Efficacy and safety of prophylactic use of ketamine for prevention of postanesthetic shivering: A system review and meta analysis

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Abstract

Background Post-anaesthetic shivering is a common complication of anaesthesia which accounts for much discomfort in postoperative patients. The main purpose of this meta analysis is to analyze and evaluate the efficacy and safety of prophylactic use of ketamine for preventing postanesthetic shivering.

Methods We searched the following databases: Medline, EMBASE and the Cochrane Central Register of Controlled Trials for randomized controlled trials. The primary outcome being observed was the incidence rate of postanesthetic shivering. The secondary outcome was the sedation score and incidence of the side effects caused by drugs utilized in the study.

Results In this meta analysis, we analyzed a total of 16 trials including 1485 patients. Ketamine did reduced the incidence rate of postanesthetic shivering compared with placebo(odd ratio [OR]: 0.13, 95% confidence interval [CI]: 0.06 to 0.26, P=0.00001). The observation related to the side effects showed no evident variability regarding the incidence rate of nausea and vomiting. Usage of ketamine was associated with a lower rate of hypotension and bradycardia when compared with placebo. Hallucination was more frequently observed in patients receiving ketamine of higher doses. No significant difference was found in the incidence of postanesthetic shivering for all comparisons between ketamine and other pharmacological interventions. The occurrence of side effects caused by ketamine or other study drugs was similar with an exception of the comparison between ketamine and ondansetron where ketamine lowered the incidence of hypotension but with a relatively higher incidence of postoperative nausea and vomiting.

Conclusions Ketamine has a preventive effect on postanesthetic shivering without causing any severe side effects. However, ketamine shows no advantage over other antishivering drugs.
Background

Postanesthetic shivering is a frequent complication of anesthesia which may cause aggravated pain to the patients. It is characterized by an involuntary movement that may affect one or more muscle groups. Postanesthetic shivering often interferes with electrocardiography (ECG) and oxygen saturation (SpO2) monitoring\(^1\). Moreover, it may also increase oxygen consumption combined with increased minute ventilation and carbon dioxide production which increases the mortality of the elderly and coronary artery diseased patients\(^2\).

The mechanism of shivering after anesthesia has not been defined yet, the conventional and obvious explanation for the shivering is hypothermia induced by the exposure to the cold environment, the non-thermoregulation factor like inadequate pain control and opioid withdrawal may also contribute in postanesthetic shivering\(^3\). Typical anesthetic agents linearly decrease the shivering thresholds and result in a wider inter-threshold range\(^4\). Different pharmacological treatments have been used to prevent the postanesthetic shivering including the administration of meperidine, alfentannil, tramadol, magnesium sulfate, ondansetron, dolasetron and dexmedetomidine\(^5, 6, 7, 8, 9\). But there is not enough evidence for nominating any one ideal drug for this purpose. Ketamine is a noncompetitive NMDA receptor antagonist and it may prevent postanesthetic shivering by decreasing core-to-peripheral heat distribution. Many published literatures have investigated the potential effects of ketamine for prevention of postanesthetic shivering. However, there is no consensus reached regarding whether ketamine is an appropriate drug to prevent postanesthetic shivering. An evidence-based understanding of the benefit and risk of the of ketamine would identify its rational and optimal use, so we conducted the meta-analysis to assess the efficacy and safety of ketamine for the prevention of
shivering in patients undergoing various kinds of surgery procedures.

Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Search strategy

Two authors (Y.Z., A.M.) independently searched MEDLINE (2000 to March 2018), EMBASE (2000-2018) and the Cochrane Central Register of Controlled Trials (March 2018) with no language restrictions. By reviewing the references of the eligible articles, we identified additional studies in our meta-analysis. The following search-term strategy was used: 1) shivering; 2) tremor; 3) shake; 4) hypothermia; 5) anesthesia; 6) postanesthetic; 7) postoperative; 8) surgery; 9) ketamine; 10) 1 or 2 or 3 or 4; 11) 5 or 6 or 7 or 8; 12) 9 and 10 and 11

Criteria for considering studies for this review

The selection criteria were pre-established. Inclusion criteria included: (1) controlled clinical trial; (2) prophylactic use of ketamine as a comparison with placebo or other pharmacological interventions; (3) reported the incidence of postoperative shivering. Trials were not considered for the following reasons: (1) other anti-shivering drugs were also administrated during the anesthesia induction or maintenance period besides ketamine; (2) data from abstracts, letters, or reviews. We included any participants undergoing operative procedures under general or spinal anesthesia. The following outcomes were measured: (1) incidence of postanesthetic shivering; (2) sedation score; (3) incidence of other side effects.

