Preemptive analgesia effects of Ketamine in patients undergoing surgery. A meta-analysis[1]

Liqiao Yang[I], Jianwei Zhang[II], Zheng Zhang[III], Chengmi Zhang[IV], Di Zhao[V], Jingjie Li[VI]*

DOI: http://dx.doi.org/10.1590/S0102-86502014001900009

[I]Master of Medicine, Department of Anesthesiology, Xin Hua Hospital Affiliated to Jiao Tong University School of Medicine, Shanghai 200092, China. Design of the study, Acquisition of data
[II]Doctor of Medicine, Department of Anesthesiology, Shanghai Children's Medical Center Affiliated to Jiao Tong University School of Medicine, Shanghai, 200127, China.
[III]Master of Medicine, Department of Anesthesiology, Xin Hua Hospital Affiliated to Jiao Tong University School of Medicine, Shanghai 200092, China. Design of the study, Acquisition of data
[IV]Master of Medicine, Department of Anesthesiology, Xin Hua Hospital Affiliated to Jiao Tong University School of Medicine, Shanghai 200092, China. Acquisition of data, carrying out the study.
[V]Master of Medicine, Department of Anesthesiology, Xin Hua Hospital Affiliated to Jiao Tong University School of Medicine, Shanghai 200092, China. Acquisition of data, carrying out the study.
[VI]Master of Medicine, Department of Anesthesiology, Xin Hua Hospital Affiliated to Jiao Tong University School of Medicine, Shanghai 200092, China. Manuscript writing.

ABSTRACT

PURPOSE: To evaluate the preemptive analgesia effects of ketamine for postoperative pain.

METHODS: PubMed, EMBASE and Cochrane Library were searched to identify randomized controlled trials (RCTs) involved in ketamine for preemptive analgesic up to March 2013. The relative risk (RR) or mean difference (MD) as well as the confounding 95% confidence interval (CI) were calculated by the Revman 5.0 software.

RESULTS: A total of five studies including 266 patients were included in this meta-analysis. Overall, ketamine could reduce the postoperative morphine consumption and significantly prolong the time to first analgesic ($p < 0.00001$, MD = 0.91, 95% CI: 0.56 to 1.26). However, there was no significant difference in indicators of nausea and vomiting ($p = 0.87$, RR = 1.04, 95% CI: 0.67 to 1.60), surgical time ($p = 0.41$, MD = -2.13, 95% CI: -7.21 to 2.95) and anesthetic time ($p = 0.53$, MD = -1.54, 95% CI: -6.34 to -3.26) between ketamine and control group.

CONCLUSIONS: Ketamine was able to accomplish some preemptive analgesic effects of reducing postoperative morphine consumption and prolonging the time to first analgesic. Meanwhile, ketamine was as safe as physiological saline in side effects of nausea and vomiting.

Key words: Ketamine. Preemptiva Analgesia. Pain, Postoperative. Meta-Analysis.

Introduction

Preemptive analgesia is considered as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input[1]. By decreasing the altered central sensory processing, preemptive analgesia is thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery[2]. Currently, the drugs for preemptive analgesia included such as opioids[3], N-methyl-D-aspartic acid (NMDA) receptor antagonists[4] and non-steroidal anti-inflammatory drugs (NSAIDs)[5].

Among them, NMDA receptor antagonists have been demonstrated as an effective treatment option in the management of chronic pain, particularly for pain which has been refractory to other treatment modalities[6]. Ketamine, as a noncompetitive NMDA receptor antagonist[7], has a history of fifty years of pain management[8]. Ketamine has served as a useful tool to provide a compelling rationale for developing other NMDA antagonists[9]. It was reported that ketamine might disrupt dopaminergic neurotransmission in the prefrontal cortex as well as cognitive functions associated with this region, in part, by increasing the release of glutamate, thereby stimulating postsynaptic non-NMDA glutamate receptors[10,11].

