Efficacy of ondansetron for spinal anesthesia during cesarean section: a meta-analysis of randomized trials

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Abstract
Objective: To investigate the efficacy and safety of ondansetron during cesarean section under spinal anesthesia.

Methods: We sought randomized controlled trials (RCTs) on ondansetron during spinal anesthesia for cesarean section in The Cochrane Library, PubMed, MEDLINE, and Web of Science from their inception to September 2016.

Results: Altogether, 21 RCTs were included in this study. Meta-analysis showed that the ondansetron group had a lower incidence of nausea/vomiting and bradycardia than the placebo group during cesarean section under spinal anesthesia [relative risk (RR) = 0.43, 95% confidence interval (CI) (0.36, 0.51) and RR = 0.45, 95% CI (0.26, 0.80), respectively]. There were no significant differences in the incidences of pruritus, hypotension, or shivering during cesarean section under spinal anesthesia [RR = 0.92, 95% CI (0.83, 1.02); RR = 0.72 (0.50, 1.06), 95% CI (0.50, 1.06); and RR = 0.89, 95% CI (0.71, 1.11), respectively].

Conclusion: Ondansetron effectively reduces the incidences of nausea/vomiting and bradycardia under spinal anesthesia during cesarean section.

Keywords
Ondansetron, spinal anesthesia, cesarean section, meta-analysis, RCT, shivering, nausea/vomiting

Introduction
The focus of obstetric anesthesia is to ensure the safety of mother and child. Therefore, it is essential to select the anesthesia and its administration carefully. Spinal anesthesia, because it is a simple medication that has little impact on the fetus, has become a preferred choice for cesarean section.

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The Apgar score of the fetus under spinal anesthesia for cesarean section was higher than that under general anesthesia.\textsuperscript{1,2} Although spinal anesthesia is ideal for cesarean section, it also causes adverse reactions. Spinal anesthesia can lead to severe bradycardia or hypotension in puerperae who display unstable hemodynamics.\textsuperscript{3} Yeh et al.\textsuperscript{4} found that, because of the special physiological characteristics of obstetrics, the postoperative incidence of pruritus may be as high as 85\% in patients who have epidural analgesia with morphine after cesarean section. In addition, according to Teresa and Cartoon,\textsuperscript{5} the incidence of shivering during cesarean section is as high as 57\%. Patient-controlled intravenous analgesia is commonly used after cesarean section. As most analgesic drugs are opioids, however, they often trigger nausea, vomiting, and other adverse puerperal reactions after cesarean section.

Currently, ondansetron is widely used during cesarean section, and numerous related high-quality studies have been published. To date, however, there has been no meta-analysis of ondansetron used during cesarean section under spinal anesthesia. We therefore conducted a meta-analysis to investigate the efficacy and safety of ondansetron during cesarean section under spinal anesthesia.

**Materials and methods**

**Inclusion criteria**

- **Study design:** randomized controlled trials (RCTs), regardless of whether allocation concealment and blinding were used.
- **Study subjects:** patients given ondansetron during cesarean section under spinal anesthesia.
- **Interventions:** (1) ondansetron administration (experimental group); (2) administration of a placebo (control group).
- **Outcome measures:** Main: incidence of nausea/vomiting. Secondary: incidence of pruritus, bradycardia, shivering, hypotension.

**Exclusion criterion**

- Literature had no specific data or full text.

**Search strategy**

The Cochrane Library, PubMed, MEDLINE, and Web of Science were searched for RCTs studying ondansetron given under spinal anesthesia for cesarean section from the database inception to September 2016. English search terms included “randomized controlled trial,” “controlled clinical trial,” “cesarean section,” “ondansetron,” “epidural,” “spinal,” among others. For example, a specific search strategy in PubMed is described in Box 1.

#1 epidural
#2 subarachnoid space
#3 spinal
#4 ondansetron
#5 cesarean section
#6 randomized controlled trial
#7 #1 OR #2 OR #3
#8 #4 AND #7 AND #5 AND #6

**Literature screening, data extraction, and quality evaluation.** Two reviewers independently selected the literature, extracted the data, and assessed the quality according to the inclusion and exclusion criteria. When there was a disagreement, it was resolved by further discussion. The contents of the data extraction included the title, author, publication year, study objects and characteristics, sample size, interventions, outcome measures and measurement results, quality evaluation, and other related contents.
Jadad scores were performed in terms of the randomization method employed and if there was allocation concealment. Also considered were the presence of blinding, withdrawal, or dropouts.