Data collection and analysis

Two review authors (Y.Z., A.M.) independently screened all the titles and abstracts of the
studies during the initial search to identify the included studies. After removing the duplicates, potentially relevant studies were retrieved in full-text version for the further assessment. We resolved the disagreement by discussion with another author (G. H. L) of our group.

Data extraction was conducted by two authors (Y.Z., A.M.) independently using the data collection form established before. The following characteristics of studies were collected: primary author, publication year, anesthetic methods, demographic characteristics of participants, surgery types, comparisons and other non-pharmacological warming methods. We recorded the number of patients experiencing shivering in each group for dichotomous data.

We used the Review Manager software of the Cochrane Collaboration (RevMan 5.2) to perform the quantitative analysis. We expressed the results from dichotomous data as odds ratio (OR) and 95% confidence intervals (CIs). Heterogeneity testing was performed with the Z score and $X^2$ statistical analysis, with $P<0.1$ considered to indicate heterogeneity. The fixed effect model or the random effect model was applied according to the heterogeneity of the studies. A fixed effect model was used when $I^2<50\%$. We reported the results of included studies when the pooled analysis was not appropriate.

Sensitivity and subgroup analysis were performed to explore the reason for the heterogeneity. Subgroup analysis was conducted based on the anesthetic methods, various doses of ketamine used and the types of surgery. Publication bias was evaluated by Begg’s test using Stata 13.1 software (Stata, college, Station, TX, USA).

Results

Search results and characteristics of the studies

The flowing diagram (Figure 1) shows the process of studies which were searched. A total
of 361 potential articles were then identified. We reviewed 30 records in full-text version after screening the titles and the abstracts. In the end, a total of 16[10-25] studies with 1485 patients fulfilled our criteria to be included in the analysis (Table 1).

In 15 trials participants were adults over 18 years old, only 1 trial [23] included children aged 5-12 years old. Participants in 7 trials[10,12,13,18,19,23,24] undergoing operation procedures were under general anesthesia, and in 9 trials[11,14,15,16,17,20,21,22,25] participants were under spinal anesthesia. In 13 trials[10,12,14,15,16,17,18,19,20,21,22,23] ketamine was compared against placebo, while in 4 trials[12,13,23,24] ketamine was compared with pethidine and in the other 4 trials[11,15,16,22] ketamine was compared with tramadol, ketamine was also compared with ondansetron in 4 trials[10,15,17,21]. The administration time or routes were different among included trials. In 10 trials [11,14,15,16,17,20,21,22,23,25] the intervention drugs were given immediately after the induction of anesthesia or intrathecal injection, in 5 trials[10,12,18,19,24] drugs were administrated before the completion of surgical procedure, while in 1 trial[13] patients received the study drugs before the wound closure. Study drugs were given as a i.v. bolus 14 trials[10-22,24], in two single trials patients received the study drugs epidurally[25] or intramuscularly[24]. In 4 trials[14,15,18,19] researchers included patients receiving orthopedic surgery, patients in 2 studies[21,22] underwent abdominal surgery, 2 studies[16,17] included patients undergoing cesarean section surgery, 2 studies[20,25] included patients undergoing urological surgery, and in 3 trials participants received ENT surgery[10], endoscopic sinus surgery[12] or tonsillectomy surgery[23] respectively.

With regard to the measurement the intensity of shivering in a patient, 13 trials[10,13-
utilized a scale with variation points ranging from 0-4: 0, no shivering; 1, piloerection or peripheral vasoconstriction but no visible shivering; 2, muscular activity in only one muscle group; 3, muscular activity in more than one muscle but not generalized; 4, shivering involving the whole body. 1 trial\textsuperscript{[12]} applied a 0-3 scale for evaluating the intensity: 0, no shivering; 1, mild fasciculation of face or neck; 2, visible tremor involving more than one muscle; 3, gross muscular activity involving the entire body. 2 studies\textsuperscript{[11,18]} did not assess the intensity of postanesthetic shivering.