Currently, the efficacy and safety of ketamine for the management of postoperative pain has been studied by many experts. However, the inconsistent conclusions of a beneficial effect and safety of ketamine for preemptive analgesic remains existed. Subramaniam *et al*.[12] reported that the addition of epidural ketamine 1 mg/kg to morphine 50 μg/kg improved analgesia after major upper abdominal surgery without increasing side effects. While another recent studies found that the preoperative administration of 0.5 mg/kg ketamine in patients undergoing cesarean section did not elicit a preemptive analgesic effect[13]. Moreover, Hala *et al*.[14] reported that intranasal ketamine could enhance the postoperative analgesia after endoscopic nasal surgery, but the psychomimetic side effects of ketamine still occurred with intranasal administration. Thus, whether preemptive analgesic of ketamine is effective and safety in managing postoperative pain remains need more strong evidence to determine. In this study, the purpose of our meta-analysis was to assess the efficacy and safety of ketamine for preemptive analgesic by analyze the data from the randomized clinical trials (RCTs) and double-blind controlled trials.

Methods

Literature search

A literature search without language limitation was conducted for screening studies that reported the preemptive analgesic effects of ketamine. PubMed, EMBASE and Cochrane Library were searched to identify RCTs involved in the preoperative ketamine efficacy for preemptive analgesic up to March 2013. The key words used in this literature search included: "preemptive", "ketamine", "analgesic efficacy" and "randomized controlled trials". Similarly, a manual search of the relevant references was performed.

Criteria for inclusion and exclusion

Articles that met the following criteria were included in this meta-analysis: (1) Studies had been published; (2) they should be RCTs; (3) the intervention was preoperative ketamine in ketamine group; (4) physiological saline instead of ketamine was used in control group; (5) the manner and dosage of anesthesia were same in two groups; (6) at least one of the following indicators were contained: postoperative pain score, postoperative morphine consumption, surgical time, anesthetic time, time to first analgesic and side effects. We excluded trials when there were less than 10 patients in each group or the studies were lack of available data or experimental results. In addition, animal studies and reviews were not considered.

Quality assessment

Two investigators independently assessed the quality of the included studies according to the descriptions provided by the authors of the included trials and the disagreement was subsequently resolved by discussion with each other or another investigator. Jadad scale[15] was used to independently assess the methodological quality of selected clinical trial. Research with the score more than 3 was regarded as high quality study.

Data extraction

Original data were extracted independently by two investigators, including general information (first author name, year of publication and country, documents source), trial characteristics (surgery type, sample size, pain evaluation criteria and the dosage of ketamine), participant-related data (participant age and weight) and all the experimental results.

Statistical analysis

In this study, the relative risk (RR) and mean difference (MD) as well as the confounding 95% confidence interval (CI) were

calculated to assess the categorical variables and continuous variables, respectively. Heterogeneity was explored using I^2 statistic and Chi-square test with $p<0.05$[16]. The fixed effects model was used if no heterogeneity was existed. Otherwise, random effects model was used.

The statistical analysis in this meta-analysis was performed by using Revman 5.0 software. When the data of the included studies could not be analyzed using software, the descriptively qualitative analysis was performed.

Results

Literature search

The initial literature search identified 142 potentially relevant studies. According to inclusion criteria in our analysis, a total of five English studies[13,17-20] matched the selection criteria finally (Figure 1).

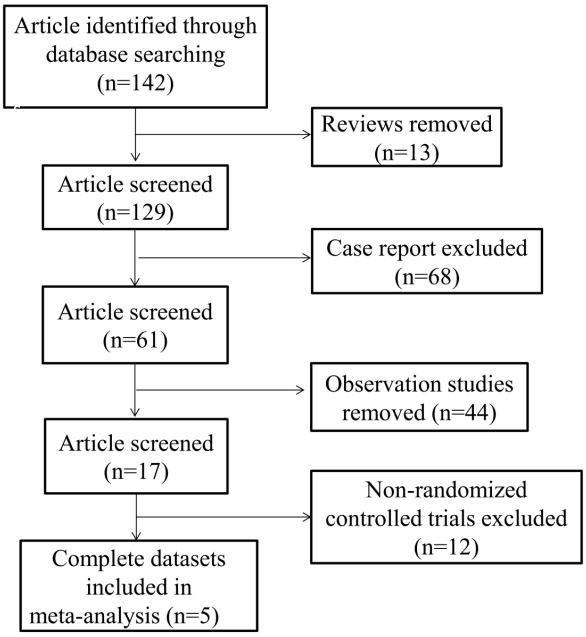

FIGURE 1 - The flow diagram of literature search.

