Clinical trial to assess role of ketamine in post operative analgesia after laparoscopic cholecystectomy

By:

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Abstract:

Background: The physiological consequences of post-operative pain including Stress response to surgery, Respiratory complications, cardiovascular complications, Thromboembolic complications, Gastrointestinal complications, Musculoskeletal complications and Psychological complications, all of which could delay or impair postoperative recovery and increase the economic cost of surgery as a result of the longer period of hospitalization. Inadequate post-operative pain control may also lead to the development of chronic pain after surgery .**Aim of This study:** is to evaluate the preemptive analgesic effect of intravenous ketamine in laparoscopic cholecystectomy. **Patients and Methods:** double blinded randomized clinical trial conducted at Al-Yarmouk teaching hospital, over a period of one year from March 2013 to March 2014 on a total of 120 adult patients scheduled for elective laparoscopic cholecystectomy, Patients were divided in to three groups of 40 patients each, the study drug administered intravenously during induction. Groups A and B received ketamine in a dose of 1 and 0.5 mg/kg, respectively, whereas group C received isotonic saline. The degree of pain at rest and deep breathing postoperatively were estimated using VAS, time of first analgesic dose, total opioid consumption, nausea, vomiting and hallucination were recorded for 24 h postoperatively.**Results:** postoperative pain scores were significantly low in group A when compared with the other groups at most times in the first 24 hours. Highest pain score was in group C at 0 h. Postoperative analgesic consumption was minimum in group A then group B and highest in group C. There was little significant difference in the pain scores between groups B and C. Group A had a significantly higher blood MAP than group B at 0, 0.5 and 1 h. 7.5% incidence of hallucinations were in group A.**Conclusion:** According to this study we conclude that preemptive ketamine in a dose of 1 mg/kg has a definitive role in reducing postoperative pain and analgesic requirement in patients undergoing laparoscopic cholecystectomy. A low dose of 0.5 mg/kg had little significant in preemptive analgesic effect and in reducing analgesic requirement.

Key words: Ketamine, NMDA, pain relief, laparoscopic cholecystectomy, preemptive analgesia

Introduction:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1] , The visual analogue scale is a psychometric response scale which can be used in questionnaires.It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. There is evidence showing that visual analogue scales have superior metrical characteristics than discrete scales[2,3]. The VAS can be compared to other linear scales and the sensitivity and reproducibility of the results are broadly very similar, although the VAS may outperform the other scales in some cases [4, 5].

Pain control is important for optimal care in surgical patients. Various treatment modalities and their combinations have been used; however, adequate pain control is still not achieved in a majority of patients. Preemptive analgesia has been proposed to result in better pain management, reduced analgesic consumption, and improved patient satisfaction [6,7].

Laparoscopic cholecystectomy is associated with less pain and disability, nonetheless many patients experience considerable pain in the postoperative period and improvement in analgesia is desirable. Pain after laparoscopic cholecystectomy involves several components and may be due to peritoneal stretching due to insufflation and diaphragmatic irritation [8].

N-methyl d-aspartate (NMDA) receptor antagonists have a role in central sensitization and neural modulation so has received greatest attention [9]. NMDA receptor is receptor for the excitatory neurotransmitter glutamate, which is released with noxious peripheral stimuli. The activation of NMDA receptors has been associated with hyperalgesia, neuropathic pain, and reduced functionality of opioid receptors. Hyperalgesia and neuropathic pain are a result of increased spinal neuron sensation, leading to heightened level of pain. The reduced function of opioid receptors is caused by a decrease in the opioid receptor's sensitivity .This decreased sensitivity ,in turn, translates to opioid tolerance as patients will require higher doses of opioids to

achieve the same therapeutic effects. Therefore, NMDA antagonists may have a role in these areas of pain management [10].

Ketamine is a strong NMDA antagonist. In adult, adverse effect of NMDA antagonists are mainly central nervous system (CNS) side effects including hallucinations, light headedness, dizziness, fatigue, headache, out-of-body sensation, nightmares, and sensory changes. [11]. Many studies demonstrate that a single dose of ketamine administered perioperatively can reduce postoperative pain and analgesic requirement [12-15], whereas other studies had been demonstrated that there was no beneficial effect of pre-emptive Ketamine [16-18]. These variable results could be because the studies were done in different types of surgeries, which can influence the degree of pain perceived and thus the dose requirement of preemptive analgesic [9].