Assessment of the risk of bias of the included studies

Two authors (Y.Z., A.M.) independently assessed the following domains by the Cochrane ‘Risk of bias’ tool.

- Sequence generation
- Allocation concealment
- Blinding of participants, personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We completed ‘Risk of bias’ figures for each included study (Figure 2). See more details in Appendix.

Publication bias

Begg’s tests showed that there was no publication bias for the primary outcome (p=0.055).

Effects of interventions

**Primary outcome**

**Ketamine vs placebo** The incidence of postanesthetic shivering was compared between ketamine and placebo in 13 trials including 1166 patients (Figure 3). Ketamine has shown to significantly decrease the incidence of shivering (pooled OR = 0.13; 95% CI: 0.06 to 0.26, P<0.00001). There was significant and prominent heterogeneity for this outcome.
(I²=74%). The Begg’s test showed that there was no risk of publication bias (P=0.06). A subgroup analysis was being performed to explore the evidence-based reason. In subgroup analysis of anesthetic methods, the heterogeneity was down to 67% in the GA (general anesthesia) group (Figure 4.). Sensitivity analysis was performed to remove a trial [22] utilizing air forced warmer intraoperatively which showed a similar result favoring ketamine (pooled OR = 0.18; 95% CI: 0.09 to 0.37) and decreased heterogeneity (I² from 67% to 21%). Ketamine reduced the incidence of postanesthetic shivering in general anesthesia (pooled OR = 0.13; 95% CI: 0.06 to 0.26) and in spinal anesthesia (pooled OR = 0.08; 95% CI: 0.03 to 0.18). In the subgroup analysis based on the dose of ketamine used in the included trials (Figure 5), ketamine reduced the incidence of postanesthetic shivering in the dose of 0.25mg/kg (pooled OR = 0.12; 95% CI: 0.03 to 0.52) and in the dose of 0.5mg/kg (pooled OR = 0.14; 95% CI: 0.07 to 0.28) respectively. As the type of surgery may influence the incidence of postanesthetic shivering, we also performed a subgroup analysis based on it (Figure 6). Ketamine significantly lowered the incidence of postanesthetic shivering in patients during orthopedic surgery (pooled OR = 0.32; 95% CI: 0.13 to 0.77). Among patients undergoing abdominal surgery, cesarean section surgery, urological surgery, ENT surgery or endoscopic surgery, ketamine also reduced the incidence of postanesthetic shivering.

**Ketamine vs other pharmacological interventions** A total of 4 studies [12, 13, 23, 24] investigated the effect of ketamine for prevention of shivering compared with pethidine. The pooled analysis showed a definite difference in favor of pethidine (pooled OR = 4.38; 95% CI: 1.76 to 10.92). No significant difference of postanesthetic shivering was found between ketamine and other pharmacological interventions (Figure 7).

**Secondary outcomes**
**Ketamine vs placebo** In comparison to the other side effects (Table 3), there was no significant difference of incidence of postoperative nausea and vomiting between ketamine and placebo (pooled RR = 0.72; 95% CI: 0.48 to 1.08). Ketamine reduced the incidence of hypotension and bradycardia compared with placebo (pooled RR = 0.28; 95% CI: 0.17 to 0.47; pooled RR = 0.18; 95% CI: 0.05 to 0.65, respectively). The incidence of hallucination was more significant and dominant in the patients received the dose of 0.5mg/kg of ketamine (Table 4) and there was only 1 episode of hallucination occurred in the patients receiving the dose of 0.25mg/kg. Seven studies\(^{[14,15,16,20,21,22,25]}\) reported the sedation score of patients on a 5-point scale. 1= fully awake and oriented, 2= drowsy, 3= eyes closed but arousable to command, 4= eyes closed but arousable to mild physical stimulation and 5= eyes closed but unarousable to mild to physical stimulation. The pooled analysis was not performed because of the lack of uniform sedation score scales in the trials. All these studies showed that the sedation score was higher in group ketamine than placebo. 5 trials\(^{[14,16,17,19,23]}\) reported a significant decrease in core temperature in both group ketamine and group placebo compared with the baseline temperature of participants, but it was not significant at any time points between groups. 3 trials\(^{[20,21,22]}\) reported a significant difference of core temperature between ketamine and placebo while a greater decrease in temperature was found in group placebo.

