KETAMINE HAS NO PRE-EMPTIVE ANALGESIC EFFECT IN CHILDREN UNDERGOING INGUINAL HERNIA REPAIR

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Abstract- Previous studies have suggested that ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, provides a pre-emptive analgesic effect and pre-emptive analgesia improves postoperative pain management. The aim of this study was to determine the effict of pre-incisional vs. post-incisional intravenous low dose of racemic ketamine in postoperative pain in children undergoing inguinal hernia repair. Seventy-five children aged 1-6 years who were scheduled for inguinal herniorrhaphy were included in a prospective, double-blind randomized controlled trial. Patients were randomly allocated to three groups (pre-incisional, post-incisional and control). Patients in pre-incisional group received an intravenous bolus of racemic ketamine (0.25 mg/kg) before surgical incision and patients in post-incisional group received the same dose of racemic ketamine after surgical incision. Children of control group received intravenous boluses of normal saline. In post anesthesia care unit and pediatric surgical ward, the degree of pain and sedation, additional analgesic requirements and side effects were evaluated. There were no differences between groups with respect to demographic and hemodynamic parameters. Pain and sedation scores were not statistically different between groups during 24 h study. In addition, there was no significant difference among groups in number of supplementary analgesic requirements and postoperative nausea and vomiting in the first 24 h. No other side effects were reported during the study period. We found that low dose racemic ketamine administered prior to surgical incision has no pre-emptive effect on post-operative pain and supplementary analgesic requirement during the first 24 h after herniorrhaphy in pediatric patients.

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INTRODUCTION

Glutamate is the major excitatory transmitter in the central nervous system contributing to pain processing and pain phenomena such as wind up, spinal neural plasticity and hyperalgesia (1). Intra-operative and post-operative noxious inputs may cause N-methyl-D-aspartate (NMDA) glutamate receptor activation and central sensitization, but analgesic intervention before the noxious stimulus may attenuate or block sensitization and hence reduce acute pain. This process is being referred to as pre-emptive analgesia (2).

Ketamine is an NMDA receptor antagonist that has been used in clinical setting for more than three decades (3). The use of NMDA receptor antagonists

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in general and ketamine in particular is being actively investigated as a modality for prevention of post-operative pain. Other than NMDA receptor, many targets have been reported for action of ketamine, but are probably not greatly relevant at plasma levels attained in clinical setting (4).

The use of NMDA receptor antagonists for pre-emptive analgesia remains controversial. While some authors suggest that low dose ketamine has a pre-emptive analgesic effect (5-13), others have failed to demonstrate any effect (14-20). Two meta-analyses conducted on the effects of peri-operative ketamine on adult patients showed that treatment with ketamine reduced 24-h patient-controlled analgesia morphine consumption and post-operative nausea and vomiting (21, 22). It must be considered that the retrieved studies were heterogeneous and the result of the meta-analysis can not be translated into any specific administration regimen with ketamine (21). Few studies have been undertaken in children, which carry contradictory results (23-25).

The aim of this study was to evaluate the efficacy of pre-incisional vs. post-incisional intravenous low dose of racemic ketamine on postoperative pain in children undergoing inguinal hernia repair.

MATERIALS AND METHODS

After obtaining approval from local ethical committee and written informed consent from parents, 75 male children, ASA class I or II, aged between 1 and 6 years, scheduled for inguinal hernia repair, were included in this prospective, double-blind, randomized controlled trial.

This study was performed within a 5-month period at Bahrami Children Hospital in Tehran. Patients were randomly allocated to one of three groups (n = 25, pre-incisional, post-incisional and control) through computer generated codes. The opaque envelopes that were sequentially numbered were used to maintain the codes. Children were excluded if they regularly took analgesics, or had used opioids within 1 week before surgery, or had any history of severe reactions to NSAIDS, bleeding disorders, hepatic, renal, central nervous system, or psychiatric diseases.

