Pharmacological treatment of post-anesthetic shivering: a systematic review and meta-analysis

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Background: Shivering is one of the most common unpleasant complications in the postoperative period. Many clinical trials have been published and revealed various efficacious drugs for the treatment of postanesthetic shivering.

Objective: To perform an updated quantitative review of randomized controlled trials (RCTs) studying efficacy of pharmacological treatment of post-anesthetic shivering.

Methods: We initiated a systematic search for original articles of randomized, controlled studies of drugs for postanesthetic shivering. Reports were appraised, and binary data of shivering within 15 minutes after treatment were extracted. Relative risk (RR) and the number-needed-to-treat (NNT) were subsequently analyzed and then reported with 95% confidence interval (CI).

Results: The efficacy of anti-shivering drugs was analyzed by using data from 32 RCTs. Meperidine 25 to 50 mg, tramadol 0.5 to 1 mg/kg, clonidine 30 to 150 μg, ketanserin 10 mg, doxapram 25 to 100 mg, and nalbuphine 0.05 to 0.1 mg/kg, reported in at least two trials, were significantly more effective than placebo within 15 minutes after treatment. The NNT of meperidine 25 to 50 mg was 1.39, of tramadol 0.5 to 1 mg/kg was 1.56, of ketanserin 10 mg was 2.44, of doxapram 25 to 100 mg was 1.82, and of nalbuphine 0.05 to 0.1 mg/kg was 1.75. The efficacy of tramadol 0.5 to 1 mg/kg was not significantly different from meperidine 0.5 mg/kg (25 mg) at 15 minutes of observation (p = 0.34). Moreover, clonidine 30 to 150 μg was more effective in treating tremor than placebo, with the NNT of 1.43. Studies in efficacy of alfentanil, magnesium sulfate, fentanyl, ondansetron, nefopam, pentazocine, urapidil, morphine, lignocaine, metamizol, and butorphanol, were inadequate for quantitative analysis.

Conclusion: Meperidine 25 to 50 mg, tramadol 0.5 to 1 mg/kg, clonidine 30 to 150 μg, doxapram 25 to 100 mg, ketanserin 10 mg, and nalbuphine 0.05 to 0.1 mg/kg can effectively treat postanesthetic shivering within 15 minutes. Tramadol 0.5 to 1 mg was found to be a good alternative compared to meperidine 25 to 50 mg. Side effects of treatments were mild and treatable.

Keywords: Meta-analysis, post-anesthetic, shivering, treatment, tremor.
induced by volatile anesthetic agents, the effects of ventilatory techniques used for prolonging anesthesia, surgical stresses, and hypothermia [1, 4, 5]. Oxygen consumption can increase by 100% to 600%; the end tidal carbon dioxide also increases and this could adversely affect patients who have impaired cardiopulmonary reserve. The intraocular and intracranial pressures also increase. Postanesthetic shivering could also stretch surgical wounds and irritate the parturient during labor [1, 5]. If treatment of post-anesthetic shivering is effective, the incidence of sequelae could be reduced [3].

There are still no evidence based guidelines for treatment of post-anesthetic shivering. Several drugs (such as meperidine, clonidine, ketanserin, alfentanil, fentanyl, doxapram, magnesium, and tramadol, etc.) were used. Some intravenous regimens were recommended in standard textbooks: pethidine (meperidine) 0.33 mg/kg, clonidine 2 μg/kg, doxapram 1.5 mg/kg and physostigmine 0.04 mg/kg [5-7]. These therapies acted by various mechanisms. Meperidine is a μ-receptor agonistic opioid directly acting on a thermoregulatory center, while clonidine is an α-agonist reducing vasoconstriction and threshold of shivering [5]. However, only meperidine 25 mg, clonidine 150 μg, ketanserin 10 mg, and doxapram 100 mg were mentioned, by Kranke P et al., in a previous quantitative systematic review of randomized controlled trials as effective anti-shivering drugs than placebo control [8].

There were several studies regarding treatment of post-anesthetic shivering among scientific community. This systematic review aims to evaluate pharmacological treatments to stop post-anesthetic shivering, reported during 1984 to 2008. Effective regimens were compared to placebo or other treatments. The hazards of each regimen were also determined.

Methods

Inclusion and exclusion criteria

We searched for randomized controlled trials (RCTs) on pharmacological treatment of post-anesthetic or postoperative shivering, from an electronic database. We defined the term ‘pharmacological treatment’ as medical intervention given to patients who experienced shivering or tremor postanesthetically or postoperatively, based on complaints by patients or confirmed observation by physicians. Additionally, not only the RCTs with placebo control, but the RCTs with treatment control or directly comparative studies were included. We found that recent studies were rarely performed with a control group of placebo. All studies mentioned on prevention, prophylaxis, non-pharmacological treatments, and ventilated patients postoperatively were not included. We included reports in English and other languages. We excluded data from only-abstract reports, non-randomized trials, non-binary-data studies, and small studies (<10 per group).

