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Low-Dose Ketamine for Postoperative Analgesia in Elective Open Cholecystectomy

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Abstract: There are conflicting results in the literature concerning preemptive effect of ketamine. The aim of our study was the clinical evaluation of preemptive perioperative analgesia with low-doses ketamine. We conducted a randomized, prospective and double blind study: Thirty patients undergoing elective cholecystectomy under general anesthesia were allocated randomly to receive boluses of either ketamine 0.15 mg kg^{-1} or normal saline (placebo) 5 min before surgical incision. Induction and maintenance of anesthesia were similar in two groups. After surgery the following parameters were considered: 1- time of first request for analgesic and total dose of consumed analgesic; 2-VAS and VRS in 12 h intervals for 2 day, for assessment of the effectiveness of analgesia; 3-postoperative nausea and Vomiting 93.3% of patients in control group and 66.6% of patients in ketamine group received analgesic postoperatively and the relation between the *first analgesia request time* and *ketamine use* was significant (t = 2.68 and 0.95 t_{14} = 1.76). Frequency and total dose of analgesic between 2 groups were different and were lower in ketamine group than control group ($p<0.003$). Mean VAS in 12 ($p<0.028$), 24 ($p<0.027$), 36 ($p<0.012$) and 48 h ($p<0.028$) after operation was significantly lower in ketamine group than control group. Also, Mean VRS in 12 ($p<0.02$) and 24 h ($p<0.042$) after operation was significantly lower in ketamine group than control group, but Mean VRS in 36 ($p<0.02$) and 48 h ($p<0.042$) after operation was not significantly different between 2 groups ($p<0.13$). We conclude that ketamine provide clinicians with tool to improve postoperative pain management and to reduce analgesic doses after surgery.

Key words: Pain, postoperative, ketamine, general anesthesia, cholecystectomy

INTRODUCTION

Persistent noxious stimuli lead to the development of a phenomenon known as central sensitization whereby stimuli of stable intensity result in progressively higher pain intensity. N-Methyl-D-Aspartate-Receptor (NMDA-R) contributes to the process of sensitization by generating pain hypersensitivity upon a variety of post-translational modifications (Brenner *et al*., 2004). Conversely, NMDA-R antagonists, including Ketamine and methadone, are well known to attenuate central sensitization and palliate neuropathic pain (Okon, 2007).

Tissue trauma during surgery modifies the central processing pathway for pain perception. These changes decrease stimulus threshold and amplify postoperative pain. The induction and maintenance of such central sensitization may be dependent on the activation of NMDA receptors. Therefore, preoperative administration of ketamine, should prevent central sensitization and may improve postoperative pain relief. This is termed preemptive analgesia (Kwok *et al*., 2004).

Preemptive analgesia is currently in use in the management of postoperative pain. The administration of ketamine as intraoperative analgesic agent is well-known since a long time, the analgesic properties of this drug are related to its actions as a non-competitive NMDA receptors antagonist, these receptors present an excitatory function on pain transmission and this binding seems to prevent or reverse the central sensitisation of every kind of pain, including postoperative pain (Launo *et al*., 2004).

Ketamine hydrochloride is a well known general anesthetic and short acting analgesic in use for almost 3 decades (Schmid *et al*., 1999). Ketamine's role in clinical anaesthesia is developing as a result of the evolving concepts of its mechanism of action and the advantages of its alternative routes of administration (Erk *et al*., 2007). Ketamine demonstrates a potent analgesic effect by central blockage of perception of pain with sub-anesthetic doses (Erhan *et al*., 2007). Research has demonstrated

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significant reductions in postoperative pain scores as well as opioid consumption with low-dose ketamine administration without side effects associated with its induction doses (Harper, 2007).

This study reviews the use and efficacy of low-dose ketamine in the management of acute postoperative pain. In literature, the use of this anesthetic for the preemptive analgesia in the management of postoperative pain is controversial (Launo *et al*., 2004) for this reason the aim of our study was the clinical evaluation of preemptive perioperative analgesia with low-doses ketamine.