Patients and Methods

Double blinded randomized clinical trial conducted at Al-Yarmouk teaching hospital, Baghdad, Iraq over a period of one year from March 2013 to March 2014 on a total of 120 adult patients scheduled for elective laparoscopic cholecystectomy After obtaining written informed consent from all patients, the study was conducted in a randomized double blinded clinical trial on a total of 120 adult patients of either gender, aged between 18 to 45 years, belonging to American Society of Anaesthesiologists (ASA) grades I and II and scheduled for elective laparoscopic cholecystectomy with an approximated duration of 45 minutes to one hour.

Exclusion criteria: Patient (refusal ; who had contraindication to any of the used drugs; with a history of chronic use of analgesia; Uncooperative patients ; with mental illness or communication difficulties; with body mass index equal or more than 35 ; and patients with previous history of upper or lower abdominal surgery).

Patients were divided into three groups of 40 patients each. Group [A] patients received ketamine in dose of 1 mg/kg, group [B] patients received ketamine in dose of 0.5 mg/kg, whereas group [C] received equal volume isotonic saline.The study drug was drawn and diluted to a fixed volume of 5 mL with a coded label. Both observer and patient were blinded.

During the preoperative visit patients were checked-up for detailed history, general and systemic examination and review of routine investigations, the VAS scale were shown to all the patients enrolled in the study and illustrate to them how to use it as a tool for measuring pain

and inform them that they can ask for analgesia if they felt pain in post operative period, analgesia was i.v. meperidine 0.5-1 mg/kg.

All patients were premedicated with ranitidine tablet 150 mg at the night before surgery. All patients instructed for routine preoperative fasting.

At day of surgery patients shifted to operation theater and the vital parameters were recorded. After achieving intravenous access, all patients received intravenous injection (i.v.) of diazepam 5 mg and metoclopramide 5-10 mg, fentanyl citrate 1μg/kg was given for intraoperative analgesia. Patients were then randomly allocated to one of the three groups A, B or C and after preoxygenation with 100% O2, the study drug administered intravenously. Anaesthesia was induced with propofol 1- 2.5 mg/kg i.v. (sleeping dose). Laryngoscopy and endotracheal intubation was facilitated by suxamethonium 1 mg/kg i.v.

Anaesthesia was maintained with oxygen and halothane (0.5-1.5%) on controlled mechanical ventilation. Vital parameters were monitored throughout the operation. Neuromuscular blockade was achieved with pancuronium 0.04-0.08 mg/kg. At the end of surgery, the neuromuscular blockade was reversed with injection of neostigmine 0.04 mg/kg plus atropine 0.01 mg/kg i.v. Tracheal extubation was done once the patient being awake and establishing an adequate spontaneous respiration. Patients were then transferred to recovery room where observations and recording were made by a blinded observer and then to the post anaesthesia care unit.

All patients included in the study were observed for pain severity using VAS every half hour for first 2 h, every 1 h for the next 4 h, and then at 12 and 24 h postoperatively. Time 0 h was taken as the time of shifting the patient to recovery room. Each time the pain was evaluated at rest and at deep breathing. Analgesia was administered using boluses of meperidine 0.5-1 mg/kg i.v. when the patient asked for it.

Analgesics other than i.v. meperidine, which is strong and moderate acting analgesic, were not allowed during the first 24 h to allow making comparisons of opioid consumption between groups.

Time of first analgesia required, and the total opioid doses consumed in the first 24 h were recorded.Nausea, vomiting, and hallucinations that may associate with ketamine were also recorded.

Statistical analysis: Sample size was determined taking into consideration that a sample size of 40 patients per group would give a power of 80% at an α-level of 0.05. Data were analyzed with the SPSS statistical program using Student's *t*-test, and analysis of variance (ANOVA) test. Data of the different groups were compared by Student's t test for unpaired comparisons for normally distributed data, Kruskal–Wallis test for non normally distributed data or Chi-square test for

qualitative data. Differences among group means were compared using ANOVA. Incidence of side effects and number of patients receiving rescue analgesia were analyzed using Fisher's exact test. Significance levels throughout this study were considered at *P value* less than 0.05.

Results:

Group A has the lowest VAS in all groups at time 0 h (2.7 cm) increasing steadily to reach its maximum level at 2 h (4.8 cm) which is lower than maximal VAS of the other groups.

The VAS score in groups A and B at 0, 0.5, 1, 1.5, 6, 12 and 24 h was comparable with little significant intergroup variation in between them.

