

EFFICACY OF PREEMPTIVE PREINCISIONAL USE OF KETAMINE ON POSTOPERATIVE PAIN RELIEF FOLLOWING APPENDECTOMY

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Abstract

Pain, which is often inadequately treated, accompanies the surgical procedures may persist long after tissue healing. Preemptive analgesia, involves the introduction of an analgesic regimen before the onset of noxious stimuli. Previous studies have suggested that ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, provides a preemptive analgesic effect. In literature, its use is controversial; for this reason the aim of our research is to evaluate whether the preemptive use of ketamine decreases postoperative pain in patients undergoing appendectomy.

In double-blind, randomized clinical trial, 100 patients underwent appendectomy for acute appendicitis were studied. Patients were randomly assigned into two groups. In the operating room, patients in the ketamine group received 0.5 mg/kg of ketamine IV 10 minutes before the surgical incision. In control group the same volume of normal saline was injected. Pain intensity was assessed at time 0 (the time of complete consciousness), 4, 12, 24 hours postoperatively using the visual analogue scale (VAS). One hundred patients (50 for both groups) were enrolled. For all the evaluated times, the VAS score was significantly lower (p value <0.05) in the ketamine group compared to the control group. There was a highly significant difference between the groups regarding the interval time of analgesic need. The total dose of tramadol in the first 24 hours was 2.42 ± 0.70 mg/kg in ketamine group and 3.86 ± 0.35 mg/kg in control group (p=0.009). The occurrence of nausea and vomiting in ketamine group was less than in control group. Three patients experienced brief nondisturbing hallucination in the recovery room in ketamine group. No other drug side effects in ketamine group were noticed.

In conclusion, low dose of intravenously administered ketamine had a preemptive effect in reducing pain after appendectomy.

Introduction

Pain, one of the most common symptoms experienced by surgical patients, has been poorly evaluated and frequently undertreated¹. Many patients experience pain in the postoperative period despite the use of potent techniques such as patient-controlled analgesia, epidural analgesia, and regional anesthesia².

Tissue trauma during surgery modifies the central processing pathway for pain perception. These changes decrease stimulus threshold and amplify postoperative pain^{1,3,4}. Basic and clinical studies of pain have revealed that a large

proportion of the mechanisms that produce strange signs and symptoms, such as allodynia, hyperalgesia and hyperpathia, after tissue injury are ascribed to increased excitability, or to sensitization derived from biological changes in spinal dorsal horn cells subjected to excessive noxious stimuli from injured tissues⁵.

The enhanced responsiveness of nociceptive neurons in the central nervous system, e.g., during inflammation or trauma, has been termed "central sensitization"⁶. One of the most critical observations concerning central sensitization is the role played by the first

phase of the pain response (a noxious stimulus is brief and correlates with the sharp, well-localized initial pain⁷).

Preemptive analgesia may be defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from sites of injury. The most important conditions for establishment of effective preemptive analgesia are the establishment of an effective level of antinociception before injury, and the continuation of this effective analgesic level well into the post-injury period to prevent central sensitization during the inflammatory phase⁸. The induction and maintenance of such central sensitization may be dependent on the activation of N-methyl-D-aspartic acid (NMDA) receptors. Therefore, preoperative administration of ketamine, an NMDA-receptor antagonist, should prevent central sensitization and may improve postoperative pain relief^{2,9,10}.

Ketamine is an anesthetic agent with a variety of actions within the central nervous system. Low doses of ketamine via the intravenous route can produce profound analgesia, even in situations where opioids have been ineffective, such as neuropathic pain¹¹.

Ketamine provides excellent analgesia (via stimulation of both NMDA2 and opioid receptors), particularly of the integument and less so of the intestinal tract. In increasing dosages, ketamine is used for analgesia (0.2–0.5 mg/kg intravenously) or for induction of anesthesia (1 to 2 mg/kg intravenously or intramuscularly 5–10 mg/kg). To minimize the frequency of delirium, it is given together with one of the benzodiazepines and to decrease secretions, an anti-sialogogue is added¹².

In the literature, the use of this anesthetic for the preemptive analgesia in the management of postoperative pain is controversial¹⁰.

The aim of this study is to evaluate the effectiveness of preemptive use of

ketamine on acute postoperative pain in patients undergoing appendectomy.

Patients and Methods

In a double blind, randomized clinical trial, 100 adult patients underwent surgery for acute appendicitis included in this study. Ethical approval was obtained from the Arab Board of Medical Specializations in Iraq. Patients were randomly assigned into two groups (ketamine and control). Patients were excluded if they had history of cardiovascular disease, epilepsy, hypertension, increased intracranial pressure cerebrovascular accident, psychiatric disorder, drug abuse, chronic pain, American Society of Anesthesiologists (ASA) physical status more than 1, obesity, muscle cutting incision or surgical time more than 60 minutes.

