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Review

# Meta-analysis of randomized controlled trials on the efficacy and safety of ondansetron in preventing postanesthesia shivering

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## HIGHLIGHTS

- Compared with placebo, ondansetron was associated with a significant reduction of PAS.
- Meta-analysis with all five studies suggested that ondansetron and meperidine have similar effects on the prevention of PAS.
- More high quality RCTs are still warranted to confirm the effects of different doses of ondansetron on PAS.

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## ABSTRACT

*Objectives:* Considerable controversy exists regarding the efficacy of ondansetron in preventing postanesthesia shivering (PAS). We performed a meta-analysis of randomized controlled trials to examine the controversy.

*Materials and Methods:* Randomized controlled trials assessing the effect of ondansetron on the prevention of PAS were identified from electronic databases (PubMed and EMBASE). The meta-analysis was performed with the fixed-effect model or random-effect model according to heterogeneity.

*Results:* Twelve trials randomized clinical trials met the inclusion criteria including 1205 subjects. Compared with placebo (saline), ondansetron was associated with a significant reduction of PAS (relative risk 0.33; 95% confidence interval, 0.21–0.51), Substantial heterogeneity was observed between trials ($P = 0.0002$; $I^2 = 71\%$). Trial sequential analysis showed that the cumulative Z-curve crossed the trial sequential monitoring boundary for benefit establishing sufficient and conclusive evidence. Meta-analysis with all five studies using a fixed-effects model suggested that ondansetron and meperidine have similar effects on the prevention of PAS (relative risk, 0.86; 95% confidence interval, 0.66–1.11), the heterogeneity was not significant ($P = 0.34$; $I^2 = 11\%$). No significant association of ondansetron with bradycardia was found both comparison with placebo and meperidine.

*Conclusions:* Treat with ondansetron is safe, and may reduce PAS. This finding encourages the use of ondansetron to prevent PAS, but, more high quality randomized clinical trials are still warranted to confirm the effects of different doses of ondansetron on PAS.



## 1. Introduction

Shivering is one of the most common complications of surgery [1,2]. The incidence of postoperative shivering varies from 5% to 65% after general or regional anesthesia [3]. It is primarily a response to the hypothermia that occurs during anesthesia practice. The main cause of hypothermia after anesthesia is the induced-hypothermia during surgery. It can cause serious complications such as increased mortality rate, cost and prolonged hospital stay. The prevention of postanesthesia shivering (PAS) is thus clearly an important priority on hospital resources. Unfortunately, in a survey on 33 clinical problems, anesthesiologists ranked PAS 8th when its frequency was considered and 21st when asked about the importance of preventing this complication [4]. This suggests that most anesthesiologists do not consider shivering to be a true medical problem.

In recent decades, concern has mounted regarding the

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premature incidence associated with PAS, many pharmacologic interventions have been used to prevent the development of PAS, for example, alfentanil, fentanyl, morphine, nalbuphine, and magnesium [5,6]. However, the effect of individual components or interactions between drugs is still limited. All of them are not free of side effects. Particularly, ondansetron seems to be with great promise to prevent PAS.

A previous meta-analysis of ondansetron for prevention of PAS including eight randomized controlled trials (RCTs) was published in 2016 [7]. The analysis showed that intravenous ondansetron is associated with a significant reduction in the incidence of PAS, with a relative risk (RR) of 0.33 (95% confidence interval [CI] 0.19–0.58). But this meta-analysis included some clinical studies which had a modest sample size. Moreover, the data from studies included by previous meta-analysis were limited to January 2015. Recently, an increasing number of studies on the efficacy of ondansetron on the prevention of PAS have been published [8–11]. Results from RCTs are still controversial. Therefore, we performed an updated meta-analysis only based on RCTs to re-evaluate and quantify the preventive effect of ondansetron on PAS.

## 2. Materials and Methods

### 2.1. Data sources and searches

The search strategy was conducted according to the *Cochrane Handbook for Systematic Reviews* [12]. We performed a systematic search of PubMed, and EMBASE through July 2016. Search terms included: ondansetron, shivering. Results were limited to human subjects and RCTs. To maximize the sensitivity, no language restriction was used. In addition, we reviewed the references lists of obtained articles to identify additional relevant studies. We did not include abstracts or meeting proceedings. This search strategy was performed iteratively until no new potential citations could be found on review of the reference lists of retrieved articles.