At 0.5, 1, 6, 12 and 24 h the mean VAS score at rest was comparable in all the groups with little significant intergroup variation.

Table 1 : VAS at rest in different groups (*p value* less than 0.05)

Time (hrs.)	0	0.5	1	1.5	2	3	4	5	6	12	24
Group A	2.7	3.1	3.4	4.2	4.8	2.7	3.1	3.4	3.8	4.3	3.8
Group B	3.7	4.2	4.5	5.3	3.1	4.2	4.5	4.7	3.3	3.5	4.2
Group C	5.4	3.9	3.2	3.6	4.3	5.2	3.9	3.6	4.1	3.2	3.6

Highest VAS was in Group C at 0 h with maximum value of 5.4 cm. VAS at 0, 3 and 6 h were higher in Group C when compared with VAS in groups A and B. So the VAS at 24 h was comparable in all the groups with little intergroup variation. (*p value* less than 0.05)(table2).

Table 2: VAS at deep breathing in different groups (*p value* less than 0.05)

Time in hrs	0	0.5	1	1.5	2	3	4	5	6	12	24
Group A	3.6	4.2	4.6	5.4	5.9	3.8	4.1	4.6	4.9	5.6	4.5

Group B	**5.1**	**5.3**	**5.4**	**6.7**	**5.1**	**5.3**	**5.9**	**6.3**	**5.5**	**4.6**	**4.9**
Group C	**8.3**	**5.2**	**4.6**	**4.3**	**4.5**	**7.3**	**4.8**	**5.8**	**5.9**	**4.7**	**4.4**

All groups had VAS higher than VAS scores at rest. The highest VAS scores on deep breathing were observed in Group C at 0 h with a mean of 8.3 cm followed by VAS of group B of 6.7 cm at 1.5 h and the lowest maximum VAS was in group A 5.9 cm at 2 h.
VAS was significantly more in Group C as compared with groups A and B at 0, 3 and 6.

VAS in B and C groups were higher than VAS in group A in most of the time intervals **(*p value* less than 0.05)**. **(**table3).

Table 3: MAP in different groups (*p value* less than 0.05)

Time in hrs	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**12**	**24**
Group A	**110.8**	**106.7**	**102.1**	**98.8**	**92.7**	**93.1**	**93.26**	**92.3**	**95.52**	**93.33**	**92.7**
Group B	**99.32**	**97.2**	**94.6**	**92.12**	**92.6**	**90.3**	**91.1**	**93.2**	**92.4**	**91.7**	**94.45**
Group C	**108.6**	**101.9**	**99.87**	**94.5**	**92.1**	**92.2**	**94.8**	**93.1**	**87.6**	**94.6**	**94.8**

MAP in group A and C were comparable and significantly more than group B in first 1.5 h and then became comparable in all groups to the end of 24 h (*p value* less than 0.05)(table4).

Table 4: Mean no. of analgesic doses given in the 1st 24 hrs (*p value* less than 0.05)

Groups	**A**	**B**	**C**

Mean no. of analgesic doses given	**2.6**	**4.1**	**5.6**

Total opioid consumption Was significantly more in Group C as compared with groups A and B (*p value* less than 0.05)(table5).as well as total opioid consumption Was significantly more in Group C as compared with groups A and B (*p value* less than 0.05)(table5).

Table 5: Mean time to receive 1st analgesic dose (*p value* less than 0.05)

Groups	A	B	C
Mean time to receive 1st analgesic dose	**2.17**	**1.42**	**0.28**

Patients in Group C received the first analgesic dose earlier than groups A and B **)(**table6).so regarding groups A and B the mean time to request of first analgesia and the mean number of doses of opioid required there was statistically significant intergroup difference (*p value* less than 0.05) (table6).

The incidence of nausea and vomiting was comparable in all the groups.

7.5% of patients in group A had an incidence of hallucinations, whereas none of the patients in the other group reported hallucinations (*p value* less than 0.05) (table6).

Table 6: side effects in different groups (*p value* less than 0.05)

Side effects	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Nausea	**9**	**22.5**	**7**	**17.5**	**8**	**20**
Vomiting	**5**	**12.5**	**4**	**10**	**5**	**12.5**
hallucination	**3**	**7.5**	**0**	**0**	**0**	**0**

Discussion:

Pain has been found to be one of the most common medical causes of delayed discharge after surgery, thus a number of measures used to control post-operative pain. The NMDA receptor is an excitatory amino acid receptor which has been involved in the modulation of prolonged pain states. Nociceptive stimuli increase the release of various substances including excitatory amino acids, which activate the NMDA receptors and result in their hyperexcitability and this creates a state of wind-up [20] Ketamine is an intravenous anaesthetic with analgesic property to its action on the NMDA receptor. Several trials are investigating the use of low-dose ketamine for management of postoperative pain syndrome [20].