The study was done from the 1st of October 2012 to 28th of February 2013. A double-blind technique was used in which the surgeon and house officers who were responsible for data collection were unaware of the allocation of the trial patients.

In the theater, patients in ketamine group, received 0.5mg/kg of ketamine IV, 10 minutes before surgical incision by the anesthesiologist. In control group the same volume of normal saline was injected. All patients were premeditated with diazepam 0.1 mg/kg IV before anesthesia to avoid the probable side effects of ketamine.

Postoperatively, if patients asked for analgesia, 1mg/kg of tramadol was administered intravenously. Pain intensity was assessed at time 0 (time of complete consciousness), 4, 12, 24 hours postoperatively. Pain was scored using the 10 point visual analogue scale VAS (VAS; 0= no pain, 10=worst pain imaginable). Other than the VAS score, the interval time for the request of analgesia and the number times tramadol

was injected in the 1st 24 hours were recorded. Patients were also checked for side effects of ketamine such as nausea, vomiting, hallucination, delusions, and others.

Data were presented as the mean±sd for variables. The Mann Whitney test was used to compare VAS scores, interval time of requested analgesia and total tramadol dose in the first 24 hours. Statistical analysis was done using SPSS 19.0. A P-value less than 0.05 was statistically significant.

Results

Fifty patients were randomized to the

ketamine group and fifty to control group. The mean age of patients in ketamine group was 21.62±5.5 years which is comparable to control group 23.28±6.7 (p>0.05). In ketamine group there were 29 male and 21 female and in control group there were 27 male and 23 female. The duration of surgery in ketamine group was 34.10±6.34 minutes and in control group was 36.60±6.69 minutes (p>0.05). The duration of anesthesia in ketamine group was 47.66±7.17 minutes and in control group was 49.02±7.04 minutes (p>0.05). Table I shows the comparison of the basic data in the two groups.

Table I: Comparison of basic variables

Group		Gender M/F	Age	Duration of surgery	Duration of anesthesia
ketamine	Mean	29/21	21.62	34.10	47.66
	N		50	50	50
	Std. Dev.		5.529	6.364	7.165
placebo	Mean	27/23	23.28	36.60	49.02
	N		50	50	50
	Std. Dev.		6.667	6.688	7.044
Total	Mean	56/44	22.45	34.35	48.34
	N		100	100	100
	Std. Dev.		6.150	6.500	7.101

Values are Mean±SD there where no significant difference between the two groups. VAS scores are presented in table

II and figure 1. For all evaluated times, the VAS score was significantly lower in ketamine group than that of control.

Table II: Changes of VAS Score during 24 Hours after Appendectomy

Time (hrs.)	0	4	12	24
Ketamine	4.45±1.43	4.26±1.16	3.34±0.98	2.78±0.82
Control	5.36±0.92	4.86±0.99	3.80±1.01	3.10±0.79
P	0.001	0.006	0.023	0.049

Values are Mean±SD. p value <0.05

Figure 1: Changes of VAS Score during 24 Hours after Appendectomy.