Systematic search

Sixteen authors independently searched for relevant reports from medical electronic databases, including PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez), Scopus (http://www.scopus.com), The Cochrane Library (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME), a Thai Index Medicus (http://161.200.96.194), Google Scholar (http://scholar.google.com); and by searching from reference lists cited in the relevant articles. Free text words for searching were “post-anesthetic OR postanaesthetic OR postoperative” AND “shivering OR shaking OR tremor” AND “randomized OR randomised OR random allocation”. The last electronic search was on August 12, 2008. Full texts of articles were retrieved.

Critical appraisal and data extraction

All retrieved reports were screened by authors, in order to include relevant reports. Each relevant report was reviewed for evaluating adequacy of randomization, blinding, and description of withdrawals using validated Jadad score [9], by at least three authors independently. Two of three (Areejunthawat and Kooanantkul) were authors assigned to independently reevaluate all relevant reports. According to Jadad score, the study would gain one point if ‘randomized’ was described, additional one point if the method of randomization was described appropriately, one point when the trial was described in double-blinded fashion, one additional point for blinding if it was described adequately, and the other one point when the number of withdrawals and reasons to withdraw were described in the report. The minimum score of valid trials in this systematic review was one, and the maximum was five for completely fulfilling all criteria of Jadad. In case of scoring discrepancy after evaluation, a subsequent consensus was obtained. Figure 1 shows the diagram of inclusion
and exclusion methods for retrieving appropriate RCTs from relevant reports.

Two authors, Trakulthong and Patradul, had done the extraction of relevant efficacy data from potential reports, Jarukasetrporn then confirmed the extraction. Ten other authors together extracted characteristics of studies: properties of patients, anesthetic technique that was used, length of observation periods, and temperature measured before intervention. In the methodology for extracting efficacy data, our agreement was that complete absence of shivering after treatment, or shivering grade 0 to 1 according to the classification of shivering intensity by Crossley and Mahajan [10], or symptom that was unable to be noticed by physician, would be identified as ‘no shivering’ in our review. Crossley and Mahajan [10] classified intensity into 5 grades: 0 for no shivering; one for invisible muscular activity with one or more of piloerection, peripheral vasoconstriction, peripheral cyanosis without the other causes; two for visible muscular activity confined to one group of muscle; three for visible muscular activity in more than one group of muscles, and four for gross muscular activity involving entire body.

The number of patients who ceased shivering (treatment success) depended on dosage and period of observation that was extracted. Variability of dosage was determined by using average body weight of each group to convert into fixed dosage. Then, data from studies with similar design were compiled for the next stages of analysis.

Quantitative analysis - meta-analysis

The relative efficacy by comparison of intervention and placebo, or of both or more interventions in non-placebo control studies, was estimated with statistical significance by using relative risk or risk ratio (RR), the number-needed-to-treat (NNT), and 95% confidence interval (95%CI) of RR and NNT [11]. Mantel-Haenzel fixed effects model method was used for pooling analysis if group of studies was homogenous (p >0.1), clinically and statistically. If heterogeneity presented (p <0.1), DerSimonian and Laird random effects model would be used [12,13]. Pooled RR and the absolute risk reduction (ARR) [14, 15], and NNT with 95% CI by simple Wald method [16,17] were calculated. By using Review Manager Version 5 (RevMan5) (http://www.cc-ims.net/RevMan). A p-value less than 0.05 was considered as statistically significant. Sensitivity analysis [12] would be performed if appropriate.

Fig. 1 Diagram representing inclusion and exclusion methods for retrieving appropriate RCTs from relevant reports.
Results

We found 426 relevant reports: 231 from MEDLINE, 371 from Scopus, 105 from the Cochrane Library, and 5 from a Thai Index Medicus. Fifty-one potential reports were retrieved for further evaluation. Nineteen reports were excluded subsequently: three for no randomization [18-20], one for treatment of intraoperative shivering [21], one for small size of subject groups (n < 10) [23], 12 for unobtainably original articles [24-35], and two for lack of dichotomous data reported [31, 36]. Raw data of two studies [37, 38] were directly requested from the authors.

Thirty-two potential randomized controlled clinical trials [37-68] were appraised and analyzed. Three non-English articles were translated. Median of validated Jadad scores in all trials was 2.5; two trials earned 1, fourteen earned 2, six earned 3, nine earned 4, and one earned 5. Twenty-four of those were placebo-controlled trials, but eight were direct comparisons. The characteristics of studies are shown in Table 1.

The median size of subject groups that received active intervention was 20 (range 10 to 71), equal to median size of controlled group (range 10 to 69). Many trials did not fully clarify their data. Seven trials did not report ages of subject [43, 48, 49, 52, 55, 58, 67], while eleven did not report weights [43, 44, 48, 49, 53, 55, 58, 62, 66-68]. However, in most trials, age and weight of subjects, and body temperature (BT) before therapeutic intervention were reported in range or mean with or without standard deviation (SD). BT of subject was 33°C to 35°C in 2 trials [52, 56], more than 37°C in 2 trials [65, 66], and 35°C to 37°C in other trials. Age of subjects was 18 to 70 years in 2 trials [43, 53] and 21 to 50 years in others, while weight was reported as mean with or without SD, ranged between 32 to 82.5 kg in most trials. Besides, 19 studies did not identify shivering by standard grading [37, 38, 40, 44-47, 49, 51, 52, 55, 56, 58-60, 62, 63, 66, 67].

