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# Intrathecal Sufentanil Does Not Reduce Shivering During Neuraxial Anesthesia: A Meta-Analysis

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Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Background:** We performed this meta-analysis to evaluate the efficacy of intrathecal sufentanil in preventing shivering during neuraxial anesthesia.


**Material/Methods:** We searched the Cochrane Library, PubMed, and Embase for all randomized controlled trials (RCT) on use of intrathecal sufentanil for preventing shivering during neuraxial anesthesia. References of retrieved articles were also screened. The quality of the studies was evaluated by the method recommended by the Cochrane Collaboration. Meta-analysis was conducted using the Cochrane Collaboration's RevMan 5.3 software. The primary outcome was incidence and severity of shivering, and the secondary outcomes were drug-related complications of pruritus, nausea, vomiting, hypotension, and bradycardia.

**Results:** Eight original RCTs investigating a total of 1032 patients, of whom 599 received sufentanil and 473 received placebo, met the inclusion criteria. Compared to the placebo group, sufentanil did not reduce incidence of shivering (OR, 0.60; 95% CI, 0.35 to 1.01; P=0.06), but it increased the incidence of pruritus (OR, 12.52; 95% CI, 5.07 to 30.91; P<0.00001). Compared to the placebo group, sufentanil did not increase the incidence of nausea (OR, 0.69; 95% CI, 0.41 to 1.16; P=0.16), hypotension (OR, 0.93; 95% CI, 0.62 to 1.41; P=0.74), or bradycardia (OR, 0.86; 95% CI, 0.41 to 1.82; P=0.70). In addition, sufentanil reduced the incidence of vomiting during neuraxial anesthesia (OR, 0.45; 95% CI, 0.22 to 0.92; P=0.03).

**Conclusions:** Neither epidural nor subarachnoid intrathecal sufentanil reduced shivering during neuraxial anesthesia, but it did increase the incidence of pruritus.

**MeSH Keywords:** **Meta-Analysis • Shivering • Sufentanil**

**Full-text PDF:** <http://www.medscimonit.com/abstract/index/idArt/897293>

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## Background

Shivering is one of the leading causes of discomfort for patients during neuraxial anesthesia. It may be defined as an involuntary, repetitive activity in skeletal muscles. Shivering usually occurs as a thermoregulatory response to cold, although non-thermoregulatory shivering may also occur. The incidence of shivering related to neuraxial anesthesia ranges from 40% to 64% [1]. Shivering can double oxygen consumption and carbon dioxide production, although the increase in the latter is typically much smaller. Plasma catecholamines and cardiac output increase in response to this physiological stress. Shivering movements during neuraxial anesthesia may interfere with monitoring of blood pressure, electrocardiography, and pulse oximetry, as well as reducing patient comfort and satisfaction [2]. Warming is the most effective nonpharmacologic antishivering intervention in the postoperative period [3]. The use of drugs is simple and convenient in practice, and intrathecal anti-shivering drugs can significantly improve the anesthetic properties and reduce shivering and other adverse effects caused by drugs [2,4–7].

Sufentanil is an opioid, which stands out from the other drugs in this group because of its fast onset and strength of analgesic action; compared to fentanyl, the potency of intravenous sufentanil is 5 to 10 times higher. It has been registered for intravenous, epidural, and subarachnoid administration [8]. It is considered to be a suitable opioid for extradural administration due to its rapid onset of action and lipid solubility, which theoretically reduces rostral spread in cerebrospinal fluid. Sufentanil intrathecal administration can significantly shorten the onset time of anesthesia, improve the analgesic property of intrathecal anesthesia, and prolong the duration of analgesia [9–13]. Hassani et al. [14] found that the effect of the addition of sufentanil to maintain hemodynamic stability was similar to the effect of fentanyl. Intrathecal sufentanil added to bupivacaine, as compared with fentanyl, may prolong duration of analgesia, facilitate the spread of the sensory block, increase mean pulse oximetry levels, and reduce overall adverse effects. De Figueiredo [15] reported that the addition of sufentanil to hyperbaric bupivacaine and morphine during spinal anesthesia for cesarean section decreased the incidence of shivering during the immediate postoperative period; however, some other studies found that intrathecal sufentanil did not reduce shivering [16–18]. Hoshijima et al. [19] found that remifentanyl was associated with an increased incidence of postoperative shivering compared with alfentanil or fentanyl, but no significant difference was seen when compared with sufentanil. As sufentanil was not compared to placebo in their meta-analysis, it is necessary to determine whether intrathecal sufentanil can reduce shivering. Therefore, we performed this meta-analysis to evaluate the efficacy of intrathecal sufentanil in preventing shivering during neuraxial anesthesia.