**Ketamine vs other pharmacological interventions** No significant difference was found in the incidence of PONV between ketamine and pethidine (pooled OR = 0.88; 95% CI: 0.38 to 2.07). Compared with tramadol, the difference in the incidence of PONV or hypotension is not significant (OR = 0.57; 95% CI: 0.18 to 1.78; OR=0.90; 95%CI: 0.36 to 2.24, respectively). The incidence of PONV was higher in group ketamine than ondansetron (OR = 4.49; 95% CI: 1.24 to 16.21), however, ketamine could lower the incidence of
hypotension compared with ondansetron (OR = 0.09; 95% CI: 0.00 to 3.23). The result of core temperature changes was reported graphically and there was no significant difference between ketamine and other pharmacological interventions.

**Summary of findings and quality of evidence** The Summary of findings with GRADE recommendations were shown in Table 2.

**Discussion**

Postoperative shivering is a very unpleasant and physiologically stressful emotion. There are various studies conducted in order to help out in identifying the kind of different precipitating factors, including gender differentiation, the duration of the anaesthetics, spontaneous breathing techniques, the role and efficacy of different kinds of volatile agents and anticholinergic medications.

Ketamine was first synthesized in the early 1960s as a safer alternative to phencyclidine [26]. It is known as a non-competitive N-methy-D-aspartate (NMDA) receptor antagonist with an effect of thermoregulation. Other than being a competitive NMDA receptor antagonist, the other properties of ketmaine is that it can act as an opioid agonist [27], it can also cause the blockage of the amine uptake in their descending inhibitory monoaminergic pain pathways, having a local anaesthetic action and interacting with the muscarinic receptors [28]. Therefore, it can be considered that ketamine probably controls shivering by acting on the nonshivering thermogenesis [29]. Ketamine is predominantly utilized as an anaesthetic agent that induces analgesia but for a long time it has been criticized for some of its side effects which include the induction of a psychedelic state causing agitation and hallucinations [30].

Therefore, we have conducted this comparative study to better understand the role of ketamine and determine the efficacy and safety in this regard. In this analysis we
compared different studies and our goal was to idealize the beneficial aspects of ketamine. In our study we also compared the usage of ketamine and its relevance on the post anaesthetic shivering. In total 16 studies were being observed and were compared and the total number of patients were 1485. There were some evident findings which are

(A) The exposure of ketamine showed a relatively advanced effect on reducing the occurrence of postanaesthetic shivering compared to placebo. As for the comparisons between tramadol or ondansetron, ketamine slightly lowered the incidence of postanesthetic shivering while it did not reach the significance level.

(B) The effect of ketamine on postanaesthetic shivering remained equally beneficial for both spinal and general types of anaesthesia.

(C) The dose of 0.5mg/kg had an advance effect over 0.25mg/kg on the postanaesthetic shivering rate.

(D) The effect remained constant for all types of surgical procedures which includes orthopedics surgery, laprotomy, cesarian section, urological, ENT and endoscopic surgeries.

(E) In the comparison of pethidine vs ketamine, the pethidine had a slight advantage over ketamine and showed a quick responsive rate than ketamine, while there was not sufficient data in other studies which showed any advantage of other pharmacological interventions.

We also evaluated the side effects of the anesthetic drugs and the role of ketamine to prevent or overcome them. Moreover, the efficacy of ketamine is also being compared with placebo. The side effects which were being nominated in the included trials were nausea, vomiting, hypotension, bradycardia and hallucinations. The role of ketamine showed a favorable outcome in reducing the incidence rate of hypotension and
bradycardia as ketamine causes dose dependent direct stimulation of the CNS which leads to the increased sympathetic nervous system stimulation which response in increasing the systemic blood pressure and heart rate.