All children were premedicated with 0.4 mg/kg oral midazolam 30 minutes before induction of anesthesia. Anesthesia was induced with propofol 2 mg/kg and remifentanil 1 µg/kg and then a laryngeal mask airway (LMA) was placed. Anesthesia was maintained by continuous infusion of propofol 100 µg/kg/min and remifentanil 0.2 µg/kg/min. Children were permitted to breath spontaneously throughout the procedure via a D-type Mapleson circuit.

Immediately after positioning LMA, children of pre-incisional group received an intravenous bolus of racemic ketamine (0.25 mg/kg) diluted in normal saline to a total volume of 1 ml. Children of post incision and control groups received an intravenous bolus of 1 ml normal saline. After surgical incision, children of pre-incisional and control groups received an intravenous bolus of 1 ml normal saline, while children of post-incisional group received an intravenous bolus of racemic ketamine (0.25 mg/kg) in an equal manner to pre-incisional group. During surgery, children received lactated Ringer's solution given at a rate of 10 ml/kg/h. Anesthetists and nursing staff who prepared the study medication were not involved in study. All surgical procedures were performed by three pediatric surgeons. ECG, SpO_2, and $EtCO_2$ were recorded continuously throughout the surgery, and systolic arterial pressure and heart rate were recorded before induction and every 5 minutes thereafter during surgery. When blood pressure and/or heart rate increased more than 20% compared with basic values, infusion of propofol was increased by 25 µg/kg/min. If baseline values could not be achieved with two increments of propofol within 5 min (2.5 min for each increment), remifentanil infusion was increased by 0.1 µg/kg/min. Anesthetics were discontinued at the beginning of skin closure. At the end of surgery, one dose of rectal diclofenac 1 mg/kg was administered for all the patients.

When sufficiently awake and LMA removed, the children were transferred to the post anesthesia care unit (PACU). After 1 h observation in the PACU, patients were transferred to the pediatric surgical ward and discharged from the hospital after 24 h. Both in PACU and surgical ward, all assessments and recording of vital signs were made by staff anesthetists who were blinded to the study

population. Pain intensity was assessed by the Children's Hospital of Ontario Pain Score (CHEOPS) (Table 1) and sedation was evaluated by the Ramsay scale (1, anxious or restless or both; 2, cooperative, orientated and tranquil; 3, responding to commands; 4, brisk response to stimulus; 5, sluggish response to stimulus; and 6, no response to stimulus); both on arrival to PACU and then after 1, 6, 12, 24 hours. In surgical ward, patients received intravenous proparacetamol (prodafalgan, Exir) 15 mg/kg every 4 h (maximum 4 gr/day). Analgesia level of patients was defined as inadequate with a CHEOPS ≥ 9, and was treated by rectal diclofenac (1 mg/kg).

Post-operative nausea and vomiting, and number of patients receiving rescue analgesia, and total number of rescue analgesia in each group were recorded. The children and their parents and nurses were asked to report drowsiness, headache, hallucination and any other psychomimetic reactions.

Based on a pilot study, the standard deviation for the CHEOPS and Ramsay scores were ascertained. It was determined that a sample size of 25 patients per group would give a power of 80% at a α-level of 0.05 (two tailed). Differences among group means were compared using analysis of variance. 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 $P < 0.05$. All data are presented as mean ± SD.

RESULTS

Characteristics of the three study groups are summarized in Table 2. No differences between groups were detected with respect to age, weight, duration of surgery and hemodynamic parameters, before induction of anesthesia, and during surgery.

Analgesia and sedation data are reported in Table 3. CHEOPS and Ramsay scores were not statistically different between the three study groups during the 24 h study period. Additional rectal diclofenac was given to four patients in control group and two and five patients in pre-incisional and post-incisional groups, respectively. In addition, there was no statistical difference between groups in number of administered rescue analgesia (Table 2). There was no report of drowsiness, headache, or psychomimetic side effects such as hallucinations. There was no significant difference between groups with respect to postoperative nausea and vomiting (Table 2). No other side effects such as gastrointestinal (GI) bleeding were reported during the study period.