Characteristic of included studies

The characteristics of the included studies were shown in Table 1. The publication year of studies ranged from 2000 to 2012. The studies respectively come from Asian[13,18] , Europe[19,20] and America[17]. Total 266 patients (including 139 patients in ketamine group and 127 patients in control group) were included in this meta-analysis. The surgeries in the included studies were all abdominal surgery. Visual analog scale (VAS) and verbal rating scale (VRS) were used to evaluate pain in two included studies[17,20], while the pain was accessed only based on the VAS in the other three studies[13,18,19]. The range dosage of ketamine was 0.15 - 0.5 mg/kg. In addition, based on the jadad score of the studies, all the included studies were high quality studies.

Postoperative pain score

All the included studies involved in the postoperative pain score. Kwok *et al*.[18] and Nesek-Adam *et al*.[20] accessed the postoperative pain score of ketamine at a dosage of 0.15 mg/kg. Among them, the study results of Kwok *et al*.[18] indicated that the postoperative pain score during 0 - 6 h postoperatively was lower in ketamine group than that in control group and there was no difference among the two groups for the postoperative pain score at 6 - 24 h postoperatively. Nesek-Adam *et al*.[20] found the ketamine can decreased the postoperative pain at 12 h postoperatively in abdomen while the postoperative pain score during 12 - 24 h postoperatively was higher in ketamine group than that in control group. These study results of Nesek-Adam *et al*.[20] were all no statistically significant. Lenzmeier *et al*.[19] and Reza *et al*.[13] assessed the postoperative pain scores of ketamine at a dosage of 0.50 mg/kg. Lenzmeier *et al*.[19] reported that the postoperative pain

TABLE 1 - Characteristics of the trials included in the meta-analysis.

Author year	Country	Procedure	Pain evaluation	Dose of ketamine (mg/kg)	Sample size (ketamine / control)	Age (ketamine / control)	Weight (ketamine / control)	Jadad score
Dahl V 2000 [17]	USA	Hysterectomy	VAS, VRS	0.40	33 / 21	51 ± 6 / 48 ± 7	70 ± 11 / 66 ± 11	5
Kwok RF 2004 [18]	China	Gynecologic laparoscopic surgery	VAS	0.15	45 / 45	34 ± 7 / 34 ± 6	54 ± 9 / 52 ± 7	5
Lenzmeier B 2008 [19]	Netherlands	Laparoscopic abdominal procedure	VAS	0.50	11 / 11	29.72 ± 8.5 / 31.63 ± 6.68	71.36 ± 7.61 / 69.73 ± 9.67	4
Reza FM 2010 [13]	Iran	Cesarean section	VAS	0.50	30 / 30	26.96 ± 5.1 / 27.33 ± 4.54	71.54 ± 12.3 / 73.34 ± 13.4	5
Nesek-Adam V 2012 [20]	Croatia	Laparoscopic cholecystectomy	VAS,VRS	0.15	20 / 20	50.7 ± 11.9 / 53.6 ± 9.6	34.2 ± 4.1 / 32.9 ± 4.2	5

VAS: Visual Analog Scale; VRS: Verbal Rating Scale.

score (p<0.05) at post-anaesthesia care unit (PACU) were lower in ketamine group than that in control group but no significant difference were found among the two groups for the postoperative pain intensity when the patients discharged from hospital. Reza *et al*.[13] did not found the difference among the two groups for the postoperative pain score at 2, 6, 12, 24 h postoperatively. Dahl *et al*.[17] reported the postoperative pain score of ketamine at a dosage of 0.4 mg/kg. It indicated that the postoperative pain score (p = 0.02) at 0 - 6 h, 6 - 24 h and 24 - 96 h postoperatively was lower when compared ketamine group with control group. By observing these data, we did not find the evidence of the association between the dose of ketamine and its analgesic efficacy.