## Material and Methods

We performed this meta-analysis based on the QUORUM guidelines (Quality of Reporting of Meta-analyses) [20] and the recommendations of the Cochrane Collaboration [21].

### Inclusion and exclusion criteria

#### Study design

We included randomized controlled trials (RCTs) with a randomized, placebo-controlled, parallel design.

#### Participants

We included studies using neuraxial anesthesia (epidural anesthesia, combined spinal epidural anesthesia, subarachnoid anesthesia) of the surgical patients, no sex-limited, ASA I–II, no allergy to sufentanil, no organ dysfunction, and no neuraxial anesthesia related contraindication.

#### Interventions

We included studies with an experimental group receiving intrathecal sufentanil before the start of the operation, in which the dose of sufentanil was not restricted, and the control group had the same route of administration as the sufentanil group.

#### Outcome

We included studies in which the primary outcome was the incidence and severity of intraoperative and postoperative shivering, and the secondary outcome was drug-related complications such as pruritus, nausea, vomiting, hypotension, and bradycardia. Studies were excluded for the following reasons: unrelated papers, not in English, combination studies, lacking detailed data, group number less than 10, and using 2 or more anti-shivering drugs given intrathecally or in other ways (venous and oral).

### Data sources and searches

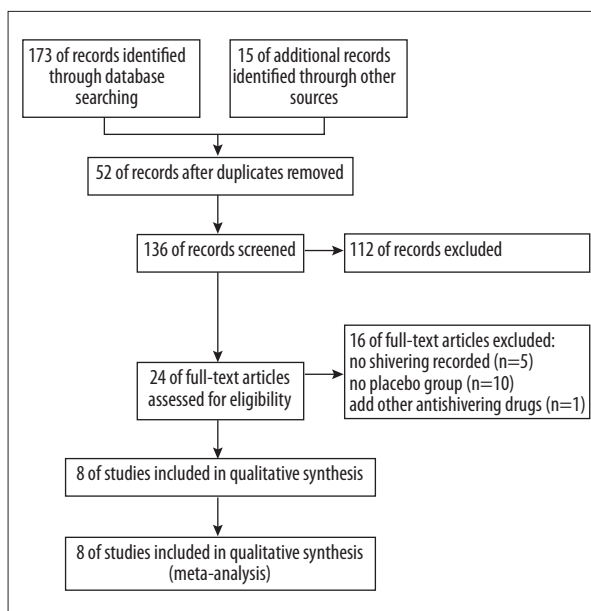
We searched PubMed, EMBASE, and the Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms were: “sufentanil” AND “shivering”. Searches were limited to randomized controlled trials in English and were performed for all types of publications. We also searched the references of retrieved articles and contacted the authors to request additional data when key information relevant to the meta-analysis was missing. The full search strategy was developed from PubMed and was adapted for the other databases.

**Data extraction**

Two of us (Lin and Li) independently screened the titles and abstracts of potentially eligible studies. The full-text articles were examined independently by 2 of us (Gao and Zhao) to determine whether they met the inclusion criteria. Two of us (Lin and Liu) independently extracted data (study characteristics and results) using data extraction forms, and then the collected data were entered into RevMan 5.3. All discrepancies were rechecked and consensus was achieved by discussion. The primary outcome was the incidence and severity of shivering, and the secondary outcomes were pruritus, nausea, vomiting, hypotension, and bradycardia.

