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

CRD summary
This review concluded that meperidine, tramadol, clonidine, ketanserin, doxapram, and nalbuphine were effective for treating post-anaesthetic shivering within 15 minutes; drugs were generally tolerated. However, clonidine was not shown to be efficacious in the results of the review. This, along with other limitations, suggest the authors' conclusions should be interpreted cautiously as they do not appear to be reliable.

Authors' objectives
To assess the efficacy of drug treatment for post-anaesthetic/post-operative shivering.

Searching
Four databases, including PubMed and The Cochrane Library, were searched from 1984 up to 2008 for relevant articles in any language. Some search terms were reported. In addition, Google Scholar and reference lists of relevant studies were searched.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) that assessed the efficacy of drugs for post-anaesthetic/post-operative shivering. Shivering or tremor was identified based on patient complaints or confirmed observation by physicians. Eligible trials had to compare drug intervention with placebo, similar drug treatment or other active controls. Trials were excluded if they did not report binary outcome data, included less than 20 patients per treatment group, or were in abstract form only. Trials on prevention, prophylaxis were also excluded, as were trials of patients on ventilation.

The outcome of interest was the number of patients who ceased shivering (treatment success). ‘No shivering’ was defined as complete absence of shivering after treatment, shivering grade 0 to 1 according to previously published shivering intensity classifications (as defined in the review), or no symptoms observed by physicians. Adverse effects were also reported.

Included trials were published from 1984 to 2008. The mean age of included patients ranged from 21 to 50 years and mean patient weight ranged from 32 to 82.5 kg (where reported). Patient temperatures, where this was reported, ranged between 33 and 37 degrees centigrade. Patients underwent a variety of operations, including orthopaedic, general and gynaecological. Most patients received general anaesthesia (where reported).

Opioids, especially meperidine, were the most frequently used active interventions, but a variety of non-opioids were also administered. Treatment doses were variable, as were the assessment times of shivering (ranging from five to 120 minutes).

At least two reviewers screened studies for inclusion.

Assessment of study quality
At least two reviewers assessed the quality of trials according to the Jadad scale (maximum score of 5). At least two reviewers independently re-assessed quality scores, with discrepancies resolved by consensus.

Data extraction
Two reviewers extracted outcome data for both treatment groups, to calculate relative risks and their 95% confidence intervals. The number of patients needed to be treated (NNT) for one patient to benefit was also calculated. Outcome data were assessed in all studies for the first 15 minutes after treatment and drug dosage of treatment were accumulated into ‘range of dosage’. Primary authors were contacted for additional data where necessary. Data were checked for
Methods of synthesis
A fixed-effect model (or random-effects model where there was evidence of heterogeneity and it appropriate) was used to pool relative risks and NNTs, along with their 95% confidence intervals. Pooled absolute risk reductions and their 95% confidence intervals were also calculated using previously published methods. Sensitivity analysis was intended, where appropriate.

Results of the review
Thirty two RCTs (at least 2,208 patients, range 20 to 280) were included in the review; eight active comparisons and 24 placebo-controlled trials. The median Jadad score was 2.5, suggesting that the overall quality of the included RCTs was moderate to low.

Direct active treatment comparisons showed that there were no statistically significant differences in treatment success between tramadol (0.5mg/kg to 1mg/kg) and meperidine (25mg) 15 minutes after treatment for shivering (four RCTs). Five treatments were statistically significantly more effective compared with placebo within 15 minutes after treatment; meperidine 25mg to 50mg (RR 5.28, 95% CI 3.86 to 7.22; nine RCTs); tramadol 0.5mg/kg to 1mg/kg (RR 6.14, 95% CI 1.37 to 27.42; three RCTs); ketanserin 10mg (RR 1.87, 95% CI 1.41 to 2.47; 3 RCTs); doxapram 25mg to 100mg (RR 3.23, 95% CI 2.10 to 4.97; three RCTs); nalbuphine 0.05mg/kg to 0.1mg/kg (RR 4.02, 95% CI 1.10 to 14.66; two RCTs).

There were no statistically significant differences in treatment effect for clonidine 30μg to 150μg or alfentanil 250μg compared with placebo. There was evidence of statistical heterogeneity for tramadol, clonidine, nalbuphine and alfentanil.

Sensitivity analyses exploring quality score, type of anaesthesia and surgery, and patient characteristics did not significantly alter the results.

Adverse events were reported to be mild and treatable and included nausea and vomiting, drowsiness, dizziness, respiratory depression, itching, and increased blood pressure.

Results from single trials and NNTs were also reported in the review.

Authors' conclusions
Meperidine, tramadol, clonidine, ketanserin, doxapram, and nalbuphine were effective in the treatment of post-anaesthetic shivering at 15 minutes; side effects were mild and treatable.

CRD commentary
The review question and supporting inclusion criteria were broadly stated. A satisfactory number of sources were searched for relevant studies, but as only full text publications were eligible for inclusion, potentially relevant studies may have been missed. Each stage of the review process was performed in duplicate, which reduced the potential for reviewer error and bias.

Quality assessment indicated that the overall quality of included studies was moderate to low. The authors explored the effect of quality and other factors on the results. Although there was considerable variation between studies, the authors used appropriate methods to account for this. Limitations of the review included the generally small number of included studies and sample sizes, and most interventions were compared with placebo or involved only one study. In addition, confidence intervals were wide for some outcomes. All these limitations reduce the reliability of the results. In addition, the authors incorrectly stated in their conclusions that clonidine was an effective treatment, but the evidence suggested it did not provide benefit over placebo.

Given the limitations highlighted, it is recommended that the authors' conclusions are interpreted cautiously as they do not appear to be reliable.

Implications of the review for practice and research
**Practice:** The authors stated that meperidine, ketanserin, and doxapram were commonly recommended for the treatment of shivering, and that tramadol and nalbuphine should also be recommended.

**Research:** The authors stated that further research should focus on costs, adverse effects and drug availability. Further research was also needed to assess the interventions for which there was insufficient evidence in the review.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.