Opioids, particularly meperidine, were the most commonly used for active interventions. Six of eight directly comparative trials had meperidine as one comparative group. Other opioids such as tramadol, fentanyl, alfentanil, nalbuphine, morphine, butorphanol, pentaazoncine, as well as non-opioid drugs such as ondanetron (serotonin antagonist), clonidine (α2-agonist), metamizol (NSAIDs), lignocaine, doxapram, ketanserin, nefopam, and magnesium sulfate.

Accumulation of dosage and discriminated time-point of observation

We found that dosage of experimental interventions, and length of observation periods were variable. Although Kranke P et al. [8] theoretically suggested that the anti-shivering efficacy would decrease when the length of observation period increased, called this ‘time dependency’, and tried to perform pooling analysis by strictly clarifying data into fixed time-lengths of observation and dosage. We decided to pool efficacy data in different ways principally concerning the interpretation for practical uses in postanesthetic care unit (PACU).

There was no standard length of observation period in PACU in clinical practice standards [69, 70]. The anesthesia personnel in PACU usually intensively observed patients for the first 15 minutes (recommended every 5 minutes) after arrival, then observed every 15 minutes up to at least 60 minutes [71]. We, therefore, decided to analyze the efficacy of anti-shivering drugs within 15 minutes after treatment regardless of termination of each study.

Furthermore, due to high variation of dosage, it was difficult for pooled analysis. Some drugs, such as meperidine and tramadol, had been previously studied by narrow different-range of dosage: 25 to 50 mg for meperidine, and 0.5 to 2 mg/kg for tramadol. While, some drugs, such as clonidine and doxapram, had been studied by a wide range. Consequently, we decided to accumulate the dosage of interventions into ‘range of dosage’ for convenient implication.

Pooled efficacy of anti-shivering regimens

Nine RCTs reported that meperidine 25 or 50 mg was effective to treat post-anesthetic tremor. The other drugs were studied in smaller amounts of trials: three for tramadol 0.5 to 1 mg/kg, three for ketanserin 10 mg, three for doxapram 25 to 100 mg, three for clonidine 30 to 150 μg, two for nalbuphine 0.05 to 0.1 mg/kg and two for alfentanil 250 μg. There were three regimens reflected a homogeneity (p >0.1): meperidine 25 to 50 mg, ketanserin 10 mg, and doxapram 25 to 100 mg. However, we accepted the heterogeneity anticipated, due to variations in design of the study and conditions of subject administered.

By the fixed effects model or the random effects mode, we found that four regimens were significantly more effective than placebo within 15 minutes after
Table 1. Analyzed characteristics of 32 randomized controlled trials in pharmacological treatment of postanesthetic shivering.