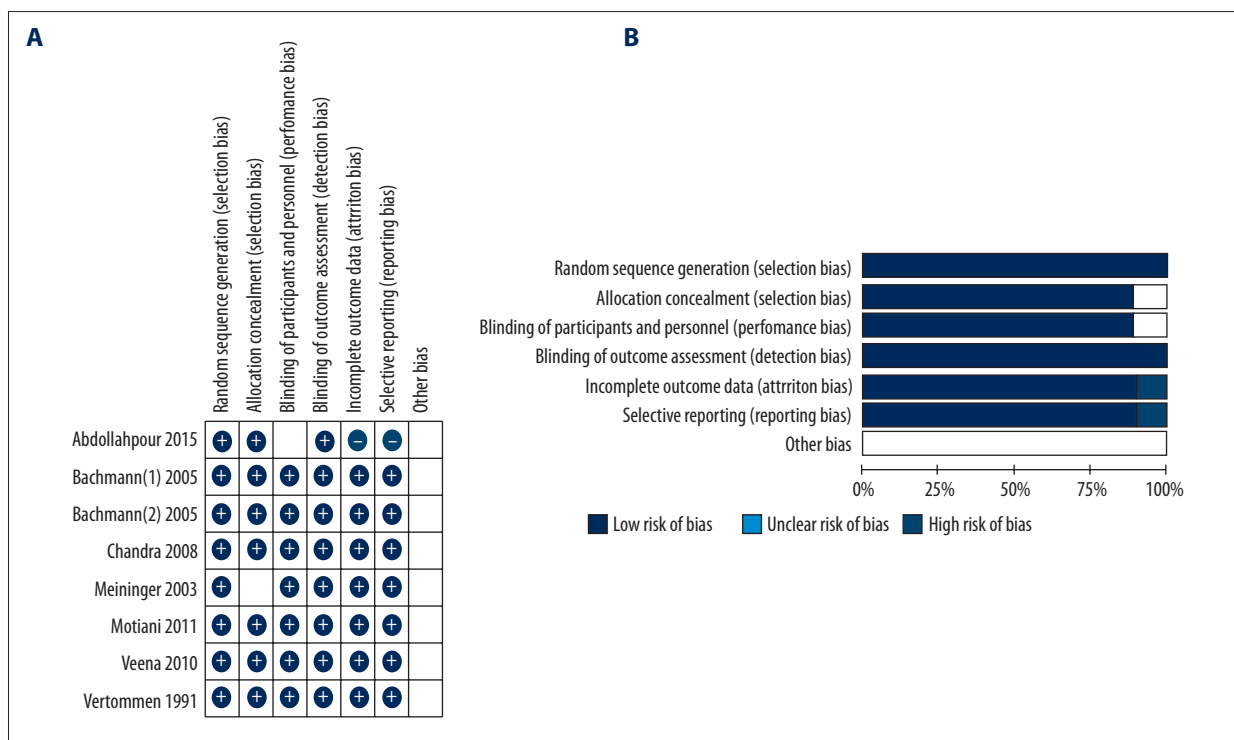
**Data collection and analysis**

Meta-analysis was conducted using the Cochrane Collaboration's RevMan5.3 software. For all included studies, odds ratio (OR) was used in evaluating incidence of shivering and the standardized mean difference (SMDs) was used as effect measures to assess severity of shivering and other outcomes, as necessary. When these values were shown in a graph without any description of absolute value, we first tried to contact the authors. Measurements from the graph were used if we could not get data from the authors. It was converted into standard deviation only when the standard error was reported.  $I^2$  statistics were used to measure heterogeneity of the RCTs. If the



**Figure 1.** Flow chart of included studies.

$I^2$  value was less than 50%, a fixed-effects model was used. If the  $I^2$  value was 50% or more, a random-effects model was used [22]. Visual assessment of the funnel plot calculated by RevMan was used to investigate potential publication bias, which can result in asymmetrical funnel plots [23].



**Figure 2.** (A) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

**Table 1.** Characteristics of the trials included in the meta-analysis.

Source	Type of surgery and Type of anesthesia	Comparisons (no. patients)	Method of shivering score	Method quality Jadad score
Vertommen 1991 [24]	Labor EA	Bupivacaine 12.5 mg + epinephrine 12.5 µg + sufentanil 10 µg (344) Placebo (318)	Yes/no	3
Meininger 2003 [16]	Caesarean section SA	Mepivacaine 60 mg + sufentanil 2.5 µg (20) Mepivacaine 60 mg + sufentanil 5 µg (20) Placebo (20)	Yes/no	4
Bachmann(1) 2005 [17]	Caesarean section EA	Ropivacaine 120 mg + sufentanil 10 µg (20) Ropivacaine 120 mg + sufentanil 20 µg (20) Placebo (20)	Yes/no	4
Bachmann(2) 2005 [25]	Caesarean section EA	Ropivacaine 120 mg + sufentanil 10 µg (20) Ropivacaine 120 mg + sufentanil 20 µg (20) Placebo (20)	Yes/no	4
Chandra 2008 [26]	Caesarean section SA	Bupivacaine 7.5 mg + sufentanil 5 µg (20) Placebo (20)	Yes/no	4
Veena 2010 [27]	Caesarean section SA	Bupivacaine 12 mg + sufentanil 10 µg (20) Placebo (20)	Yes/no	3
Motiani 2011 [28]	Lower limb surgeries SA	Bupivacaine 15 mg + sufentanil 5 µg (30) Placebo (30)	Yes/no	4
Abdollahpour 2015 [18]	Caesarean section SA	Bupivacaine 12.5 mg + sufentanil 1.5 µg (25) Placebo (25)	Yes/no	4

EA – epidural anesthesia; SA – combined spinal epidural anesthesia or subarachnoid anesthesia.