The was no evidence found to be beneficial for decreasing the incidence rate of nausea and vomiting in the favor of ketamine usage as compared to placebo. As ketamine is known to have the hallucinogenic effect it has been considered to establish an instrumental and potential role for glutamatergic signaling in psychosis, so the usage of ketamine is being associated with auditory and verbal hallucinations. In our comparative study we also found that the rate of hallucination episodes was much higher in the patients receiving the dose of 0.5mg/kg as compared to the lower dose of 0.25mg/kg and hallucinogenic effect of ketamine was much evident when being compared with the placebo drugs for there was no incident rate reported in any of the trials. Ketamine can cause sedation in postoperative patients and deep sedation is considered to be a severe adverse event for patients. However, for those experiencing shivering mild sedation may prevent them from hurting themselves. In our study we paid special attention to the sedation score of patients, although pooled analysis was not conducted because of various outcome scales we found that mild to moderate sedation was more commonly seen in patients receiving different doses of ketamine.

We also noticed an interesting finding from a recent meta analysis\(^{[31]}\) which showed that active warming for elective caesarean delivery reduced the incidence of postoperative shivering and provided more stable perioperative temperature change. Accumulating evidence has shown that active warming method including electric heating, water-circulating garments, forced-air, radiant heating is effective in preventing postanesthetic shivering. The current American Society of Anesthesiologists Task Force on Postanesthetic Care guidelines recommend forced-air warming as a common method to
reduce shivering in the perioperative setting [32]. Future research should focus on the combinations of pharmacological interventions with non-pharmacological methods to better solve this problem.

The major limitation of our study is that we previously wanted to cover the hemodynamical changes regarding the usage of ketamine but there were no standard criteria being followed by the trials causing irrelevancy and uneven data for comparing and evaluation précised outcomes in this regard. Second, the sample size of included trials was relatively small which may cause less confident conclusions. Third, the evidence level for our outcomes is low or very low. But we believed that our study is of value because it provided clear evidence of the benefit of prophylactic katamine intervention for preventing postanesthetic shivering which may be helpful to clinical practice.

Conclusions

In this meta analysis we tried to cover every aspect of the usage of ketamine for controlling the post antiesthetic shivering. It has been finally concluded that ketamine showed an advantage in reducing the incidence rate of shivering. Although it is beneficial, but it did not show any superiority over other pharmacological exposures. Ketamine has shown a good clinical value, but further studies should be performed on a wider scale to determine more emphasized results. More large clinical trials investigating the combination of different antishivering regimens are warranted.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: The datasets used in the analysis was collected by
online search.

**Competing interests:** We declare that no competing interests were involved.

**Funding:** No funding involved in the study.

**Authors' contributions:** Study design: J.L.C., Y. H., Y.Z., A.M

Writing of the manuscript: J.L.C., Y. H., Y.Z., A.M.