<table>
<thead>
<tr>
<th>Randomized controlled trials</th>
<th>Validity score of Jadad</th>
<th>Surgical procedures</th>
<th>Type of anesthesia (drug, dosage, and group size)</th>
<th>Time assessment of shivering (minute)</th>
<th>Temperature (°C) in each group before application</th>
<th>Age of subjects (year)</th>
<th>Weight of subjects (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al. 1999 [39]</td>
<td>1/2/0</td>
<td>Routine general, orthopaedic or gynaecological</td>
<td>General 1. Nalbuphine 0.08 mg kg in 30 patients 2. Mepivacaine 0.4 mg kg in 30 patients 3. Placebo in 30 patients</td>
<td>5/15/30</td>
<td>35.5 ± 0.6</td>
<td>35 ± 4</td>
<td>64 ± 1</td>
</tr>
<tr>
<td>Schwarzakopf et al. 2001 [40]</td>
<td>1/1/0</td>
<td>Elective laparoscopic or orthopaedic</td>
<td>General 1. Midazolam 25 mg in 20 patients 2. Clopromazine 0.15 mg in 20 patients 3. Urapidil 25 mg in 20 patients</td>
<td>5</td>
<td>36.3 ± 0.6</td>
<td>42 ± 15.5</td>
<td>75.5 ± 14.4</td>
</tr>
<tr>
<td>Tsai et al. 2001 [41]</td>
<td>1/1/0</td>
<td>Caesarean section</td>
<td>Epidural 1. Tramadol 0.5 mg kg in 15 patients 2. Mepivacaine 0.5 mg kg in 15 patients 3. Amantadine 15 or 20 mg in 15 patients</td>
<td>15</td>
<td>36.0 ± 0.5</td>
<td>27 ± 4</td>
<td>68 ± 9</td>
</tr>
<tr>
<td>Momot et al. 1996 [42]</td>
<td>1/1/0</td>
<td>Orthopaedic, general, and gynaecological</td>
<td>General 1. Metaraminol 25 mg in 37 patients 2. Mepivacaine 0.4 mg kg in 35 patients 3. Placebo in 32 patients</td>
<td>5/15/30</td>
<td>36.2 ± 0.5</td>
<td>42 ± 18</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Wrench et al. 1997 [43]</td>
<td>2/2/1</td>
<td>Routine general, gynaecological, orthopaedic or otorhinolaryngological</td>
<td>n/a 1. Alfentanil 25 mg in 30 patients 2. Mepivacaine 25 mg in 30 patients 3. Placebo in 30 patients</td>
<td>Every minute 36.1 ± 0.7</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Terasaka and Yamamoto 2000 [44]</td>
<td>1/2/0</td>
<td>Routine general, orthopaedic or otorhinolaryngological</td>
<td>n/a 1. Pentocaine 15 mg in 15 patients 2. Mepivacaine 17.5 mg in 15 patients 3. Placebo in 15 patients</td>
<td>Every minute 35.9 ± 0.9</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Singh et al. 1993 [45]</td>
<td>1/2/0</td>
<td>Routine orthopaedic or otorhinolaryngological</td>
<td>General 1. Dexametomidine 0.5 mg kg in 20 patients 2. Mepivacaine 33 mg kg in 20 patients 3. Placebo in 20 patients</td>
<td>Every minute 36.1 ± 0.3</td>
<td>n/a</td>
<td>18 ± 5</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Sunna and Fry 1991 [46]</td>
<td>1/2/1</td>
<td>Vaginal delivery or Caesarean section</td>
<td>General 1. Metaraminol 10 mg in 29 patients 2. Placebo in 29 patients</td>
<td>1/5</td>
<td>34.2 ± 37</td>
<td>43 ± 15</td>
<td>70 ± 9.4</td>
</tr>
<tr>
<td>Pauca et al. 1984 [47]</td>
<td>2/2/0</td>
<td>Thoracotomy, intrathoracic or extracavitary operation</td>
<td>General 1. Morphine 0.3 mg every 5 min to 25 mg in 27 patients 2. Pentazocine 0.3 mg every 5 min to 2.5 mg in 20 patients 3. Fentanyl 6.3 mg every 5 min to 25 mg in 23 patients</td>
<td>5/10/50</td>
<td>36.0 ± 0.5</td>
<td>35 ± 3</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>Cristinel et al. 1997 [48]</td>
<td>1/1/0</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>36 ± 2</td>
<td>n/a</td>
</tr>
<tr>
<td>Capogena and Cellano 1993 [49]</td>
<td>1/1/0</td>
<td>Nephrectomy</td>
<td>General 1. Ketorolac 10 mg in 21 patients 2. Placebo in 21 patients</td>
<td>5/10/50</td>
<td>35.5 ± 0.2</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Saedi et al. 2008 [50]</td>
<td>2/2/0</td>
<td>Operations of lower abdomen and extremities</td>
<td>General, balanced 1. Tramadol 0.2 mg kg in 15 patients 2. Mepivacaine 0.4 mg kg in 15 patients 3. Placebo in 15 patients</td>
<td>5</td>
<td>35.5 ± 0.5</td>
<td>32 ± 4.9</td>
<td>69 ± 8.1</td>
</tr>
<tr>
<td>Nalda et al. 1985 [51]</td>
<td>1/1/0</td>
<td>Elective gynaecological</td>
<td>General 1. Ketorolac 10 mg in 18 patients 2. Placebo in 18 patients</td>
<td>5/10/30</td>
<td>35.6 ± 1.1</td>
<td>35 ± 2</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>Alfonso et al. 1995 [52]</td>
<td>1/1/0</td>
<td>Non-infective orthopaedic or abdominal</td>
<td>General, balanced 1. Ketorolac 0.85 mg kg in 13 patients 2. Pentazocine 1.7 mg kg in 13 patients 3. Placebo in 13 patients</td>
<td>5/10/15</td>
<td>34.7 ± 0.5</td>
<td>34 ± 13</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Wrench et al. 1997 [53]</td>
<td>2/2/0</td>
<td>Routine general, orthopaedic or gynaecological</td>
<td>n/a 1. Dexametomidine 0.18 mg kg in 10 patients 2. Mepivacaine 0.125 mg kg in 10 patients 3. Placebo in 10 patients</td>
<td>5</td>
<td>36.2 ± 36</td>
<td>36 ± 0.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Lyons et al. 1995 [54]</td>
<td>1/1/0</td>
<td>Minor operation</td>
<td>General 1. Alfentanil 250 mg kg in 18 patients 2. Mepivacaine 25 mg kg in 18 patients 3. Placebo in 18 patients</td>
<td>1/5/10</td>
<td>36.5 ± 0.5</td>
<td>35 ± 3</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>Forri et al. 1993 [55]</td>
<td>1/1/0</td>
<td>General, orthopaedic, gynaecological</td>
<td>General, balanced 1. Ketorolac 0.5 mg kg in 15 patients 2. Placebo in 15 patients</td>
<td>1/5/10</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