## Results

### Flow chart

The literature search yielded 173 citations. Initially, 24 publications met our inclusion criteria. An additional 16 papers were excluded on more detailed review for the following reasons: no shivering recorded (n=5), no placebo group (n=10), and added other anti-shivering drugs (n=1). The remaining 8 studies met our selection criteria and were included in the meta-analysis [16–18,24–28] (Figure 1).

### Risk of bias assessment

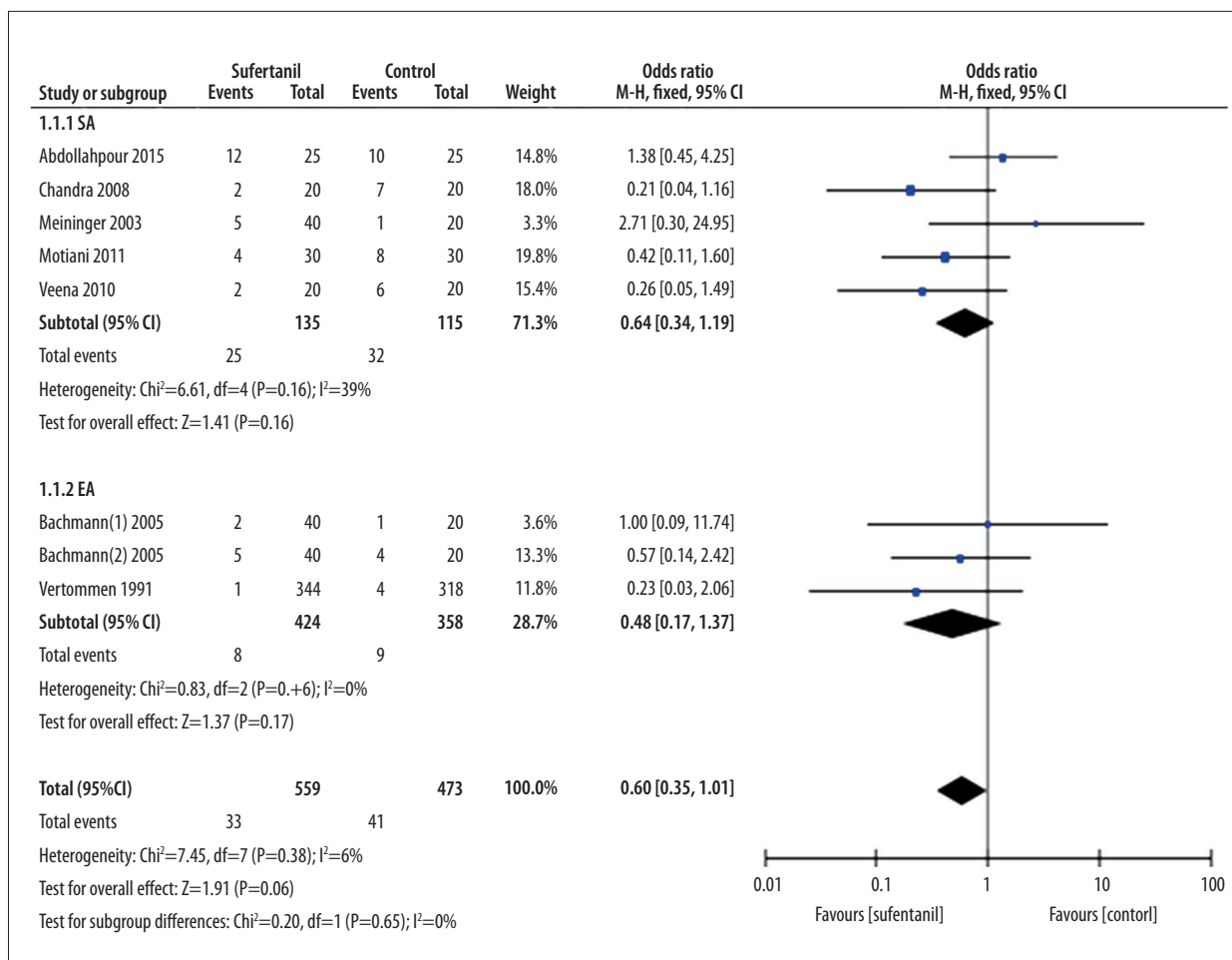
All RCTs were conducted using quality assessment based on Cochrane risk of bias assessment tools (Figure 2).