Table 1. Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

Item	Behavior score
Cry	
No cry	1
Moaning	2
Crying	3
Screaming	4
Facial expression	
Smiling	0
Composed	1
Grimace	2
Verbal	
Positive	0
None	1
Complaints other than pain	1
Pain complaints	2
Both complaints	2
Torso	
Neutral	1
Shifting	2
Tense	2
Shivering	2
Upright	2
Restrained	2
Touch	
Not touching	1
Reach	2
Touch	2
Grab	2
Restrained	2
Legs	
Neutral	1
Squirming/kicking	2
Drawn up/tensed	2
Standing	2
Restrained	2

Table 2. Patients characteristics*

Characteristic	Preincisional group	Postincisional group	Control group
Age (months)	35.0 ± 18.3 (13-58)	40.0 ± 13.8 (12-58)	32.2 ± 14.1 (12-60)
Weight (kg)	16.2 ± 3.1 (11-22)	15.5 ± 3.6 (9-20)	15.9 ± 2.8 (10-24)
Surgical duration (min)	20.5 ± 5.3 (13-33)	22.0 ± 5.2 (15-37)	24.8 ± 6.8 (15-40)
SAP before induction (mmHg)	102.2 ± 3.9 (90-109)	98.4 ± 3.1 (87-108)	95.6 ± 4.7 (83-104)
Heart rates before induction (beat/min)	116.9 ± 21.2 (75-140)	115.0 ± 20.1 (69-139)	112.2 ± 25.4 (78-149)
PONV occurrence (n)	4	4	3
Patients received rescue analgesia (n)	2	5	4
Rescue analgesia (n)	2	6	6

* Data are given as mean ± SD (range) or numbers of patients.
Abbreviations: SAP, systolic arterial pressure; PONV, postoperative nausea and vomiting.

DISCUSSION

Our study demonstrated that low dose racemic ketamine administered prior to surgical incision has no pre-emptive effect on post-operative pain and analgesic requirements during the first 24 h after herniorrhaphy in pediatric patients. However, this low dose of ketamine did not increase sedation scores after surgery, and caused no other side effects for patients undergoing this study.

Post-operative pain, although frequently encountered, is often under treated. A new method of treating postoperative pain is pre-emptive analgesia, which seeks to prevent or diminish pain before it is caused. A variety of drugs may be used that include nonsteroidal anti-inflammatory drugs, local anesthetics, opioids, and ketamine (26). Various mechanisms have been suggested for antinociceptive effects of ketamine: NMDA receptor antagonism, interaction with spinal μ receptors and activation of descending pain inhibitory monoaminergic pathways (27), which is expressed by α2 adrenoceptors at spinal level (28).

The affinity of ketamine for NMDA receptor is more than non-NMDA receptors (*i.e.* the μ receptor) (29, 30). It has been proposed that blockade of NMDA receptors could inhibit or even reverse already established central sensitization in response to noxious inputs (31). However, there are conflicting results concerning efficacy of ketamine as an analgesic agent. Some studies which examined ketamine in adults, demonstrated a positive pre-emptive analgesic effect (7, 10, 11, 32), but many others have failed to demonstrate pain improvement after ketamine (14, 33, 34). Few studies have been undertaken in children in this issue. Two studies (23, 24) compared analgesic effects of ketamine and morphine in children after adenotonsillectomy, and concluded that ketamine can provide similar postoperative analgesia as

Table 3. Ramsay score and CHEOPS during the study period*

	Preincisional Group	Postincisional Group	Control Group
Ramsay Score			
PACU	3.12 ± 0.72	3.48 ± 0.82	3.40 ± 0.76
1 h	2.28 ± 0.73	2.44 ± 0.71	2.60 ± 0.76
6 h	1.88 ± 0.66	1.92 ± 0.81	2.08 ± 0.70
12 h	1.64 ± 0.56	1.69 ± 0.78	1.76 ± 0.66
24 h	1.48 ± 0.50	1.40 ± 0.50	1.60 ± 0.70
CHEOPS			
PACU	7.00 ± 0.76	7.16 ± 1.14	7.36 ± 1.22
1 h	6.48 ± 1.00	6.96 ± 1.17	7.12 ± 1.30
6 h	6.12 ± 0.92	6.52 ± 1.08	6.76 ± 1.20
12 h	5.56 ± 0.86	6.08 ± 0.95	5.72 ± 0.79
24 h	5.28 ± 1.02	5.60 ± 1.00	5.36 ± 0.81