### 2.2. Study selection

Studies were selected for the meta-analysis if they fulfilled the following entry criteria: (1) the study had a RCT design; (2) randomly assigned to receive ondansetron or placebo (saline) or meperidine; (3) the enrolled patients underwent a surgical operation under the neuraxial anesthesia or general anesthesia; and (4) study outcomes had to report on PAS. Additionally, we excluded animal studies, commentaries and letters without sufficient data.

### 2.3. Data extraction

All data were independently abstracted in duplicate by two investigators (YT, and BPY). Discrepancies were resolved by consensus. When necessary, the original authors were contacted for Supplementary Information. The following data were extracted from each study: study design, patient characteristics, surgical setting, anesthetic type, comparisons, time of drug administration, and definition of PAS.

### 2.4. Risk of bias assessment

The risk of bias has been assessed independently by two authors (YT, and KL) according to the Cochrane risk-of-bias tool [13]. A third author was consulted if any disagreement occurred. When necessary, the original authors were contacted. Trials that met following eligibility criteria have been assessed: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and personnel); (3) detection bias (blinding of outcome assessment); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective reporting); and (6) other bias. The trials were graded as 'unclear', 'low', or 'high' risk of bias.

### 2.5. Grading quality of evidence

The quality of evidence was evaluated independently by two authors (YT, and KL) according to GRADE methodology. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were evaluated and classified as very low, low, moderate, or high. Summary tables were constructed using the GRADE Profiler (GRADE pro, version 3.6.1) [14].

### 2.6. Data synthesis and statistical analysis

The statistical significant level for a two-tailed test for each primary hypothesis was 0.05. All of the statistical analyses were conducted with the Review Manager version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and Stata version 12 (Stata Corporation, College Station, TX, USA). The results were expressed as RR, with 95% CI (using a fixed-effect approach) [15]. But if there was heterogeneity, the following methods were used to deal with it: (a) subgroup analysis (by type of anesthesia and dosage of ondansetron); (b) sensitivity analysis performed by excluding trials which potentially biased the results. If heterogeneity still potentially existed, the DerSimonian and Lair random-effects model was used. A test for heterogeneity, defined as variation among the results of individual trials for a given treatment beyond that expected from chance, was used to assess whether the magnitude of a given preventive effect varied between the trials. We tested heterogeneity between trials results using $I^2$ and $\chi^2$ test; $I^2$ less than 50% was considered to have non-important heterogeneity [16]. We performed the Begg rank correlation test and Egger's regression test to visualize a possible asymmetry [17,18]. In the case of publication bias, we used the "trim-and-fill" method to compute risk estimates corrected for this bias [19]. On the other hand, when the limited number (below 10) of studies was included in each analysis, publication bias was not assessed [20].

### 2.7. Trial sequential analysis

In a single randomized clinical trial, repeated significance testing on accumulating data is known to inflate the overall risk of type I error [21,22]. To deal with this problem, statistical monitoring boundaries can be used to decide whether a single trial could be terminated early because the P value was sufficiently small to show the anticipated effect or for futility. TSA has been introduced to assess the risk of type I errors by combining an estimation of information size with an adjusted threshold for statistical significance in the cumulative meta-analysis. The latter termed trial sequential monitoring boundaries, adjusts the confidence intervals and reduces type I errors [21,23]. Boundaries for concluding superiority or inferiority or futility were calculated with the O'Brien-Fleming $\alpha$-spending function. When the cumulative z curve crosses the trial sequential monitoring boundary, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed [24]. If the z curve does not cross any of the boundaries and the required information size has not been reached, evidence to reach a conclusion is insufficient [25].

Applying this method, we calculated the data on the effect of ondansetron on preventing PAS. Our assumptions included two-sided testing, type I error of 5%, and power of 80%. Diversity-adjusted information size was calculated based on the absolute