**Data analysis:** Y. Z., M.A.

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Tables

| Study ID | Patients | Surgery Types | Anesthesia Methods | Comparison | Non-pharmacological Warming Methods |
|----------|----------|---------------|-------------------|------------|------------------------------------|
| Abdelhalim 2014 | 120 patients 18-45yr | ENT surgery | GA | C(30): saline iv | O(30): ondansetron 8mg iv; K(30): ketamine 0.5mg/kg iv; OK(30): ondansetron 8mg+ketamine 0.25mg/kg iv | None |
| Akram 2017 | 64 patients 18-50yr | elective lower abdominal surgery | SA | K(32): ketamine 0.05mg/kg iv | T(32): tramadol 1mg/kg iv | None |
| Ayatollahi 2011 | 120 patients 20-50yr | endoscopic sinus surgery | GA | C(30): saline iv | K1(30): 0.3mg/kg iv; K2(30): 0.5mg/kg iv; M(30): meperidine 0.4mg/kg iv | Patients were covered with a cotton blanket |
| Han 2010 | 93 patients 51-78yr | transurethral resection of the prostate | SA | C(31): epidural 0.75% ropivacaine | K1(32): epidural ketamine 0.2mg/kg+0.75%ropivacaine; K2(30): epidural ketamine 0.4mg/kg+0.75%ropivacaine | None |
| Hasannasab 2016 | 120 patients 20-45yr | gynecologic surgery | GA | K(40): ketamine 0.25mg/kg iv; M(40): meperidine 20mg iv; D(40): doxapram 0.25mg/kg iv | Patients were covered with a standard blanket |
| Study          | Patients | Surgery Type | Anesthesia Type | Anesthetic Agents | Additional Details |
|---------------|----------|--------------|-----------------|-------------------|-------------------|
| Honarmand 2008 | 120 | 18-60yr | orthopaedic surgery | C(30): saline iv; K(30): ketamine 0.5mg/kg iv; M(30): midazolam 75µg/kg iv; KM(30): ketamine 0.25mg/kg + midazolam 37.5µg/kg iv; T(30): tramadol 0.5mg/kg iv; O(30): ondansetron 4mg iv; K(30): ketamine 0.25mg/kg iv | Fluids were preheated to 37°C |
| Lakhe 2017    | 120 | 18-65| gynecologic and orthopedic surgery | C(30): saline, iv | Patients covered with drapes |
| Lema 2017     | 123 | 18-39yr | cesarean section | C(41): saline iv | Patients covered with drapes |
| Lema 2017     | 117 | 18-40yr | cesarean section | C(39): saline iv | None |
| Norouzi 2011  | 120 | 18-65yr | elective orthopedic surgery | C(30): saline iv; K(30): ketamine 0.125mg/kg iv; K2(30): ketamine 0.25mg/kg iv; K3(30): ketamine 0.5mg/kg iv | None |
| Petskul 2016  | 183 | 18-65yr | orthopedic surgery | C(92): saline iv; K(91): ketamine 0.25mg/kg iv; O(91): ondansetron 4mg iv | All patients were warmed by air force warmer |
| Sagir 2007    | 160 | 18-65yr | urological surgery | C(40): saline iv; K(40): ketamine 0.5mg/kg iv; G(40): granisetron 3mg iv; KG(40): ketamine 0.25/kg + granisetron 1.5mg iv | All patients were covered with drapes and a cotton blanket. Fluids were preheated to 37°C |
| Shakya 2010   | 120 | 18-65yr | Lower abdominal surgery | C(40): saline iv; K(40): ketamine 0.25/kg iv; O(40): ondansetron 4mg iv | Patients were covered with standard single blanket |
| Wason 2010    | 200 |  |  | C(50): saline iv; K(50): ketamine | Fluids were
| Year   | Age Range | Procedure                  | Anesthesia  | Preoperative Medication | Postoperative Medication |
|--------|-----------|----------------------------|-------------|-------------------------|--------------------------|
| 2012   | 18-65yr   | Abdominal or lower limb surgery | IV          | 0.5mg/kg iv; C(50): clonidine 75mcg; T(50): tramadol 0.5mg/kg iv | Preheated to 37°C         |
| Zahra  | 2008      | 120 patients 5-12yr tonsillectomy surgery | GA          | C(40): saline           | None.                    |
| Zavareh| 2012      | 135 patients 18-70yr elective surgery | GA          | K(45): ketamine 1mg/kg; P(45): pethidine 0.5mg/kg; D(45): dexamethasone 0.6mg/kg | None                      |

Abbreviations: yr, years; GA, general anesthesia; SA, spinal anesthesia; C, control; O, ondansetron; T, tramadol; M, meperidine; D, doxapram; G, granisetron; CL, clonidine; P, pethidine.
Table 2. Summary of findings with GRADE recommendations.