MATERIALS AND METHODS

After obtaining informed written consent, 30 patients (male and female) undergoing general anesthesia for elective open cholecystectomy were studied. The patients were selected randomly for study. All of the patients had the similar physical, mental, cultural and graduate status. Inclusion criteria were:

- Age >18 years.
- Non obese patient (obese patient = patient BMI >25).
- ASA class I or II.
- Absence of psychiatric illness (past or present).
- Absence of allergies or intolerance to anesthetics.
- Absence of allergies or intolerance to ketamine and tramadol.
- Comprehending of Visual Analog Scale (VAS) and Verbal Rating Scale (VRS).

Exclusion criteria were:

- Age >65 years; having severe pulmonary and/or cardiovascular.
- Any severe perioperative complications.
- History of opiate intake.

Using a randomized double-blind method, we prospectively assigned patients to 1 of the 2 groups receiving *Ketamine* or *Normal saline*.

All cases were visited before operation and premedicated similarly. At operation room, routine measures such as vital signs control, preparation of monitoring systems, checking of equipments and anesthesia systems and preparation of materials and drugs was performed.

All patients received the same anesthesia, which consisted of:

Induction: Fentanyl (2 μg kg^{-1}), thiopental (5 mg), succinyl choline (1 mg kg^{-1}), mask ventilation (air+O2) for 2 min and then Tracheal Intubation (TI) at the 3rd min.

Maintenance of anesthesia: Controlled ventilation (N2O+O2; Halothane), + neuromuscular blockage with pancuronium.

One of the 2 vials containing 0.15 mg kg^{-1} *ketamine* or *normal saline* (placebo) was in access of injector during operation while he/she was not informed about its continuation. The vials were labeled as A or B. the drug or placebo was injected after induction of anesthesia and 5 min before surgical incision. Then, the name of used vial for injection was recorded. The type and dosage of used opiate as well as operation time was also recorded. The first postoperation visit was performed in recovery room. This visit was including question about presence and severity of pain. The patient should conscious and could answer us verbally. The answer was recorded, according to the patients' cooperation and consciousness, as VAS and VRS. However, we did not used from this item in our results because of non-accuracy of patients' responses immediately after awaking. During the recovery period, the patients comfort and symptoms were recorded.

After discharge from recovery room, the time of patient first request for analgesia injection was recorded. Analgesia administered blindly and as the ward routine. Then the patient was visited every 12 h (12, 24, 36 and 48 h) and the following variables were recorded:

- Time of patient first request for analgesia injection and its type and dosage.
- Number of patient requests for analgesia injection and its type and dosage.
- Total dosage of analgesia injection during 48 h.
- VAS (after 12 h, 24 h, 36 h, 48 h).
- VRS (after 12 h, 24 h, 36 h, 48 h).
- Adverse effects such as nausea and vomiting.

The data collected from all 15 patients in each group were with SPSS 10 statistical software using Chi-square, T-test and Fischer test.

RESULTS

In this prospective study, 30 patients in two KETAMINE and CONTROL groups received ketamine or normal saline (0.15 mg kg^{-1}), respectively. The characteristics of patients in each group are listed in Table 1.

Some patients received opiate in addition to that received during anesthesia induction (40% of ketamine group and 53.3% of control group), although according to the Chi-square test, additive opiate use was not significantly different between 2 groups.

Table 1: Characteristics of patients in ketamine and control groups

	Ketamine	Control
Age range (y)	38-60	36-60
Mean age (y)	46.7±506	48.2±7.8
Sex (female)	80%	93%

Table 2: Comparison of variables in ketamine and control groups

	Ketamine	Control
Operation time (min)	68.2±13.8	77.6±24.9
Opiate use After operation	66.6%	93.3%
First analgesia request time (h)	8.33±3.11	5.93±3.13

As showed in the Table 2 and according to the t-test, the relation between the *first analgesia request time* and *ketamine use* was significant (t = 2.68 and 0.95 t_{14} = 1.76).