### Included studies characteristics

Table 1 shows the doses of sufentanil, sample sizes, anesthetic technique, local anesthetics, and Jadad score of the studies. The 8 original RCTs investigated a total of 1032 patients; 599 received sufentanil and 473 received placebo. There were 6 studies with moderate quality (score 4) and 2 studies with score 3. The dosage of sufentanil ranged from 1.5 µg to 20 µg. No study reported the severity of shivering or respiratory depression.

### Incidence of shivering

According to  $\chi^2$  test of heterogeneity ( $I^2=6\%$ ), a fixed-effects model was used to evaluate the incidence of shivering. Compared to the placebo, intrathecal sufentanil did not reduce shivering during neuraxial anesthesia (OR, 0.60; 95% CI, 0.35 to 1.01;  $P=0.06$ ). Subgroup analysis suggested that neither



**Figure 3.** Forest plot of comparison: sufentanil vs. placebo. Outcome: shivering. EA – epidural anesthesia; SA – combined spinal epidural anesthesia or subarachnoid anesthesia.

epidural nor subarachnoid intrathecal sufentanil reduced shivering during neuraxial anesthesia (OR, 0.48; 95% CI, 0.17 to 1.37; P=0.17), (OR, 0.64; 95% CI, 0.34 to 1.19; P=0.16) (Figure 3)

**Incidence of pruritus**

According to  $\chi^2$  test of heterogeneity (I<sup>2</sup>=0%), a fixed-effects model was used to evaluate the incidence of pruritus. Compared to the placebo, intrathecal sufentanil increased the incidence of pruritus during neuraxial anesthesia (OR, 12.52; 95% CI, 5.07 to 30.91; P<0.00001) (Figure 4).

**Incidence of nausea**

According to  $\chi^2$  test of heterogeneity (I<sup>2</sup>=46%), a fixed-effects model was used to evaluate the incidence of nausea. Compared to the placebo, intrathecal sufentanil did not increase the incidence of nausea during neuraxial anesthesia (OR, 0.69; 95% CI, 0.41 to 1.16; P=0.16) (Figure 5).

**Incidence of vomiting**

According to  $\chi^2$  test of heterogeneity (I<sup>2</sup>=1%), a fixed-effects model was used to evaluate the incidence of vomiting. Compared to the placebo, intrathecal sufentanil reduced the incidence of vomiting during neuraxial anesthesia (OR, 0.45; 95% CI, 0.22 to 0.92; P=0.03) (Figure 6).

**Incidence of hypotension**

According to  $\chi^2$  test of heterogeneity (I<sup>2</sup>=12%), a fixed-effects model was used to evaluate the incidence of hypotension. Compared to the placebo, intrathecal sufentanil did not increase the incidence of hypotension during neuraxial anesthesia (OR, 0.93; 95% CI, 0.62 to 1.41; P=0.74) (Figure 7).

**Incidence of bradycardia**

According to  $\chi^2$  test of heterogeneity (I<sup>2</sup>=0%), a fixed-effects model was used to evaluate the incidence of bradycardia.