[†] Non-placebo comparative study between interventions (direct comparison)
<table>
<thead>
<tr>
<th>Randomized controlled trials</th>
<th>Validity score of Jadad</th>
<th>Surgical procedures</th>
<th>Type of anesthesia</th>
<th>Comparisons (drug, dosage, and group size)</th>
<th>Time assessment of shivering (minutes)</th>
<th>Temperature (°C) in each group before application</th>
<th>Age of subjects (years)</th>
<th>Weight of subjects (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talakoub et al. 2006 [57] §</td>
<td>1/1/10</td>
<td>Elective or emergency</td>
<td>Spinal</td>
<td>1. Tramadol 0.5 mg/kg in 36 patients</td>
<td>5/10/15</td>
<td>36.6 ± 0.5</td>
<td>29.3 ± 2.58</td>
<td>67.1 ± 8.97</td>
</tr>
<tr>
<td>Fritz et al. 2001 [58]</td>
<td>1/2/0</td>
<td>Elective general</td>
<td>General</td>
<td>2. Meperidine 0.5 mg/kg in 37 patients</td>
<td>36.6 ± 0.1</td>
<td>32.1 ± 2.3</td>
<td>72.1 ± 10.4</td>
<td>4.4 ± 1.2</td>
</tr>
<tr>
<td>Soffi et al. 2008 [59] §</td>
<td>2/2/0</td>
<td>Orthopedic</td>
<td>General</td>
<td>1. Urapidil 25 mg in 10 patients</td>
<td>35.8 ± 0.5</td>
<td>35.9 ± 0.5</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Jenas et al. 1992 [60]</td>
<td>1/1/10</td>
<td>Labour and delivery</td>
<td>Epidural</td>
<td>2. Meperidine 0.5 mg/kg in 30 patients</td>
<td>35.8 ± 0.5</td>
<td>n/a</td>
<td>5.4 ± 4</td>
<td>60 ± 3</td>
</tr>
<tr>
<td>Sejelic et al. 2006 [61] §</td>
<td>2/2/0</td>
<td>n/a</td>
<td>General</td>
<td>3. Butorphanol 1 mg in 32 patients</td>
<td>35.8 ± 0.5</td>
<td>35.8 ± 0.5</td>
<td>60 ± 3</td>
<td>60 ± 3</td>
</tr>
<tr>
<td>Mennellante et al. 1994 [62]</td>
<td>1/1/10</td>
<td>Obstetrics</td>
<td>Epidural</td>
<td>4. Tramadol 0.25 mg/kg in 32 patients</td>
<td>35.8 ± 0.5</td>
<td>35.8 ± 0.5</td>
<td>6.2 ± 13</td>
<td>6.2 ± 13</td>
</tr>
<tr>
<td>Casey et al. 1988 [63]</td>
<td>1/1/10</td>
<td>Caesarean section</td>
<td>Epidural</td>
<td>5. Alfentanil 4 µg/kg in 32 patients</td>
<td>35.8 ± 0.5</td>
<td>35.8 ± 0.5</td>
<td>6.5 ± 15</td>
<td>6.5 ± 15</td>
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<tr>
<td>Gervais et al. 1997 [64]</td>
<td>1/1/10</td>
<td>Caesarean section</td>
<td>Epidural</td>
<td>1. Clonidine 0.15 mg in 20 parturients</td>
<td>5/2/0/15/30/60</td>
<td>36.6 ± 0.2</td>
<td>29.2 ± 2</td>
<td>78.0 ± 2.6</td>
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<tr>
<td>Kizilbash et al. 2000 [65]</td>
<td>1/1/10</td>
<td>Caesarean section</td>
<td>Epidural</td>
<td>2. Meperidine 0.5 mg/kg in 20 parturients</td>
<td>36.6 ± 0.3</td>
<td>35.6 ± 0.3</td>
<td>69.2 ± 2.3</td>
<td>69.2 ± 2.3</td>
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<tr>
<td>Zhao et al. 1994 [66]</td>
<td>1/1/10</td>
<td>Caesarean section</td>
<td>Epidural</td>
<td>3. Meperidine 0.5 mg/kg in 25 patients</td>
<td>35.6 ± 0.5</td>
<td>35.6 ± 0.5</td>
<td>66 ± 15</td>
<td>66 ± 15</td>
</tr>
<tr>
<td>Makushwari et al. 2008 [66] §</td>
<td>1/2/0</td>
<td>Caesarean section</td>
<td>Epidural</td>
<td>4. Butorphanol 1 mg/kg in 25 patients</td>
<td>35.6 ± 0.4</td>
<td>27 ± 10</td>
<td>66 ± 15</td>
<td>66 ± 15</td>
</tr>
<tr>
<td>Mathew et al. 1988 [67]</td>
<td>1/0/0</td>
<td>Obstetrics</td>
<td>Epidural</td>
<td>5. Alfentanil 4 µg/kg in 32 patients</td>
<td>35.6 ± 0.4</td>
<td>35.6 ± 0.4</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Kyokong et al. 2007 [70]</td>
<td>2/2/0</td>
<td>Caesarean section</td>
<td>Spinal</td>
<td>6. Alfentanil 4 µg/kg in 32 patients</td>
<td>35.6 ± 0.4</td>
<td>35.6 ± 0.4</td>
<td>65 ± 10</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>De Witte et al. 1997 [38]</td>
<td>1/1/1</td>
<td>Elective laparoscopic, laminectomy, or diaphragm</td>
<td>General, standardized</td>
<td>7. Clonidine 150 µg in 15 patients</td>
<td>35.7 ± 0.4</td>
<td>46 ± 10</td>
<td>70 ± 9</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>Joris et al. 1993 [68] §</td>
<td>1/1/1</td>
<td>Abdominal, orthopedic, or urologic</td>
<td>General, standardized</td>
<td>8. Clonidine 150 µg in 15 patients</td>
<td>35.7 ± 0.6</td>
<td>36 ± 15</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