*Data are given as mean ± SD.
Abbreviation: PACU, post anesthesia care unit.

morphine when utilized as pre-emptive analgesia. However O'Flaherty *et al.* did not demonstrate a reduction in pain or analgesic consumption in pediatric patients undergoing tonsillectomy, when treated with a single dose of 0.15 mg/kg ketamine and/or 30 mg/kg magnesium sulfate (25). Becke *et al.* studied preventive effect of low dose ketamine on postoperative pain and morphine consumption after major urological surgery in children and failed to demonstrate efficacy of ketamine in this manner (4).

There are several possible explanations for the lack of preemptive effect of ketamine. We administered rectal diclofenac at the end of surgery and intravenous proparacetamol at regular intervals postoperatively to all of the patients, and the lack of difference between pain scores in the study groups may have been resulted from analgesic effect of paracetamol and diclofenac. Another reason may be the intensity of pain in inguinal herniorrhaphy. Inguinal herniorrhaphy accounts as a minor surgical procedure, which is accompanied with moderate pain intensity (35), and it can be postulated that intravenous paracetamol and rectal diclofenac provided effective analgesia, which masked the preemptive effects of ketamine. We have utilized a single small dose (0.25 mg/kg) of ketamine, which may contribute to the negative results. It is possible that larger doses and/or an intra-operative continuous infusion of ketamine can produce pre-emptive analgesia in children, which needs further investigations. CHEOPS is one of the objective scoring systems to assess post-operative pain in children. This system uses behavioral scale to assess intensity of pain in children and infants and it is possible that anxiety and/or fear were interpreted as pain. Also, we administered oral midazolam as a premedicant agent to our patients and the resulting sedation may mask some behavioral factors in assessment of pain in children.

In conclusion, this study failed to show the pre-emptive analgesic effect of low dose (0.25 mg/kg) ketamine in pediatric patients who were undergoing inguinal herniorrhaphy. Further investigations need to be conducted to assess the effects of larger dose of ketamine and in major surgical procedures.

Conflict of interests

The authors declare that they have no competing interests.

REFERENCES

1. Warncke T, Stubhaug A, Jørum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. Pain. 1997 Aug;72(1-2):99-106.
2. Wall PD. The prevention of postoperative pain. Pain. 1988 Jun;33(3):289-290.
3. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998 Nov;87(5):1186-1193.
4. Becke K, Albrecht S, Schmitz B, Rech D, Koppert W, Schüttler J, Hering W. Intraoperative low-dose S-ketamine has no preventive effects on postoperative pain and morphine consumption after major urological surgery in children. Paediatr Anaesth. 2005 Jun; 15(6): 484-490.
5. Adams HA. [S-(+)-ketamine. Circulatory interactions during total intravenous anesthesia and analgesia-sedation]. Anaesthesist. 1997 Dec;46(12):1081-1087. German.
6. Adams HA, Brausch M, Schmitz CS, Meyer MC, Hecker H. [Analgesic dosage with (S)-ketamine/propofol vs. (S)-ketamine/midazolam: sedation, stress response and hemodynamics--a controlled study of surgical intensive care patients]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2001 Jul;36(7):417-424. German.
7. Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology. 2000 Jun;92(6):1624-1630.
8. Burton AW, Lee DH, Saab C, Chung JM. Preemptive intrathecal ketamine injection produces a long-lasting decrease in neuropathic pain behaviors in a rat model. Reg Anesth Pain Med. 1999 May-Jun;24(3):208-213.
9. Choe H, Choi YS, Kim YH, Ko SH, Choi HG, Han YJ, Song HS. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. Anesth Analg. 1997 Mar;84(3):560-563.
10. Kwok RF, Lim J, Chan MT, Gin T, Chiu WK. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth Analg. 2004 Apr;98(4):1044-1049
11. Launo C, Bassi C, Spagnolo L, Badano S, Ricci C, Lizzi A, Molinino M. Preemptive ketamine during general anesthesia for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiol. 2004 Oct;70(10):727-34; 734-738.