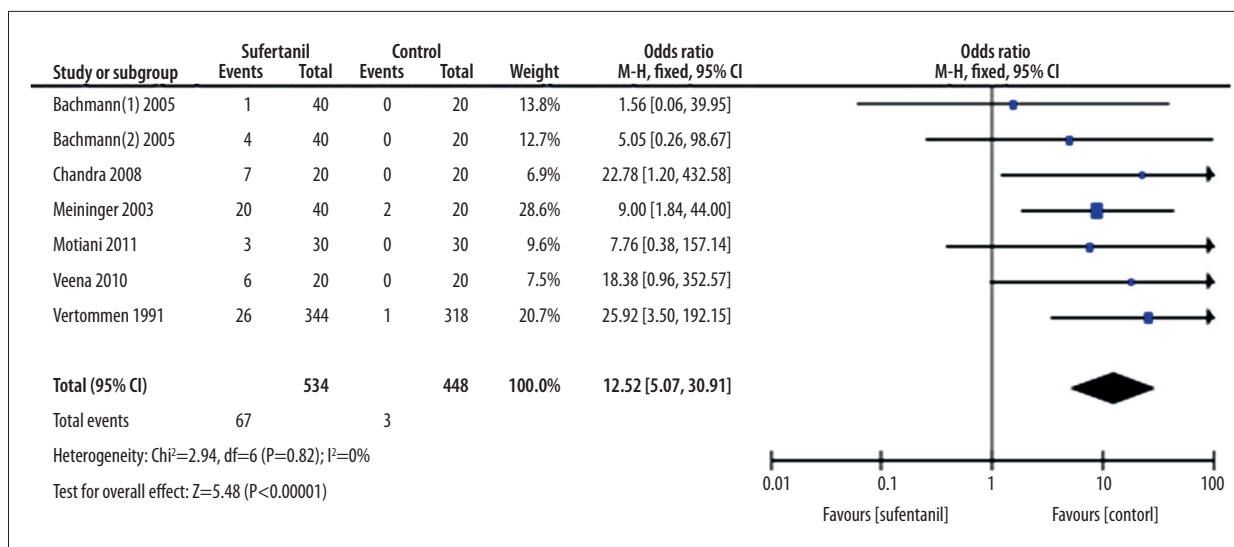


Figure 4. Forest plot of comparison: sufentanil vs. placebo. Outcome: pruritus.

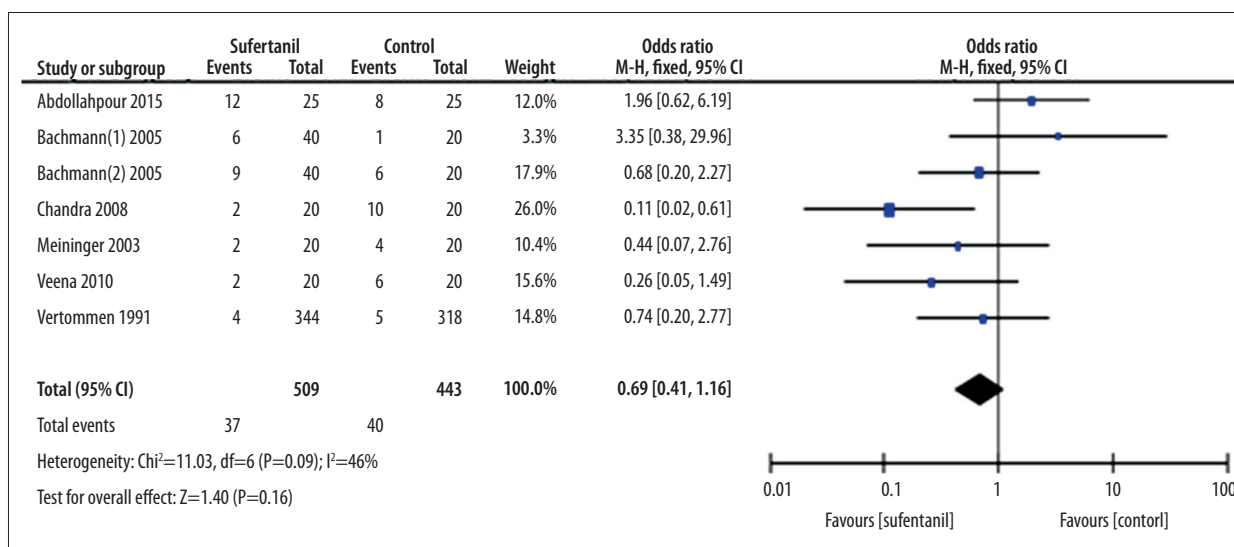


Figure 5. Forest plot of comparison: sufentanil vs. placebo. Outcome: nausea.

Compared to the placebo, intrathecal sufentanil did not increase the incidence of bradycardia during neuraxial anesthesia (OR, 0.86; 95% CI, 0.41 to 1.82;  $P=0.70$ ) (Figure 8).

## Discussion

Shivering is one of most common postoperative complications, especially during neuraxial anesthesia. Drugs and fluid warming are available ways to prevent and treat shivering [3]. Our meta-analysis showed neither epidural nor subarachnoid intrathecal sufentanil reduced shivering during neuraxial anesthesia. Sufentanil has the second shortest ultra-short context-sensitive half-time (CSHT), in the range of 10–15 min after continuous use for less than 7 h, compared with remifentanyl,

and alfentanil. The short CSHT of sufentanil may contribute to shivering.