§: Non-placebo comparative study between interventions (direct comparison); ‡: Study containing subgroups of study with different design or conditions.
treatment, by at least three RCTs: meperidine 25 to 50 mg, tramadol 0.5 to 1 mg/kg, ketanserin 10 mg, and doxapram 25 to 100 mg. Nalbuphine 0.05 to 0.1 mg/kg was significantly more efficacious than placebo, but from only 2 RCTs. The NNT of clonidine 30 to 150 μg was 1.43 with pooled relative risk of 7.93. Alfentanil 250 μg was not significantly different from placebo at 15 minutes after administration, with the NNT [11] of including infinity (p=0.12). The pooled RR and NNT of these regimens were shown in Table 2. Forest plots of pooled efficacy of the regimen are also shown in Fig. 2.

*Tramadol versus Meperidine*

We found that, during the past 8 years, the RCTs with placebo were fewer than the direct comparison or intervention-controlled trials. Four out of eight directly comparative studies included for our analysis, compared tramadol 0.5 or 1 mg/kg to meperidine 0.5 mg/kg (25 mg). It was clear that meperidine (or pethidine) 25 to 50 mg was significantly superior to placebo by pooled efficacy from nine RCTs. While tramadol 0.5 to 1 mg/kg was more effective than placebo by 3 RCTs. We, thus, subsequently analyzed the relative efficacy of tramadol 0.5 to 1 mg/kg to meperidine 25 mg, by pooled RR and NNT.

From the random effects model analysis of 4 studies [41,56,57,59], the efficacy of tramadol 0.5 to 1 mg/kg for treatment of post-anesthetic shivering in 15 minutes was not significantly different from meperidine 25 mg (p = 0.34) with 1.16 of relative risk (95%CI: 0.85 to 1.59). The Forest plot of relative risk was illustrated in Fig. 3.

Four other non-placebo-control randomized trials compared the efficacy between two or more drugs: clonidine and urapidil to meperidine [40], tramadol to tramadol in different dosages [50], meperidine to fentanyl, tramadol, sufentanyl, and alfentanil [61], and tramadol to butorphanol [66]. One study [41] also compared amitryptiline (the tricyclic antidepressant) to tramadol and meperidine. All of those regimens were unable to be analyzed quantitatively.

### Table 2. Pooled relative efficacy of anti-shivering therapeutic interventions for postanesthetic shivering.

<table>
<thead>
<tr>
<th>Drug regimens</th>
<th>References</th>
<th>Absolute number stopped shivering / total number of patients (%)</th>
<th>Pooled relative risk (95%CI)</th>
<th>Pooled number-needed-to-treat (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine 25 to 50 mg&lt;sup&gt;f&lt;/sup&gt;</td>
<td>[39,42,43,45, 52-54,62,63]</td>
<td>182/206 (88) 33/200 (17)</td>
<td>5.28 (3.86-7.22)</td>
<td>1.39 (1.27-1.54)</td>
</tr>
<tr>
<td>Tramadol 0.5 to 1 mg/kg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[37,38,65]</td>
<td>105/133 (79) 23/115 (20)</td>
<td>6.14 (1.37-27.42)</td>
<td>1.56 (1.23-2.17)</td>
</tr>
<tr>
<td>Ketanserin 10 mg&lt;sup&gt;f&lt;/sup&gt;</td>
<td>[48,51,68]</td>
<td>56/63 (89) 29/61 (48)</td>
<td>1.87 (1.41-2.47)</td>
<td>2.44 (1.79-3.70)</td>
</tr>
<tr>
<td>Doxapram 25 to 100 mg&lt;sup&gt;f&lt;/sup&gt;</td>
<td>[45,46,53]</td>
<td>79/99 (80) 17/69 (10)</td>
<td>3.23 (2.10-4.97)</td>
<td>1.82 (1.47-2.38)</td>
</tr>
<tr>
<td>Clonidine 30 to 150 μg&lt;sup&gt;r&lt;/sup&gt;</td>
<td>[49,62,68]</td>
<td>69/90 (77) 12/89 (13)</td>
<td>7.93 (0.98-64.02)</td>
<td>1.43 (1.18-1.85)</td>
</tr>
<tr>
<td>Nalbuphine  0.05 to 0.1 mg/kg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[37,39]</td>
<td>75/100 (75) 24/99 (24)</td>
<td>4.02 (1.10-14.66)</td>
<td>1.75 (1.11-4.17)</td>
</tr>
<tr>
<td>Alfentanil 250 μg&lt;sup&gt;r&lt;/sup&gt;</td>
<td>[43,54]</td>
<td>27/48 (56) 9/45 (20)</td>
<td>2.95 (0.81-10.74)</td>
<td>2.32 (NNTB 1.03 to ∞ to NNTH 9.09)</td>
</tr>
</tbody>
</table>