**ketamine for postoperative shivering**

**Patient or population:** patients with postoperative shivering  
**Settings:** hospitals  
**Intervention:** ketamine

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|-----------------------------------------|--------------------------|------------------------------|---------------------------------|----------|
| **Incidence of shivering** | | | | | |
| | Control | Ketamine | | | |
| Study population | 468 per 1000 | 103 per 1000 (50 to 186) | OR 0.13 (0.06 to 0.26) | 1166 (13 studies) | ⊕⊕⊝ ⊝ low^1 |
| Moderate | 500 per 1000 | 115 per 1000 (57 to 206) | | | |
| **Nausea and vomiting** | | | | | |
| | Control | Ketamine | | | |
| Study population | 123 per 1000 | 89 per 1000 (58 to 136) | OR 0.7 (0.44 to 1.12) | 986 (11 studies) | ⊕⊕⊕ ⊝ low^1 |
| Moderate | 125 per 1000 | 91 per 1000 (59 to 138) | | | |
| **Hypotension** | | | | | |
| | Control | Ketamine | | | |
| Study population | 225 per 1000 | 80 per 1000 (50 to 125) | OR 0.3 (0.18 to 0.49) | 573 (7 studies) | ⊕⊕⊕ ⊝ very low^1 |
| Moderate | 200 per 1000 | 70 per 1000 (43 to 109) | | | |
| **Bradycardia** | | | | | |
| | Control | Ketamine | | | |
| Study population | 136 per 1000 | 22 per 1000 (6 to 76) | OR 0.14 (0.04 to 0.52) | 193 (2 studies) | ⊕⊕⊕ ⊝ very low^1 |
| Moderate | 165 per 1000 | 27 per 1000 (8 to 93) | | | |
| **Hallucination** | | | | | |
| | Control | Ketamine | | | |
| Study population | 0 per 1000 | 0 per 1000 (0 to 0) | OR 4.41 (1.14 to 17.07) | 423 (5 studies) | ⊕⊕⊕ ⊝ very low^1 |
| Moderate | 0 per 1000 | 0 per 1000 (0 to 0) | | | |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.
Table 3. Comparisons of incidence of other side effects

| Side effects     | Number of studies | Ketamine Events/Total | Placebo Events/Total | Risk Ratio (95% CI) |
|------------------|-------------------|-----------------------|----------------------|---------------------|
| Nausea and vomiting | 11                | 48/523                | 57/463               | 0.72 (0.48, 1.08)   |
| Hypotension      | 6                 | 23/302                | 61/271               | 0.28 (0.17, 0.47)   |
| Bradycardia      | 2                 | 3/112                 | 11/81                | 0.18 (0.05, 0.65)   |
| Hallucination    | 5                 | 16/242                | 0/151                | 22.07 (1.31, 370.68) |

Table 4. Episodes of hallucination based on the dose of ketamine.

| Study ID     | Dose of ketamine | Ketamine Events/Total | Placebo Events/Total |
|--------------|------------------|-----------------------|----------------------|
| Ayatollahi 2011 | 0.5mg/kg         | 3/30                  | 0/30                 |
| Han 2010         | 0.4mg/kg         | 2/30                  | 0/31                 |
| Honarmand 2008 | 0.5mg/kg         | 3/30                  | 0/30                 |
| Norouzi 2011 | 0.25mg/kg        | 1/30                  | 0/30                 |
| Norouzi 2011 | 0.5mg/kg         | 4/30                  | 0/30                 |

Figures
Figure 1
Flow diagram showing the process of studies selection.

Figure 2
Risk of bias graph and summary.
Figure 3

Forest plots of effects of ketamine on postanesthesia shivering. CI indicates confidence interval.
### Figure 4

Result of subgroup analysis according to different anesthetic methods. CI, confidence interval; GA, genaral anesthesia; SA, spinal anesthesia.
### 1.7.1 Orthopedic Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| Homarmand 2008   | 7        | 30      | 15     | 30    | 23.6%  | 0.30 (0.10, 0.92) |               |
| Lakhe 2017       | 3        | 30      | 17     | 30    | 19.3%  | 0.09 (0.02, 0.34) |               |
| Norouz 2011      | 41       | 90      | 17     | 30    | 28.3%  | 0.04 (0.02, 0.14) |               |
| Patsal 2016      | 13       | 91      | 15     | 30    | 28.8%  | 0.06 (0.03, 0.18) |               |
| Subtotal (95% CI)| 241      | 494     | 162    | 300   | 100.0% | 0.40 (0.17, 0.91) |               |
| Total events     | 64       | 64      |        |       |        |               |               |

Heterogeneity: $Tau^2 = 0.51$, $P = 0.04$, $I^2 = 67%$

Test for overall effect: $Z = 2.09$ ($P = 0.04$)