Postoperative morphine consumption

Three trials[13,18,19] reported the morphine consumption after surgery. Kwok *et al*.[18] reported that the overall postoperative morphine consumption (p<0.05) of patients in the ketamine group (1.5 ± 2.0 mg) was less than that in control group (3.4 ± 2.7 mg). Lenzmeier et al.[19] found that the postoperative morphine consumption (p<0.05) in the postanesthesia care unit (PACU) was reduced by ketamine group compared with control group. The study result of Reza *et al*.[13] indicated that the postoperative morphine consumption (p<0.01) at 2h postoperatively was less in ketamine group than that in control group. There results suggested that ketamine could reduce the postoperative morphine consumption.

Surgical time

In this meta-analysis, all the included studies reported the data of surgical time. There was no significant heterogeneity (p = 0.21, I^2 = 32%) among the five studies. So a fixed effects model was used. Our results showed that there was no significant differences (p = 0.41, MD = -2.13, 95% CI: -7.21 to 2.95) among the two groups in the surgical time (Figure 2).

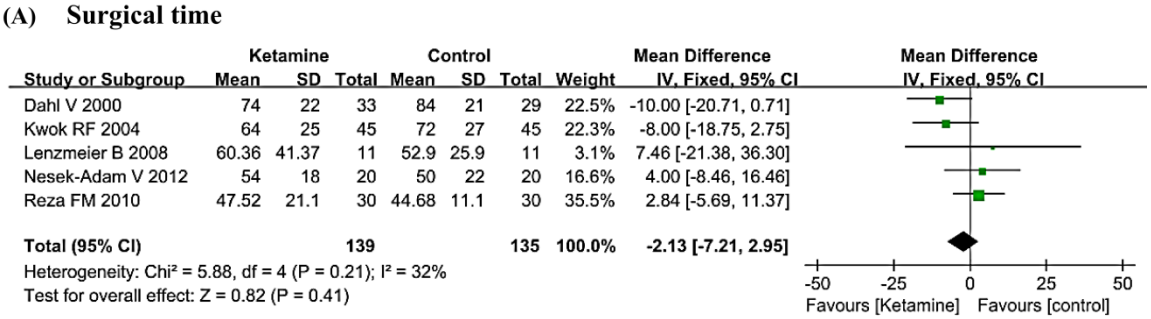

FIGURE 2 - The forest plots of the evaluation indicators of preemptive analgesic effect (Surgical time).
RR; risk ratio; MD: mean difference; 95% CI: 95% confidence interval.

Anesthetic time

In our analysis, total 4[13,17,18,20] out of the included studies assessed the anesthetic time between ketamine groups and controls. The fixed effects model was used because of no significant heterogeneity (p = 0.28, I^2 = 23%) among the studies. The results indicated that there was no significant difference (p = 0.53, MD = -1.54, 95% CI: -6.34 to 3.26) between ketamine and control group (Figure 3).

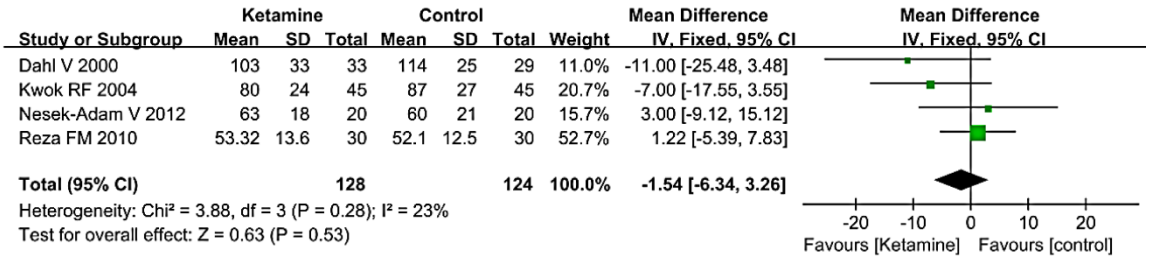

FIGURE 3 - The forest plots of the evaluation indicators of preemptive analgesic effect (Anesthetic time).
RR; risk ratio; MD: mean difference; 95% CI: 95% confidence interval.