<sup>f</sup>Mentel-Haenzel fixed effects model method; <sup>e</sup>DerSimonian and Laird random effects model method. 95% CI of relative risk included 1; the relative efficacy to placebo was not statistically significant. 95%CI of the number-needed-to-treat included the infinity; the upper limit was in range of negative value [11]. 95%CI= 95% confidence interval. NNTB= the number of patients needed to be treated for one additional patient to benefit. NNTH= the number of patients needed to be treated for one additional patient to be harmed.
Fig. 2 The Forest plots demonstrated single-study and pooled relative risks (RR) with 95% confidence interval (CI) of five pharmacological regimens (meperidine 25 to 50 mg, tramadol 0.5 to 1 mg/kg, ketanserin 10 mg, doxapram 25 to 100 mg, and nalbuphine 0.05 to 0.1 mg/kg) for treatment of post-anesthetic shivering, consisting of higher efficacy than placebo within 15 minutes, by statistical significance (p < 0.05), in meta-analysis.

Fig. 3 The pooled and single-study relative risks (RR) and the absolute risk reduction (ARR) with 95% confidence interval (CI) of tramadol 0.5 to 1 mg/kg compared to meperidine 0.5 mg on the anti-shivering efficacy within 15 minutes after administration were presented by the Forest plot. The result showed statistical insignificance (p > 0.05). Insignificant RR (included 1). j Insignificant ARR (included 0). *Insignificant NNT (included ∞) [11].
Other regimens

There were 9 drugs that had been studied in one randomized placebo-controlled trial included by our criteria. Those were metamizol [42], lignocaine [52], magnesium sulfate [64], morphine [47], pentazocine [44], ondansetron [37], nefopam [55], urapidil [58], and butorphanol [60].

Metamizol 25 mg/kg, urapidil 25 mg, magnesium sulfate 30 mg/kg, butorphanol 1 mg, ondansetron 0.1 mg/kg, and nefopam 0.2 mg/kg were significantly more effective than placebo (p < 0.05) for treatment of post-anesthetic shivering, while efficacy of morphine 2.5 mg, pentazocine 7.5 mg, and lignocaine 1 mg/kg were not significantly different from placebo (p > 0.05).

In direct comparison between treatments of post-anesthetic shivering, meperidine 25 mg contained higher efficacy than urapidil 25 mg [40] and amitryptyline 15 to 20 mg [41], statistically different (p < 0.05). In other study, tramadol 1 mg/kg was significantly more effective than butorphanol 20 μg/kg [66].

Adverse side effects

Most of studies reported adverse side effects of each therapeutic regimen by words of ‘statistically significant’ with p-value less than 0.05, without the absolute number of incidence.

We found that several drugs produced nausea and vomiting (alfentanil [61], butorphanol [66], doxapram [46, 53], fentanyl [52, 61], meperidine [42, 47, 62, 63], morphine [47], nalbuphine [37], ondansetron [37], sufentanil [61], and tramadol [37, 57, 61, 66]). Meperidine significantly produced drowsiness [41, 52, 63] in approximately 33 to 65%; and caused dizziness, 20 to 27% [41, 57], nausea or vomiting, 3 to 45% [42, 47, 62, 63] and respiratory depression 3 to 7% [42, 45, 52, 59]. Tramadol produced nausea or vomiting, 2 to 77% [37, 57, 61, 66], drowsiness, 7 to 55% [41, 57, 66], and itching, 17% [37]. One study [59] revealed that tramadol produced significantly less drowsiness than meperidine. Clonidine could affect patients significantly by increasing systolic blood pressure and decreasing heart rate, more than placebo [49, 68].

Sensitivity analysis

From the sensitivity analysis conducted for determining the robustness of analysis [12], the results of the comparisons between alfentanil 250 mg, nalbuphine 0.05 to 0.1 mg/kg, doxapram 25 to 100 mg, meperidine 25 to 50 mg, tramadol 0.5 to 1 mg/kg and ketanserin 10 mg with placebo, and meperidine 0.5 mg/kg versus tramadol 0.5 to 1 mg/kg can be regarded with a higher degree of certainty as that they are not affected by the different factors, such as validity score of Jadad, type of anesthesia or surgery, age and gender of patients, etc.