In this study we notice that intravenous 1 mg/kg ketamine given before induction has preemptive effect on postoperative pain and reduced analgesic requirements during the first 24 h after laparoscopic cholecystectomy. VAS had been assessed at rest and on deep breathing.
VAS assessments on deep breathing are more reproducible than the VAS at rest [9].

VAS at rest and on deep breathing in group A when compared with groups B and C were lower at most time intervals except at 1.5, 2 and 12 h. This means that patients in this group who received 1 mg/kg ketamine had significantly less pain than the patients in the other groups.
VAS in group B were lower than that of group C at time 0 h this imply that patients who received 0.5 mg/kg ketamine has less pain than group C in the recovery time. This implies that a dose of 0.5 mg/kg ketamine had a little preemptive analgesic effect when compared with a higher dose of 1mg/kg ketamine that had a good preemptive analgesic effect.
VAS of group C became comparable with that of group A at 1, 1.5 and 2 h post operatively due to that the patients in group C received first dose analgesia earlier than those in group A.
We used I.V meperidine for rescue analgesia as it is strong analgesic and had moderate duration of action thereby decreasing biased assessments of the efficacy of study drug.

The MAP was studied as an indirect estimation of the pain control in various groups [9]. Patients in Group C had higher VAS and MAP at time 0 h and had early requirement of rescue analgesics. This implies that patients in this group had more pain.

In contrast to other anaesthetic agents, ketamine increases arterial blood pressure due to central stimulation of the sympathetic nervous system and inhibition of the reuptake of norepinephrine after release at nerve terminals **[11].** This could explain the significantly higher MAP in Group A than group B that received less dose of ketamine. Harsimran *etal.*, in study on Preemptive analgesia with Ketamine for Laparoscopic Cholecystectomy found that 1mg/kg ketamine patients had good preemptive analgesic effect, but 0.5 mg/kg ketamine also had good preemptive analgesic effect in Harsimran study and this is controversy to our results this could be due to the small number of patients in Harsimran study (20 patients) compared to 40 patients in our study **[9]**.

Launo *etal.*, in study on Preemptive ketamine during general anesthesia for postoperative analgesia in patients undergoing laparoscopic cholecystectomy found that ketamine had a good preemptive analgesic effect and it decreases postoperative analgesia required **[12]**.as well as Elena *etal.*, in study on Clinical study regarding preemptive analgesic effect of ketamine and remifentanyl in laparoscopic cholecystectomy concluded that ketamine had good preemptive analgesic effect [13].but Kevin *etal.*, in study on ketamine for postoperative analgesia found that intravenous ketamine is effective in reducing total opioid requirements and delaying the time to first analgesic dose for many patients with postoperative pain in different types of operations [14].

So , Kwok *etal.*, on study on role of ketamine in reducing post operative analgesia in gynaecologic laparoscopic surgery find that ketamine had preemptive analgesic effect **[15].**The role of preemptive analgesia with ketamine has been also reported in laparoscopic appendectomy surgery **[16].** in result study of Gharaei *etal.*, on preemptive effect of low dose Ketamine in opioids addicts patients undergoing extracorporeal shock wave lithotripsy find that ketamine had moderate analgesic effect **[17].**

Ketamine in a dose of 0.3 mg/kg has insignificant preemptive analgesic effect had been proved by Naghibi K, et al. In a study on comparison of preemptive effects of propofol, remifentanil and ketamine on post-operative pain scores and analgesic requirements in elective lower abdominal surgery under general anaesthesia **[18].** Three patients (7.5%) In current study were had hallucinations and all of them were in Group A. This result is less than the incidence reported in the literature with similar preemptive doses this may be due to diazepam that had been used in our study instead of midazolam [9].Patients in group B who

received less ketamine doses did not experts any hallucinations.The incidence of nausea and vomiting was comparable in all the groups.

Conclusion:

1) According to this study we conclude that preemptive ketamine in a dose of 1 mg/kg has a definitive role in reducing postoperative pain and analgesic requirement in patients undergoing laparoscopic cholecystectomy.
2) A low dose of 0.5 mg/kg had little significant in preemptive analgesic effect and in reducing analgesic requirement.

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