According to the Chi-square test, there were also significant difference in number of patient requests for analgesia injection and its dosage within 48 h between Ketamine and Control groups; so that the requests of patients and the dosage of administered analgesia were higher in Control group than Ketamine group ($p<0.003$).

The rate of adverse effects such as nausea and vomiting was studied as a criterion of the patients' comfort and pain severity. Because expected frequency in one item was less than 5, we used Fischer Exact test. The analysis suggest that the rate of nausea and vomiting was significantly lower in ketamine group than control group ($p<0.014$).

The postoperative pain severity was measured with VAS and VRS which are quantitative and qualitative scales, respectively. VAS scales were compared using Chi-square test and considering Yates' corrected criterion. Mean VAS in 12 ($p<0.028$), 24 ($p<0.027$), 36 ($p<0.012$) and 48 h ($p<0.028$) after operation was significantly lower in ketamine group than control group.

Also, Mean VRS in 12 ($p<0.02$) and 24 h ($p<0.042$) after operation was significantly lower in ketamine group than control group, but Mean VRS in 36 ($p<0.02$) and 48 h ($p<0.042$) after operation was not significantly different between 2 groups ($p<0.13$).

DISCUSSION

Postoperative pain is a common complication of cholecystectomy (Aspevik and Irtun, 2005) showed that 80% of patients underwent cholecystectomy, had experienced sudden bursts of pain after the operation.

Some studies report the recent discovery of the N-Methyl-D-Aspartate (NMDA) receptor which seems to play a role in the pain transmission and according to other studies, ketamine binds to these receptors with a nonselective antagonism, reducing hyperalgesia. (Launo *et al*., 2004).

Ketamine acts on nicotinic and muscarinic receptors; it blocks sodium channels in the peripheral and human central nervous system and interacts with opioid receptors, μ, δ and κ and with calcium channels. Ketamine also acts as a non-competitive antagonist at the phencyclidine receptor site in the NMDA receptor complex channel. The role of NMDA receptor in the processing of nociceptive input is antagonized by low-doses ketamine, which induces a noncompetitive blockade; this raises the possibility that ketamine can become trapped in the receptor channel until the channel reopens after agonist activation (Launo *et al*., 2004; Orser *et al*., 1997).

There are conflicting results in the literature concerning preemptive effect of ketamine. Studies have documented a preemptive effect (Menigaux *et al*., 2000; Fu *et al*., 1997; Suzuki *et al*., 1999) and others have not (Dahl *et al*., 2000; Yaksch *et al*., 2002; Van *et al*., 2004). The efficacy of ketamine is linked to activation of NMDA receptors of the dorsal horn of the spinal cord. In case of adequate perioperative analgesia, NMDA receptors activation is likely to be suppressed and ketamine administration useless. In the studies that have documented a preemptive effect of ketamine (Menigaux *et al*., 2000; Fu *et al*., 1997; Suzuki *et al*., 1999), the perioperative opioid analgesia is questionable and likely to have induced intraoperative activation of NMDA receptors (Van *et al*., 2004).

However, ketamine is a well-known general anesthetic and short acting intraoperative analgesic in use for almost 4 decades, it is almost clear that high-doses ketamine acts as intravenous anesthetic and low-doses ketamine acts as analgesic agent (Launo *et al*., 2004).