We also considered the difference in time of observation and range of dosage in the other drugs, but those factors did not show much effect to our results. For instance, meperidine 25 [39, 42, 47, 53, 54] and 50 mg [53, 62] showed significantly more (p < 0.0001) therapeutic effectiveness than placebo at 5 minutes with RR of 8.62 (95%CI, 4.83-15.39) and 4.71 (95%CI, 2.36-9.43), respectively. The NNT at 5 minutes of both dosages are 1.51 (25 mg) and 1.54 (50 mg), which were closed to the NNT of meperidine 25 to 50 mg within 15 minutes.

Discussion

Our meta-analysis showed that meperidine, doxapram and ketanserin have statistically significant more potency in controlling post-anesthetic shivering within 15 minutes as compared with placebo. This is consistent with previous quantitative systematic review [8]. The NNT of meperidine 25 to 50 mg was 1.39 (RR=5.28, 95%CI=3.86-7.22), the NNT of doxapram 25 to 100 mg was 1.82 (RR=3.23, 95%CI=2.10-4.97), the NNT of ketanserin 10 mg was 2.44 (RR=1.87, 95%CI=1.41-2.47), and the NNT of nalbuphine 0.05 to 0.1 mg/kg was 1.75 (RR=4.02, 95%CI=1.10-14.66). Our results also showed that meperidine 25 to 50 mg is superior to ketanserin 10 mg as treatment of post-anesthetic shivering in 15 minutes. In addition, our meta-analysis confirmed that tramadol 0.5 to 1 mg/kg was also an effective drug, with comparable efficacy to meperidine 25 to 50 mg or tramadol 0.5 to 1 mg/kg in stopping postanesthetic tremor. Therefore, studies of other aspects, apart from efficacy, should be considered for cost-minimization, cost-benefit analysis, adverse effects and drug availability.

Meperidine, ketanserin, and doxapram were commonly recommended for the treatment of shivering [5, 6]. Therefore, tramadol and nalbuphine should also be recommended. There was no evidence supporting physostigmine for the treatment of tremor despite effective prophylactic efficacy [22].
Clonidine was also mentioned in the textbooks [5, 6]. Kranke P et al. [8] showed that clonidine 150 mg could be effectively used to stop postoperative shivering at 5 and 10 minutes after administration. Our subgroup analysis also showed that clonidine 30 to 150 μg was significantly more effective than placebo within 5 minutes in patients who recovered from epidural anesthesia in obstetric procedures, by the pooled RR of 13.8 (95%CI=4.15-45.93, p <0.0001) and the pooled NNT of 1.25 (95%CI=1.08-1.49, p <0.00001) [49, 62].

Regarding the adverse effects, nausea and vomiting were commonly reported [37, 42, 46, 47, 52, 53, 57, 61-63, 66]. Drowsiness and dizziness were also frequently found [41, 52, 57, 63]. Tramadol seems to cause nausea and vomiting more often than meperidine. However, these side effects were mild and treatable.

From our meta-analysis of non-placebo-control randomized studies, we recommend tramadol 0.5 to 1 mg/kg as an effective regimen as meperidine 25 mg, while meperidine is the most common regimen in clinical use for the treatment of postoperative shivering.

There were few limitations in this review. First, there was difficulty in translation during process of article appraisal. We had to consult the linguists for assistance in translation of three non-English full articles (French [48], Italian [55], and Chinese [65]). Second, in some retrieved articles, the dichotomous data [31,36] and the absolute numbers of incidences in the placebo control groups [37, 38] were not provided. The authors, therefore, contacted the authors for raw data [37].

There were other interventions such as metamizol [42], magnesium sulfate [64], sufentanyl [61], ondansetron [37], nefopam [55], urapidil [58], and butorphanol [60] proved to be more effective compared to placebo. However, the data are adequate for quantitative analysis and need further study.

Conclusion
Meperidine 25 to 50 mg/kg and tramadol 0.5 to 1 mg/kg are effective in the treatment of postanaesthetic shivering at 15 minutes and both of them have no statistically significant difference in efficacy. In addition, clonidine 30 to 150 mg, ketanserin 10 mg, doxapram 25 to 100 mg and nalbuphine 0.05 to 0.1 mg/kg can be used as therapeutic alternatives. Studies in efficacy of alfentanil, magnesium sulfate, fentanyl, ondansetron, nefopam, pentazocine, urapidil, morphine, lignocaine, metamizol and butorphanol, are inadequate for quantitative analysis. The side effects of each regimen are mostly non-hazardous.

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All authors: searched and selected relevant studies CT, CP, CJ: extraction of data. Other authors: extraction and grouping of characteristics of studies, types of patient, choice of anesthesia, length of observation, and temperature measurement. All authors: selection of RCT 8 analysis. CT, CJ, CM: statistical analysis. SC, CM, JA: writing of the manuscript.

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