**Statistical analysis**

A meta-analysis was performed via using RevMan 5.2 provided by the Cochrane Collaboration. Enumeration data were presented as relative risk (RR) or odds ratio (OR) with a 95% confidence interval (CI). Measurement data were expressed as the mean difference (MD) with a 95% CI. The heterogeneity among included studies was tested by the $\chi^2$ test. If homogeneity was found ($P > 0.10$, $I^2 < 50\%$), a fixed-effects model was employed for the meta-analysis. If $P < 0.1$ and $I^2 \geq 50\%$, we further analyzed the source of heterogeneity. A random-effects model for the meta-analysis was used in the absence of significant clinical heterogeneity, and a subgroup analysis or descriptive analysis was used in the presence of significant clinical heterogeneity.

**Results**

**Literature search results**

Initially, 728 related articles were detected, with 21 RCTs finally enrolled after step-by-step screening. The literature screening process and results are shown in Figure 1.

For the basic characteristics of the included studies see Table 1. The methodological quality assessment of the included studies is also shown in Table 1 (Jadad score).

**Meta-analysis results**

Maternal side effects, including hypotension, nausea/vomiting, and shivering, were compared between the ondansetron and placebo groups. There were no significant differences in the incidences of pruritus, hypotension, or shivering during cesarean

![Figure 1. Flow diagram for the study. RCTs, randomized controlled trials.](image-url)
section under spinal anesthesia \([RR = 0.92, 95\% \text{ CI } (0.83, 1.02); \text{ RR } = 0.72, 95\% \text{ CI } (0.50, 1.06); \text{ and RR } = 0.89, 95\% \text{ CI } (0.71, 1.11), \text{ respectively}] \) (Figure 2, Figure 3).

**Table 1.** Characteristics and Jadad scores of the included studies in the meta-analysis.

| Study         | Country   | Head count (E/P) | Ondansetron treatment targeta | Jadad score |
|---------------|-----------|-----------------|------------------------------|-------------|
| Abouleish 1999| USA       | 74 (36/38)      | 2.3                          | 6           |
| Browning 2013 | Australia | 116 (56/60)     | 4                            | 5           |
| Charuluxananan 2003 | Thailand       | 120 (60/60)     | 1.2                          | 5           |
| El-Deeb 2011 | Egypt     | 300 (150/150)   | 2                            | 5           |
| Fattahi 2015  | Iran      | 212 (106/106)   | 2                            | 6           |
| Koju 2015     | Nepal     | 50 (25/25)      | 2.4                          | 5           |
| Marciniak 2015 | Poland       | 70 (36/34)      | 1.25                         | 6           |
| Moustafa 2016 | Egypt     | 60 (24/28)      | 1.24                         | 6           |
| Ortiz-Gómez 2014 | Spain       | 64 (32/32)      | 1.2                          | 5           |
| Pan 1996      | Virginia  | 32 (16/16)      | 2                            | 5           |
| Pan 2001      | Canada    | 105 (54/51)     | 2                            | 5           |
| Rashad 2013   | Egypt     | 40 (20/20)      | 2.45                         | 5           |
| Sahoo 2012    | India     | 52 (26/26)      | 2.4                          | 5           |
| Sarvela 2006  | Finland   | 59 (30/29)      | 1.2                          | 6           |
| Siddik-Sayyid 2007 | Lebanon     | 87 (42/45)      | 1.2                          | 5           |
| Terkawi 2015  | USA       | 86 (44/42)      | 1.23                         | 5           |
| Trabelsi 2015 | Tunisia   | 80 (40/40)      | 2.35                         | 6           |
| Wang M 2014   | China     | 60 (30/30)      | 2.35                         | 5           |
| Wang Q 2014   | China     | 65 (33/32)      | 2.35                         | 5           |
| Yazgi 2002    | Lebanon   | 100 (50/50)     | 1.2                          | 5           |
| Yeh 2000      | Taiwan    | 40 (20/20)      | 1                            | 5           |

E/P: intervention group (ondansetron)/placebo (saline) group

\(^a\)1, Pruritus; 2, nausea/vomiting; 3, hypotension; 4, shivering; 5, bradycardia

**Figure 2.** Studies reporting pruritus with ondansetron administration.

**Nausea/vomiting.** A total of 18 RCTs including 1630 patients were enrolled in this study. The incidences of nausea/vomiting caused by spinal anesthesia during cesarean section
were reported. The meta-analysis results of the fixed-effects model showed that the incidence of nausea/vomiting was significantly lower in the ondansetron group than in the placebo group \( RR = 0.43, 95\% \text{ CI} (0.36, 0.51), P < 0.00001 \) (Figure 4).

Bradycardia. A total of 7 RCTs, with 449 people, were included in the study. Bradycardia triggered by spinal anesthesia during cesarean section was reported. The meta-analysis results of the fixed-effects model showed that the incidence of bradycardia in the ondansetron group was statistically significantly lower than that in the placebo group \( RR = 0.45, 95\% \text{ CI} (0.26, 0.80), P = 0.006 \) (Figure 4(c)).