Time to first analgesic

Two included[18,20] studies investigated the time to first analgesic of the patients after operation. The fixed effects model was used due to no heterogeneity ($p = 0.12$, $I^2 = 59\%$) among the studies. Our results showed that the time to first analgesic was significantly longer in ketamine group than that in control group ($p < 0.00001$, MD = 0.91, 95% CI: 0.56 to 1.26) (Figure 4).

Nausea and vomiting

Nausea and vomiting, as the side effects of ketamine, were reported in three included studies[13,18,20]. The fixed effects model was used to pooled the data because of no significant heterogeneity ($p = 0.65$, $I^2 = 0\%$). Our results showed that there was no significant difference between ketamine and control groups ($p = 0.87$, RR = 1.04, 95% CI: 0.67 - 1.60). It indicated that the safety of ketamine for preemptive analgesia was equally with physiological saline (Figure 5).

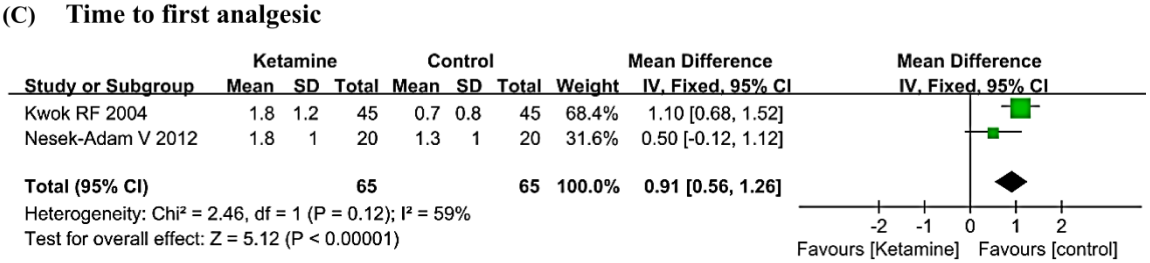

FIGURE 4 - The forest plots of the evaluation indicators of preemptive analgesic effect (Time to first analgesic).
RR; risk ratio; MD: mean difference; 95% CI: 95% confidence interval.

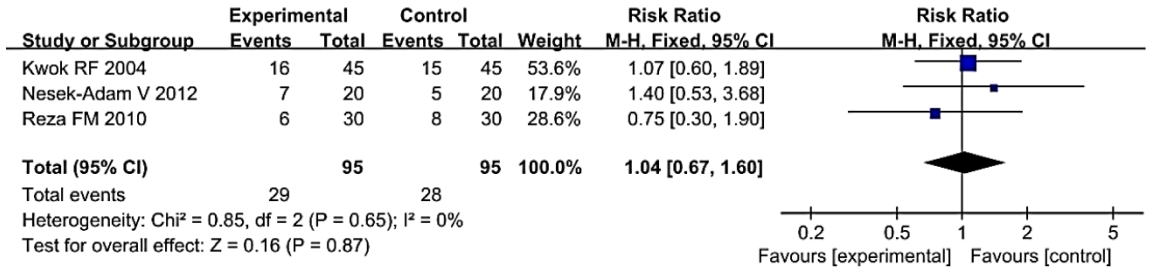

FIGURE 5 - The forest plots of the evaluation indicators of preemptive analgesic effect (Nausea and vomiting).
RR; risk ratio; MD: mean difference; 95% CI: 95% confidence interval.

Discussion

Preemptive analgesia is a treatment initiated before the surgical procedure in order to reduce this sensitization[21]. In the present meta-analysis, we assessed the efficacy and safety of ketamine. For postoperative pain, we could not conclude that ketamine could decrease the pain intensity because of the inconsistent conditions and results of the included studies. For the indicators of postoperative morphine consumption and time to first analgesic, ketamine could reduce the postoperative morphine consumption and significantly prolong the time to first analgesic. It suggested that ketamine had some beneficially preemptive analgesic effects. However, the results demonstrated that ketamine didn't play any role in reducing surgical time, anesthetic time. For nausea and vomiting, the result indicated that the ketamine for preemptive analgesia was as safe as physiological saline.