Some authors evaluated the subcutaneous administration of this general intravenous anesthetic; it has been showed that low doses (1.7 $\mu g\ kg^{-1}$ per min) *s.c.* ketamine administered after major abdominal surgery did not produce adverse effects and provided postoperative analgesia equivalent to a *s.c.* morphine infusion of 2 $mg\ h^{-1}$ (Launo *et al*., 2004). More commonly ketamine is administered via the intravenous route; in postoperative pain management, ketamine has been administered as either a single bolus injection. Bolus injection followed by a continuous infusion continuous infusion, continuous infusion combined with either morphine, meperidine, fentanyl, benzodiazepines, or with a Patient Control Analgesia (PCA). Ketamine can be administered via intraspinal route. Preincisional treatment with low-dose IV ketamine and local infiltration with ropivacaine 1% reduces postoperative pain after laparoscopic cholecystectomy. In postoperative pain management, a variety of doses ketamine have been administered at a dose of 0.44 $mg\ kg^{-1}$ 21 or 1 $mg\ kg^{-1}$; intramuscular ketamine has been administered as a sole analgesic agent 23 or in combination with meperidine (Launo *et al*., 2004;

Wilder-Smith *et al*., 1998; Stubhaug *et al*., 1997; Papziogas *et al*., 2001).

Our findings were compatible with results obtained by Schmid *et al*. (1999) which suggested that ketamine may provide clinicians with a tool to improve postoperative pain management and to reduce opioid related adverse effects. The evidence suggests that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to local anesthetics, opioids, or other analgesic agents.

Kwok *et al*. (2004) demonstrated that a small dose of ketamine, given before skin incision, decreases postoperative pain, reduces morphine consumption and delays patients' request for analgesia after laparoscopic gynecologic surgery. However, as postoperative analgesia was not improved in patients receiving ketamine after skin closure, these findings suggest that timing of ketamine treatment was critical in its analgesic efficacy. We believe our data confirm the preemptive effect of ketamine analgesia.

Launo *et al*. (2004) suggested that preemptive low-doses ketamine is able to produce an adequate postoperative analgesia and increases the analgesic effect of tramadol. In their study, the algometric measurements (VAS, VRS, PID, rescue doses) showed that ketamine provides good analgesia at the awakening, even if of short duration (about 1 h). moreover some patients who received preemptive ketamine didn't required any postoperative analgesia within the first 24 h, confirming that ketamine, in some cases, is able to provide a lasting control of postoperative pain.

The postoperative pain severity was measured with Visual Analog Scale (VAS) and Verbal Rating Scale (VRS) which are quantitative and qualitative scales, respectively. VAS in 12, 24, 36 and 48 h after operation was significantly lower in ketamine group than control group. Also, Mean VRS in 12 and 24 h after operation was significantly lower in ketamine group.

In a randomized, double-blind study by Roytblat *et al*. (1993) postoperative pain was assessed in 22 patients undergoing elective open cholecystectomy with 2 types of anesthesia: Standardized general anesthesia (control group) and low-dose ketamine as an addition to the same method of general anesthesia, before surgical incision (ketamine group). After the operation they found that the time from the end of surgery to the first request for analgesic was longer in the ketamine group. Postoperatively, patients in both groups were treated with Patient-Controlled Analgesia (PCA) in exactly the same way. The major difference in the study was the reduced dose requirement of morphine in the ketamine group compared with the control group after the operation. Mean VAS and VRS were higher in patients in the control group during the first 5 h after surgery, but between 5 and 24 h after surgery VAS and VRS were not significantly different. They concluded that postoperative pain can be decreased when ketamine in low doses is added to general anesthesia before surgical stimulation.

The rate of adverse effects such as nausea and vomiting was studied as a criterion of the patients' comfort and pain severity. Our findings showed that the rate of nausea and vomiting was significantly lower in ketamine group. In the similar study by Roytblat *et al*. (1993) hemodynamic stability was used as indirect measure of patients comfort. This study suggested that at small dose of ketamine, there were higher hemodynamic stability and lower nausea and vomitting.

CONCLUSION

In conclusion, we can assert that a small dose of ketamine, given before skin incision, produces preemptive analgesia in patients undergoing elective open cholecystectomy. According to the possible side effects of postoperative pain after higher abdominal surgeries and because conventional analgesic methods such as Patient-Controlled Analgesia (PCA) and opiate injection have disadvantages, low dose ketamine can be a suitable alternative for prior methods, in postoperative pain control.

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