**Discussion**

We conducted subgroup analyses on the 21 included studies according to the outcome indicators of the control group. The results showed that the ondansetron group experienced significantly lower incidences of bradycardia and nausea/vomiting than the placebo group under spinal anesthesia during cesarean section. The two groups,
however, differed little in their incidences of pruritus, hypotension, or shivering.

Ondansetron is a potent, highly selective serotonin (5-HT3) receptor antagonist. It can prevent the combination of 5-HT released by activated platelets with 5-HT3 receptors in the vagal nerve endings of the left ventricle, attenuate Bezold–Jarisch reflexes produced by left ventricular mechanoreceptors stimulated by 5-HT, inhibit further expansion of peripheral blood vessels, and increase venous return, thereby reducing the incidence of hypotension.27,28

Owczuk et al. 29 observed that intravenously injecting 8 mg ondansetron 5 min before spinal anesthesia can curb the reduction of systolic blood pressure without affecting the diastolic blood pressure or heart rate. Sahoo et al.14 reported that intravenous injection of 8 mg ondansetron 5 min before spinal anesthesia can significantly reduce the incidences of hypotension, nausea, and vomiting in puerperae undergoing spinal anesthesia and reduce the use of vasoconstrictor drugs. Ondansetron is structurally similar to 5-HT3 and has a high selectivity of dense region in the 5-HT3 receptor. It can block vomiting reflexes caused by the 5-HT3 receptor-induced vagal stimulation and inhibit 5-HT release in the fourth ventricle caused by vagal excitement, effectively controlling vomiting. Several studies have demonstrated that ondansetron can significantly reduce the incidence of postoperative nausea/vomiting.30

Giving ondansetron to prevent pruritus and shivering is still debatable. A possible mechanism for initiating pruritus is opioid spread via cerebrospinal fluid to the head, where it acts on the medulla oblongata and spinal L receptors or 5-HT3 receptors. Ondansetron, a selective 5-HT3 receptor antagonist, is commonly used to prevent or treat nausea/vomiting after surgery and chemotherapy. Several clinical studies have confirmed8,31 that it can effectively control pruritus due to intrathecal injection of morphine. In the present study, ondansetron did
not effectively prevent skin pruritus caused by intrathecal injection of sufentanil, possibly because the ondansetron had not yet reached the location to make the difference. In addition to medulla oblongata and 5-HT3 receptors, opioids have many other ways to produce pruritus. Ondansetron can effectively prevent morphine- or fentanyl-induced skin pruritus. Yazigi et al.\textsuperscript{32} believed that ondansetron’s antagonism cannot be used effectively as sufentanil has higher fat solubility than the former two drugs, thus acting on the medulla oblongata and spinal cord more rapidly.

Shivering is a common complication of anesthesia. Currently, the mechanism of postoperative shivering is not entirely clear. It may relate to dysfunctional temperature regulation, or it may be associated with the recovery sequence of the nerve center after anesthesia. One study showed that 5-HT secreted by the hypothalamus plays an important role in thermoregulation.\textsuperscript{33} In animal models, intravenous injection of 5-HT into mice can induce hemangiectasis, causing shivering,\textsuperscript{34} suggesting that the 5-HT system plays an important role in controlling postoperative shivering. Studies have shown that 5-HT3 antagonists play a part in preventing postoperative shivering, and its mechanism may be associated with inhibition of 5-HT in the preoptic anterior hypothalamus.\textsuperscript{35}

The adverse reactions of ondansetron often present as neurological symptoms (e.g., headache, dizziness) or digestive symptoms (e.g., abdominal discomfort, abnormally elevated alanine aminotransferase), but the overall incidences are relatively low.

There are some limitations of this systematic review. (1) The included studies differ in regard to the patient’s position, the anesthesia puncture points, measurement indicators, and use of drugs—each of which could affect the conclusions of this study. (2) The heterogeneity of the included studies is distinct, which may influence the reliability of the meta-analysis. (3) RCTs included in some subgroup analyses were not enough. (4) Some RCTs did not give enough information to judge the scientific rationality of the trial, and there was a possibility of implementation biases and measurement biases. Meanwhile, as we only covered the published literature, the search strategy and publication bias could also affect the results of this study.

In summary, ondansetron can effectively reduce the incidences of nausea, vomiting, and bradycardia during spinal anesthesia for cesarean section, and its safety is relatively good. Because of the small sample size of this study, this conclusion remains to be confirmed by studies with a larger sample size and multi-center studies.

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Declaration of conflicting interest
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