10%)	2(6.67%)	0.534	Not significant

Values are expressed in Percentage

Discussion

Ketamine has been found to have a preventive role in animal neuropathic pain models[9]. It is possible that ketamine can preemptively reduce postoperative pain and supplemental opioid requirements and doses ranged from 0.15 to 1 mg/kg, and the success of treatment in reducing postoperative pain did not depend on the type of surgery[10]. The most likely mechanism is a reduction in N-methyl D-aspartate (NMDA) receptor mediated central sensitization[11] which seems to play a role in pain transmission and according to other studies[12], ketamine binds to these receptors with a nonselective antagonism reducing hyperalgesia. Ketamine acts on nicotinic[13,14] and muscarinic receptors; it blocks sodium channels in the peripheral and human central nervous system and interacts with opioid receptors, (mu , kappa and delta) with calcium channels[15]. Ketamine also acts as a non-competitive antagonist at the phencyclidine receptor site in the NMDA receptor complex channel[16,17]. The role of NMDA receptors in the processing of nociceptive input is antagonized by low-doses of ketamine, which induces a noncompetitive blockade[18-21]; this raises the possibility that ketamine can become "trapped" in the receptor channel until the channel reopens after agonist activation.

The main finding of this study shows that preemptive intravenous low dose ketamine decreased postoperative pain in patients undergoing laparoscopic cholecystectomy. The overall results of preemptive studies with ketamine in humans have been mixed. In one systemic review of 24 studies, ketamine was found to have a significant immediate and preventive analgesic benefit in 58% of the studies (including both intravenous and neuroaxial administration)[22]. In another meta-analysis study of the efficacy of preemptive analgesia for acute postoperative pain, systemic NMDA antagonists, primarily intravenous ketamine, had poor efficacy[23]. Findings of our study best correlates with the findings of Roytblas et al[24] who used low-dose ketamine (0.15 mg/kg) in addition to general anesthesia in cholecystectomy patients, and observed that the cumulative dose of morphine required, was reduced by about 40% in the ketamine group. Results of this study demonstrated that the addition of low dose ketamine in general anaesthesia delays the first request for analgesic in the immediate postoperative period. During the first 24 hour total opioid consumption was less with preemptive ketamine. Similarly, some of the most impressive results with a reduction in morphine consumption of 47% were from orthopaedic patients[25,26]. Finding of decreased postoperative opioid consumption was noted in systemic review (included were children) of 53 randomized trials[27]. Similar efficacy of reduced opioid consumption was concluded from a systemic review of 37 randomized trials of ketamine when utilized at small doses in the perioperative period[28].

The risk of psychomimetic adverse effects such as hallucinations is the main reason for many clinicians to be apprehensive in using ketamine. This is not a major concern for patients undergoing general anaesthesia. Side effects such as nausea, vomiting, delirium and hallucination were observed as a criterion of patient's comfort and pain severity. Incidences of postoperative side effects were less and similar in Group A with preemptive ketamine like Group B without preemptive administration of ketamine and differences were statistically not significant. In a recent database review, perioperative ketamine added to morphine reduced postoperative opioid consumption, postoperative nausea and vomiting (PONV) and pain intensity in 27 out of 37 trials[29]. Some trials stated that there were no psychotomimetic adverse effects such as hallucinations, bad dreams or dysphoria[30,31]. Royblat et al[24] also suggested that small dose of preemptive ketamine had lower nausea and vomiting.

Conclusion

Low dose of intravenously administered ketamine has a preemptive effect in reducing postoperative pain, delays the first request for analgesic in the immediate post-operative period and postoperative analgesic requirements after laparoscopic cholecystectomy.

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