12. Lee IH, Lee IO. Preemptive effect of intravenous ketamine in the rat: concordance between pain behavior and spinal fos-like immunoreactivity. Acta Anaesthesiol Scand. 2005 Feb;49(2):160-165.
13. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesth Analg. 1993 Dec;77(6):1161-1165.
14. Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J. Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesth Analg. 1999 Aug; 89(2):444-447.
15. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg. 2000 Jun;90(6):1419-1422.
16. Daley MD, Norman PH. Improved, but not preemptive, analgesia. Anesthesiology. 2001 Aug; 95(2): 565.
17. Gilabert Morell A, Sánchez Pérez C. [Effect of low-dose intravenous ketamine in postoperative analgesia for hysterectomy and adnexectomy]. Rev Esp Anestesiol Reanim. 2002 May;49(5):247-253. Spanish.
18. Holthusen H, Backhaus P, Boeminghaus F, Breulmann M, Lipfert P. Preemptive analgesia: no relevant advantage of preoperative compared with postoperative intravenous administration of morphine, ketamine, and clonidine in patients undergoing transperitoneal tumor nephrectomy. Reg Anesth Pain Med. 2002 May-Jun;27(3):249-253.
19. Jaksch W, Lang S, Reichhalter R, Raab G, Dann K, Fitzal S. Perioperative small-dose S(+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. Anesth Analg. 2002 Apr;94(4):981-986.
20. Kucuk N, Kizilkaya M, Tokdemir M. Preoperative epidural ketamine does not have a postoperative opioid sparing effect. Anesth Analg. 1998 Jul;87(1):103-106.
21. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand. 2005 Nov;49(10):1405-1428.
22. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004603.
23. Elhakim M, Khalafallah Z, El-Fattah HA, Farouk S, Khattab A. Ketamine reduces swallowing-evoked pain after paediatric tonsillectomy. Acta Anaesthesiol Scand. 2003 May;47(5):604-609.
24. Marcus RJ, Victoria BA, Rushman SC, Thompson JP. Comparison of ketamine and morphine for analgesia after tonsillectomy in children. Br J Anaesth. 2000 Jun;84(6):739-742.
25. O'Flaherty JE, Lin CX. Does ketamine or magnesium affect posttonsillectomy pain in children? Paediatr Anaesth. 2003 Jun;13(5):413-421.
26. Goodwin SA. A review of preemptive analgesia. J Perianesth Nurs. 1998 Apr; 13(2): 109-114.
27. Pekoe GM, Smith DJ. The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine. Pain. 1982 Jan;12(1):57-73.
28. Howe JR, Wang JY, Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by intrathecal prazosin and intrathecal yohimbine. J Pharmacol Exp Ther. 1983 Mar; 224(3):552-558.
29. Maurset A, Skoglund LA, Hustveit O, Oye I. Comparison of ketamine and pethidine in experimental and postoperative pain. Pain. 1989 Jan; 36(1):37-41.
30. Smith DJ, Azzaro AJ, Zaldivar SB, Palmer S, Lee HS. Properties of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. Neuropharmacology. 1981 Apr; 20(4): 391-396.
31. Woolf CJ, Chong MS. Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993 Aug; 77(2): 362-379.
32. Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg. 1997 May;84(5):1086-1090.
33. Jaksch W, Lang S, Reichhalter R, Raab G, Dann K, Fitzal S. Perioperative small-dose S(+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. Anesth Analg. 2002 Apr;94(4):981-986.
34. Mathisen LC, Aasbø V, Raeder J. Lack of pre-emptive analgesic effect of (R)-ketamine in laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 1999 Feb; 43(2):220-224.
35. Baris S, Karakaya D, Kelsaka E, Güldogus F, Ariturk E, Tür A. Comparison of fentanyl-bupivacaine or midazolam-bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. Paediatr Anaesth. 2003 Feb;13(2):126-131.