Post-operative shivering can be divided into thermoregulatory and non-thermoregulatory [29], and it can be triggered by surgical stress and several aspects of anesthetic management. It is frequently preceded by a decrease in peripheral blood flow due to thermoregulatory vasoconstriction [30]. Hypothermia causes thermoregulatory shivering; the expansion of blood vessels leads to lower body temperature caused by heat loss after neuraxial anesthesia. If intrathecal sufentanil can reduce the shivering threshold, even in patients with low body temperature, due to a reduced shivering threshold, shivering will not occur. Alfonsi et al. [31] found that at a given dose, sufentanil inhibited shivering 2800 times better than meperidine, showing



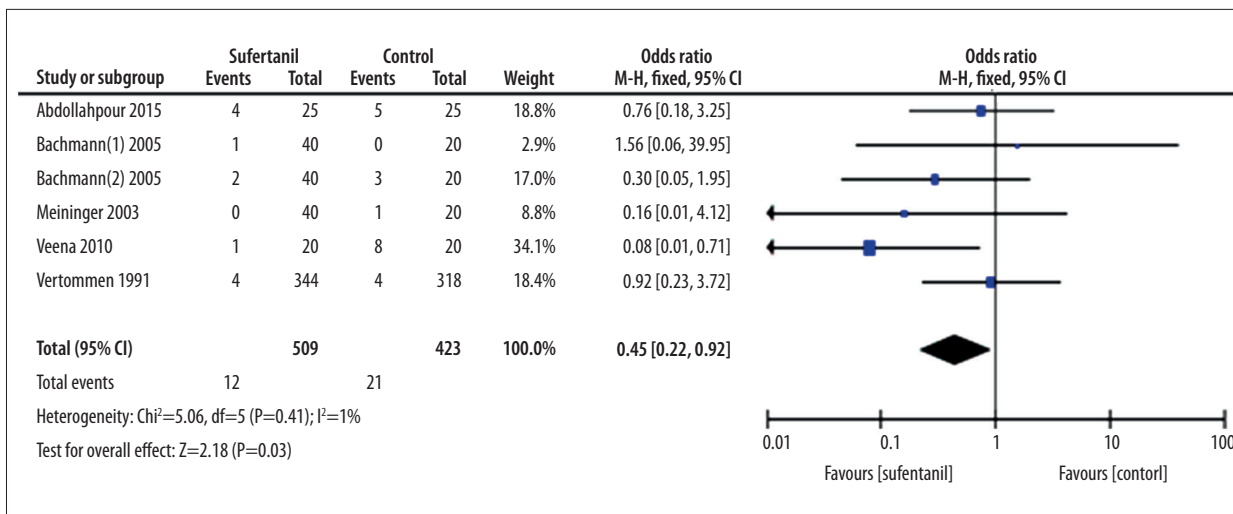


Figure 6. Forest plot of comparison: sufentanil vs. placebo. Outcome: vomiting.

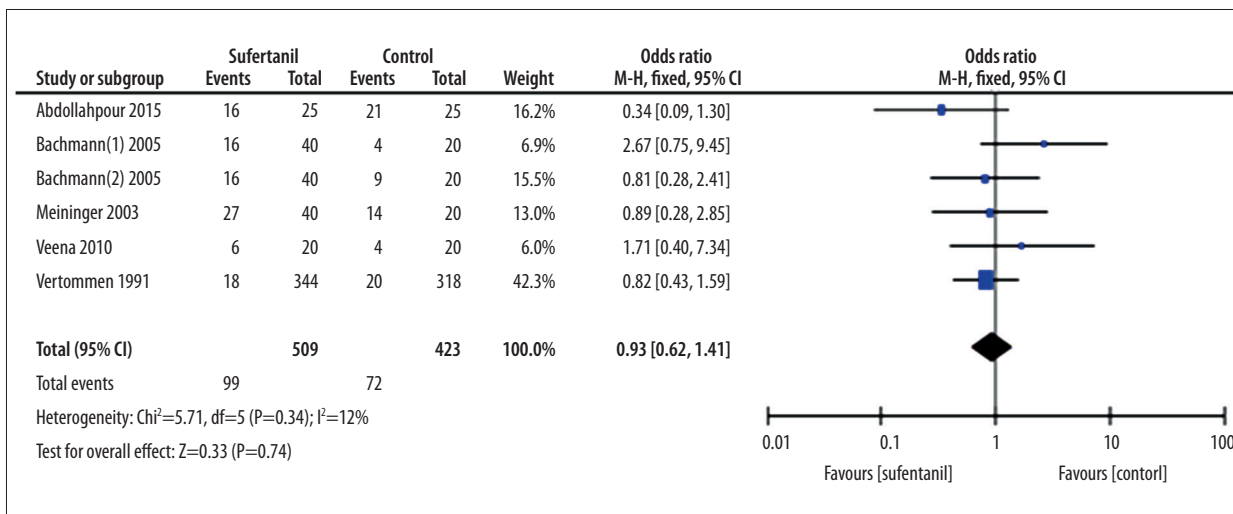


Figure 7. Forest plot of comparison: sufentanil vs. placebo. Outcome: hypotension.