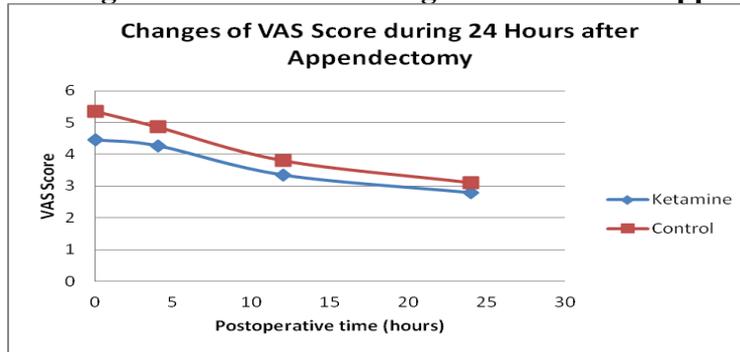


Table III: The interval time for analgesic request

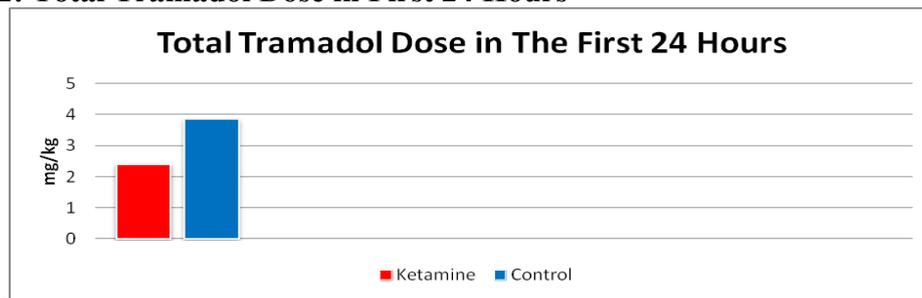
Group		1st dose (minutes)	2nd dose (hours)	3rd dose (hours)	4th dose (hours)
ketamine	Mean	33.34	9.70	18.47	20.50
	N	50	50	36	10
	Std. Dev.	12.248	3.352	4.539	1.581
placebo	Mean	22.20	5.20	12.94	19.72
	N	50	50	50	43
	Std. Dev.	6.863	1.178	2.944	1.737
P value		0.006	0.004	0.007	0.014

Table 3 shows that there was a highly significant difference between the groups regarding the interval time of analgesic need, which was 33.34±12.25 minutes in ketamine group and 22.20±6.86 minutes (p=0.006). The second analgesic dose was

9.70±3.35 hours in ketamine group and 5.20±1.18 hours (p=0.004). The total dose of tramadol in the first 24 hours was 2.42±0.70mg/kg in ketamine group and 3.86±0.35mg/kg in control group (p=0.009).

Table IV: Total tramadol dose mg/kg

Group	Mean mg/kg	N	Std. Dev.
ketamine	2.42	50	.695
placebo	3.86	50	.351

Figure 2: Total Tramadol Dose in First 24 Hours

The occurrence of nausea in ketamine group was 18% (9 patients) while in control group was 28% (14 patients), and the occurrence of vomiting in ketamine group was 12% (6 patients) while in control group 18% (9 patients). Three patients experienced non-disturbing hallucinations (in the recovery room) in ketamine group, with no other drug side effects in this group.

Discussion

The principle of preemptive analgesia is to apply antinociceptive treatment before surgical trauma. This should prevent N-methyl-D-aspartate (NMDA) receptor activation and remodeling of the central nervous system². Some studies have reported the presence of NMDA receptor, which seems to play a role in pain transmission, and according to other studies, ketamine binds to these receptors as a nonselective antagonist reducing hyperalgesia, and acts as a non-competitive antagonist in the NMDA receptor complex channel¹¹⁻¹⁴.

There are conflicting results concerning efficacy of ketamine as a preemptive analgesic. Some studies which examined ketamine, demonstrated a positive preemptive analgesic effect^{15,16}, but others have failed to demonstrate pain improvement after ketamine^{9,15}. There are several possible explanations for this, They either administered analgesia at regular intervals postoperatively to all patients upon a minor surgical procedure^{9,17,18} which masked the preemptive effects of ketamine; others have utilized a single small dose

(<0.25mg/kg) of ketamine; or some studies included major prolonged procedures upon single preincisional dose of ketamine that cannot cover the whole duration of the noxious stimulus¹⁶. We believe an insufficient afferent block may account for the many studies that have found a lack of evidence for preemptive analgesia.

Low pain scores in ketamine group should be interpreted together with the significant tramadol sparing effect. In this study, VAS measurements showed that ketamine provided good analgesia; there was a statistical difference between the two groups in the total dose of tramadol consumption and in the time interval for analgesia. The (VAS) showed that ketamine provided good analgesia at the awakening, even of short duration and upgrades the analgesic effect of tramadol during the recovery period.

Large doses of ketamine (>2mg/kg) are associated with unacceptable side effects, like delusions, delirium, hallucinations, nystagmus, photophobia, and psychomotor excitation. However, side effects are rare with a low dose of ketamine from 0.15 to 0.5 mg/kg¹¹. In addition, we use diazepam premedication which significantly can reduce these side effects. In our study, nausea and vomiting occurred more in control group 28% as compared with 18% in ketamine group (p value <0.05), this may be due to higher doses of tramadol consumption postoperatively in control group.

In conclusion, a small dose of IV ketamine given before skin incision, produces preemptive analgesia in patients

undergoing appendectomy, decreases total tramadol consumption and decreases the frequency of postoperative nausea and vomiting. We believe that our results confirm the preemptive analgesic effect of ketamine.

Recommendation:

We recommend conducting further studies to evaluate the preemptive analgesia of other drugs and of ketamine on major surgeries with consideration to maintain its analgesic level during the whole procedure.

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