The mechanism of ketamine for preemptive analgesia is based on the induction and maintenance of central sensitization[22]. Central sensitization produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations[23]. The proposed mechanism of this preemptive effect is that analgesia administered before a nociceptive stimulus reduces the degree of sensitization produced in the nervous system by the stimulus, and facilitates subsequent pain treatment[24]. Therefore, there is reliable theory basis for ketamine as the drug of preemptive analgesia and further studies of ketamine for preemptive analgesia are worth doing.

It was reported that morphine administration after surgery carries a high risk of side-effects such as nausea, vomiting, pruritus, urinary retention and apnoea[25]. Thus, the reduction of postoperative morphine consumption can decrease the postoperatively adverse reactions. It provided beneficial information for the clinical application of ketamine.

In addition, we did not find any difference between ketamine and control group for the incidence of nausea and vomiting in our analysis. However, it was reported that large doses of ketamine (> 2 mg/kg) can produce unpleasant side effects[26]. So for the safety of ketamine, more studies must be done to verify the conclusion of this study or find the other evidences for the side effects of ketamine.

This meta-analysis has some advantages compared with the previous review[27]. The first one is that the included studies were updated up to 2012. Second, the studies included in this meta-analysis were all high quality studies. Third, the control was only physiological saline and the intervention was only preoperative ketamine. It was benefit for the accuracy of the results in this study.

However, some limitations must be mentioned in this study. The first one is that the data of postoperative pain score could not be statistically analyzed. New methods must be established to evaluate the pain intensity. Second, the association of the dose of ketamine with the pain intensity was not found by the observation of the data from the included studies. More studies were needed to find the association of the dose of ketamine with the pain intensity and the preemptive analgesic effect. The second limitation is the small size of subjects. Third, the sensitivity analysis and evaluation of publication bias were not performed for lack of enough available data.

Conclusions

Ketamine was able to accomplish some preemptive analgesic effects of reducing postoperative morphine consumption and prolonging the time to first analgesic. For the safety of ketamine, ketamine for preemptive analgesia was as safe as physiological saline side effects of nausea and vomiting.