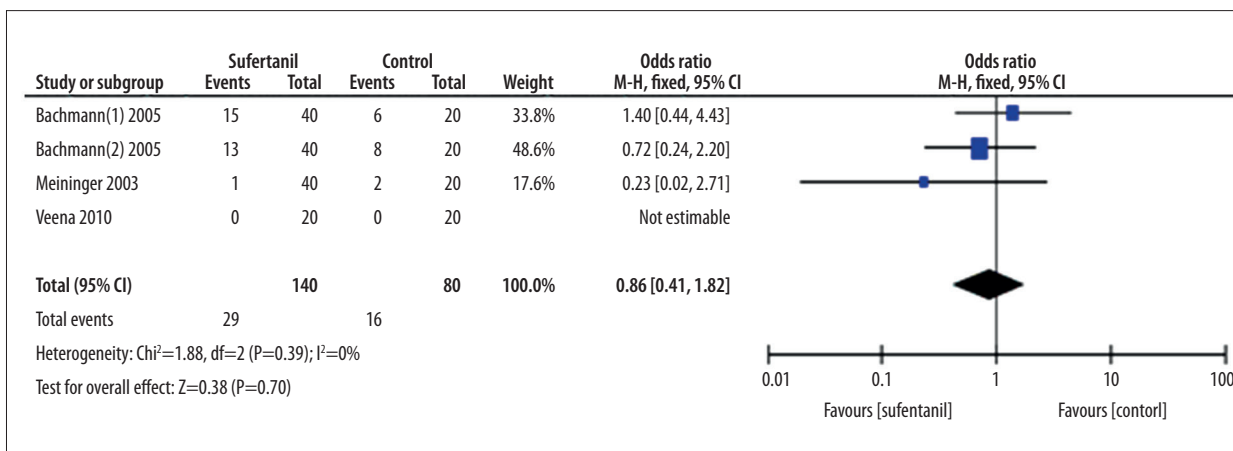


Figure 8. Forest plot of comparison: sufentanil vs. placebo. Outcome: bradycardia.

that sufentanil can significantly reduce shivering threshold. Sevarino et al. [32] confirmed that high-dose sufentanil could reduce the occurrence of shivering. Johnson et al. [33] also reported that a parturient's shivering was stopped after epidural injection of 100 µg sufentanil. However, the doses of sufentanil (range 1.5–20 µg) included in our meta-analysis were much lower than in these other studies. We found that low-dose sufentanil did not effectively reduce shivering threshold and that intrathecal sufentanil did not effectively reduce the incidence of shivering.

Our meta-analysis showed that pruritus was the only adverse effect that was related to sufentanil. Pruritus is a common adverse effect of intrathecal fentanyl and sufentanil; it decreases patient satisfaction and may delay hospital discharge [34]. There were no significant differences between groups in terms of nausea, hypotension, or bradycardia. Our meta-analysis showed that sufentanil reduced vomiting, but not effectively.

Although neither epidural nor subarachnoid intrathecal sufentanil reduced shivering during neuraxial anesthesia, it can significantly shorten the onset time of anesthesia, improve analgesic properties, and prolong the duration of intrathecal analgesia, regardless of the only adverse effect, which is pruritus.

### Limitation

The present meta-analysis has certain limitations. First, local anesthetics [35] and different doses of sufentanil may have

affected the results. Because of the small size effect and limited number of included studies, we did not perform a further layer of analysis. Secondly, no trials included in our meta-analysis contained intraoperative and postoperative temperature data, so we could not determine whether hypothermia was a direct cause of postoperative shivering. Finally, the included studies did not record the severity of shivering. Therefore, further analysis is needed to determine whether sufentanil can reduce the severity of shivering.

### Conclusions

This systematic review and meta-analysis suggests that neither intrathecal nor subarachnoid sufentanil epidural can reduce shivering during neuraxial anesthesia. In addition, it increases the incidence of pruritus. No other adverse effects were found to make a significant difference. Further analysis is needed to confirm whether sufentanil can reduce the severity of shivering.

### Statement

This study received no financial support. We have no conflicts of interest in this study.

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