General Anesthesia

Best evidence in anesthetic practice

Treatment: meperidine, clonidine, doxapram, ketanserin, or alfentanil abolishes short-term post-operative shivering

Article appraised

Kranke P, Eberhart LH, Roewer N, Tramèr MR. Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; 94: 453-60.

Structured abstract

Question: In postoperative non-ventilated patients, what is the efficacy and harm of pharmacological interventions in treating postoperative shivering?

Data sources: Studies were identified by computerized searches (MEDLINE, EMBASE, Cochrane Library) up to August 2000, citation review, hand searches of locally available anesthesia journals, and contact of the German manufacturers of meperidine (Aventis Pharma) and clonidine (Boehringer Ingelheim). No language restrictions were applied.

Study selection: Studies were selected if they were randomized controlled trials comparing a drug, used to treat shivering, to placebo in postoperative non-ventilated patients with at least ten patients per group.

Data extraction: Data were extracted in duplicate on trial design, interventions, surgical setting, type of anesthetic, and outcomes including adverse events. The main outcome was the complete absence of shivering after drug administration.

Main results: Twenty trials with a total of 1375 patients met the selection criteria. Studied drugs included opioids, other centrally acting analgesics, sodium channel blockers, α_2 -agonists, methylphenidate, doxapram, ketanserin, and magnesium. The observation period after drug administration varied between trials (mode five minutes; range one minute to 45 min). Meta-analyses were only performed for drugs tested in at least two trials. Compared to placebo, meperidine 25 mg, clonidine 150 μ g, doxapram 100 mg, ketanserin 10 mg, and alfentanil 250 μ g were efficacious in abolishing postoperative shivering. Meperidine 25 mg appeared to be the best drug with the numbers-needed-to-treat (NNT) consistently lower than the NNT for other drugs regardless of the duration of the observation period (Table). Few trials reported adverse events. No

TABLE Efficacy of pharmacological interventions *vs* placebo in abolishing postoperative shivering

Drug*	Active Drug	Placebo	Relative benefit (95% CI)†	NNT (95% CI)‡
Meperidine 25 mg	133 / 153	13 / 147	9.55 (5.72 – 15.9)	1.3 (1.2 – 1.4)
Clonidine 150 μ g	39 / 45	6 / 49	6.82 (3.28 – 14.2)	1.3 (1.1 – 1.6)
Doxapram 100 mg	46 / 59	14 / 69	3.97 (2.42 – 6.5)	1.7 (1.4 – 2.3)
Ketanserin 10 mg	41 / 65	13 / 64	3.10 (1.88 – 5.13)	2.3 (1.7 – 3.6)
Alfentanil 250 μ g	24 / 48	4 / 45	5.56 (2.04 – 15.1)	2.4 (1.7 – 4.0)

CI = confidence interval; NNT = number-needed-to-treat. *Results from the five-minute observation period are presented in this table. Additional results for 1-, 10-, 15-, and 30-min periods are available in Table II of the appraised article. †Relative benefit less than 1 favours the placebo group; relative benefit greater than 1 favours the active drug group. A 95% CI that does not include the value of 1 indicates a statistically significant result at a *P*-value > 0.05.‡ The NNT is the number of patients that need to be treated to abolish post-operative shivering in one patient.

statistically significant differences in adverse events (nausea, vomiting, respiratory depression, bradycardia) were reported between active drug and placebo.

Conclusion: Meperidine, clonidine, doxapram, ketanserin, and alfentanil abolish short-term postoperative shivering.

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Correspondence: Dr. med. Peter Kranke, Department of Anesthesiology, University of Würzburg, Josef-Schneider-Str. 2, D-97080 Würzburg, Germany. Email: peter.kranke@mail.uni-wuerzburg.de

Commentary by D. Sessler

Kranke *et al.* report a comprehensive meta-analysis of drugs for treatment of postoperative shivering. Meta-analyses depend critically on their underlying studies. Nearly all patients in the studies evaluated by Kranke *et al.* were not warmed or inadequately warmed — and thus presumably hypothermic. The protocols were similar in that shivering postoperative patients were given a bolus of various drugs and the outcome was cessation of shivering. This is a reasonable study design if the question is simply how to stop shivering in hypothermic postoperative patients.

However, shivering is arguably among the least important consequences of perioperative hypothermia. Randomized, blinded trials have shown that mild hypothermia (1–2°C) also causes numerous serious complications including morbid myocardial outcomes, coagulopathy and increased transfusion requirement, surgical wound infections, negative nitrogen balance, reduced drug metabolism, sympathetic nervous system activation, delayed discharge from the postanesthesia care unit, and prolonged hospitalization.¹ It has thus become standard-of-care to keep surgical patients normothermic. A consequence of this policy is a marked reduction in the incidence of postoperative shivering. The need to treat shivering has, naturally, decreased proportionately.

Most postoperative rhythmic tremor is normal thermoregulatory shivering in response to intraoperative hypothermia. However, a fraction of this involuntary muscular activity is not thermoregulatory. The etiology of this activity remains unknown, although it is highly linked to inadequate treatment of surgical pain.² Since shivering-like tremor is non-thermoregulatory, it seems unlikely that drugs like meperidine, clonidine, and doxapram will prove effective treatments. Non-thermoregulatory tremor may thus account from some of the treatment failures observed in the studies evaluated by Kranke *et al.*

Shivering is characterized by its threshold, defined by the triggering core temperature. The normal shivering threshold ranges from approximately 35.5 to 36.5°C depending on the time of day.³ Core temperatures were reported in most of the studies included in the meta-analysis of Kranke *et al.* and were typically near this range. Core temperature is important because there is a strong dose-dependence with anti-shivering drugs.^{4,5} Thus, even relatively ineffective treatments will often block shivering in patients whose temperature is only a few tenths of a degree less than the threshold, whereas only an effective drug will work consistently at much lower temperatures. Apparent efficacy of pharmacologic interventions reported in the underlying trials depends critically on core temperature of the participants.

An additional concern is that all anesthetics profoundly inhibit thermoregulatory responses.^{6,7} However, none of the underlying studies quantified residual anesthetic concentration. Apparent efficacy of interventions reported in the underlying trials also depends critically on residual anesthetic type and concentration.

Variability in residual anesthetic concentration and core temperature to some extent restricts validity of comparisons across studies, which is the defining characteristic of any meta-analysis. There is nonetheless little reason to doubt the primary conclusion of Kranke *et al.* that the relative anti-shivering efficacy is similar for meperidine, clonidine, and doxapram. However, the actual number-needed-to-treat in any given clinical situation will depend on the patients' core temperatures and the types and concentrations of residual anesthesia.

Daniel I. Sessler MD

Louisville, Kentucky

References

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