### 1.7.2 Abdominal Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| Shamia 2019      | 1        | 40      | 17     | 40    | 17.2%  | 0.03 (0.00, 0.28) |               |
| Wason 2012       | 9        | 50      | 36     | 50    | 83.8%  | 0.08 (0.03, 0.22) |               |
| Subtotal (95% CI)| 90       | 90      | 50     | 90    | 100.0% | 0.07 (0.03, 0.17) |               |
| Total events     | 10       | 53      |        |       |        |               |               |

Heterogeneity: $Tau^2 = 0.00$, $P = 0.63$, $df = 1$, $I^2 = 0%$

Test for overall effect: $Z = 0.22$ ($P = 0.8281$)

### 1.7.3 Cesarean Section Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| Lemos 2017       | 17       | 41      | 23     | 41    | 52.1%  | 0.55 (0.22, 1.32) |               |
| Montali 2016     | 2        | 39      | 28     | 38    | 47.9%  | 0.02 (0.00, 0.10) |               |
| Subtotal (95% CI)| 80       | 80      | 50     | 80    | 100.0% | 0.12 (0.00, 2.99) |               |
| Total events     | 19       | 51      |        |       |        |               |               |

Heterogeneity: $Tau^2 = 5.07$, $P = 0.0003$, $df = 1$, $I^2 = 92%$

Test for overall effect: $Z = 1.30$ ($P = 0.19$)

### 1.7.4 Urological Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| Han 2010         | 1        | 62      | 12     | 63    | 64.9%  | 0.03 (0.00, 0.21) |               |
| Sagri 2007       | 0        | 40      | 22     | 40    | 55.2%  | 0.01 (0.00, 0.18) |               |
| Subtotal (95% CI)| 102      | 102     | 73     | 102   | 100.0% | 0.02 (0.00, 0.10) |               |
| Total events     | 1        | 34      |        |       |        |               |               |

Heterogeneity: $Tau^2 = 0.00$, $P = 0.29$, $df = 1$, $I^2 = 0%$

Test for overall effect: $Z = 4.61$ ($P = 0.0001$)

### 1.7.5 ENT Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| AbdAllah 2014    | 3        | 30      | 12     | 30    | 100.0% | 0.17 (0.04, 0.67) |               |
| Subtotal (95% CI)| 30       | 30      | 12     | 30    | 100.0% | 0.17 (0.04, 0.67) |               |
| Total events     | 3        | 12      |        |       |        |               |               |

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.51$ ($P = 0.01$)

### 1.7.6 Endoscopic Sinus Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| Ayabadali 2011   | 4        | 60      | 9      | 69    | 100.0% | 0.17 (0.05, 0.60) |               |
| Subtotal (95% CI)| 60       | 60      | 9      | 69    | 100.0% | 0.17 (0.05, 0.60) |               |
| Total events     | 4        | 9       |        |       |        |               |               |

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.74$ ($P = 0.006$)

### 1.7.7 Tonsillectomy Surgery

| Study or Subgroup | Ketamine | Control | Events | Total | Weight | OR and 95% CI | OR and 95% CI |
|------------------|----------|---------|--------|-------|--------|---------------|---------------|
| Zehro 2008       | 1        | 40      | 17     | 40    | 100.0% | 0.03 (0.00, 0.28) |               |
| Subtotal (95% CI)| 40       | 40      | 17     | 40    | 100.0% | 0.03 (0.00, 0.28) |               |
| Total events     | 1        | 17      |        |       |        |               |               |

Heterogeneity: Not applicable

Test for overall effect: $Z = 3.16$ ($P = 0.002$)

Test for subarous differences: $Chi^2 = 14.96$, $df = 6$, $P = 0.029$, $I^2 = 59.6%$

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**Figure 5**

Result of subgroup analysis according to different doses of ketamine administrated. CI indicates confidence interval.
Result of subgroup analysis according to different types of surgeries. CI indicates confidence interval.

Forest plots of effects of ketamine on postanesthesia shivering compared with other study drugs. CI indicates confidence interval.

**Supplementary Files**

This is a list of supplementary files associated with the primary manuscript. Click to download.

1.grd

PRISMA checklist.doc