References

1. Kissin I. Preemptive analgesia. Anesthesiology. 2000 Oct;93(4):1138-43. PMID: 11020772.
2. Wilder-Smith OH. Pre-emptive analgesia and surgical pain. Prog Brain Res. 2000 Dec;129:505-24. doi: 10.1016/S0079-6123(00)29037-7.
3. Wilson RJ, Leith S, Jackson IJ, Hunter D. Pre-emptive analgesia from intravenous administration of opioids. No effect with alfentanil. Anaesthesia. 1994 Jul;49(7):591-3. PMID: 8042723.
4. Helmy SA, Bali A. The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements. Anesth Analg. 2001 Mar;92(3):739-44. PMID: 11226111.
5. Sittl R, Irnich D, Lang PM. Update on preemptive analgesia: options and limits of preoperative pain therapy. Anaesthesist. 2013 Oct;62(10):789-96. doi: 10.1007/s00101-013-2225-3.
6. Niesters M, Dahan A. Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. Expert Opin Drug Metab Toxicol. 2012 Nov;8(11):1409-17. doi: 10.1517/17425255.2012.712686.
7. Davies SN, Alford ST, Coan EJ, Lester RA, Collingridge GL. Ketamine blocks an NMDA receptor-mediated component of synaptic transmission in rat hippocampus in a voltage-dependent manner. Neurosci Lett. 1988 Oct 5;92(2):213-7. PMID: 2903476.
8. Persson J. Ketamine in pain management. CNS Neurosci Ther. 2013 Jun;19(6):396-402. doi: 10.1111/cns.12111.
9. Chizh BA. Low dose ketamine: a therapeutic and research tool to explore N-methyl-D-aspartate (NMDA) receptor-mediated plasticity in pain pathways. J Psychopharmacol. 2007 May;21(3):259-71. doi: 10.1177/0269881105062484.
10. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci. 1997 Apr 15;17(8):2921-7. PMID: 9092613.
11. Lorrain DS, Baccei CS, Bristow LJ, Anderson JJ, Varney MA. Effects of ketamine and N-methyl-D-aspartate on glutamate and dopamine release in the rat prefrontal cortex: modulation by a group II selective metabotropic glutamate receptor agonist LY379268. Neuroscience. 2003;117(3):697-706. PMID: 12617973.
12. Katalinic N, Lai R, Somogyi A, Mitchell PB, Glue P, Loo CK. Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. Aust N Z J Psychiatry. 2013 Aug;47(8):710-27. doi: 10.1177/0004867413486842.
13. Reza FM, Zahra F, Esmaeel F, Hossein A. Preemptive analgesic effect of ketamine in patients undergoing elective cesarean section. Clin J Pain. 2010 Mar-Apr;26(3):223-6. doi: 10.1097/AJP.0b013e3181bff86d.
14. He H, Chen J, Xie WP, Cao S, Hu HY, Yang LQ, Gong B. Ketamine used as an acesodyne in human breast cancer therapy causes an undesirable side effect, upregulating anti-apoptosis protein Bcl-2 expression. Genet Mol Res. 2013 Jun 13;12(2):1907-15. doi: 10.4238/2013.January.4.7.
15. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12. PMID: 8721797.
16. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006 Jun;11(2):193-206. doi: 10.1037/1082-989X.11.2.193.
17. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesthesia and analgesia. 2000 Jun; 90(6): 1419-22. PMID: 10825333
18. 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):1044-9. PMID: 15041596.
19. Lenzmeier B, Moore RL, Cordts P, Garrett N. Menstrual cycle-related variations in postoperative analgesia with the preemptive use of N-methyl D-aspartate antagonist ketamine: a pilot study. Dimens Crit Care Nurs. 2008 Nov-Dec;27(6):271-6. doi: 10.1097/01.DCC.0000338875.08153.6f.
20. Nesek-Adam V, Grizelj-Stojcic E, Mrsic V, Rasic Z, Schwarz D. Preemptive use of diclofenac in combination with ketamine in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. Surg Laparosc Endosc Percutan Tech. 2012 Jun;22(3):232-8. doi: 10.1097/SLE.0b013e31824f8ae4.
21. Dahl JB, Moiniche S. Pre-emptive analgesia. Br Med Bull. 2004 Dec 13;71:13-27. doi: 10.1093/bmb/ldh030.

22. Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Can J Anaesth. 1997 Jan;44(1):31-7. doi: 10.1007/BF03014321.
23. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009 Sep;10(9):895-926. doi: 10.1016/j.jpain.2009.06.012.
24. Karaaslan D, Sivaci RG, Akbulut G, Dilek ON. Preemptive analgesia in laparoscopic cholecystectomy: a randomized controlled study. Pain Pract. 2006 Dec;6(4):237-41. doi: 10.1111/j.1533-2500.2006.00092.x.
25. Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth. 2005 Apr;94(4):505-13. doi: 10.1093/bja/aei085.
26. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999 Aug;82(2):111-25. PMID: 10467917.
27. Elia N, Tramer MR. Ketamine and postoperative pain--a quantitative systematic review of randomised trials. Pain. 2005 Jan;113(1-2):61-70. doi: 10.1016/j.pain.2004.09.036.

Correspondence:
Department of Anesthesiology, Xin Hua Hospital
Jiao Tong University
No.1665 Kongjiang Road
Shanghai 200092, China
jingjieli0012@hotmail.com
Received: Aug 19, 2014
Review: Oct 17, 2014
Accepted: Nov 21, 2014
Conflict of interest: none
Financial source: none
LiJingjie [jingjieli0012@hotmail.com]
[1]Research performed at Xin Hua Hospital, Jiao Tong University, School of Medicine, . School of Medicine, Shanghai 200092, China