Single-Dose Parenteral Pharmacological Interventions for the Prevention of Postoperative Shivering: A Quantitative Systematic Review of Randomized Controlled Trials

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Shivering is a frequent complication in the postoperative period. The relative efficacy of pharmacological interventions to prevent this phenomenon is not well understood. We performed a systematic search for full reports of randomized comparisons of prophylactic, parenteral, single-dose antishivering interventions with inactive control (placebo or no treatment). Variable doses were converted to fixed doses. Dichotomous data on the absence of shivering were analyzed by using relative benefit (RB) and number needed to treat (NNT) with 95% confidence intervals (CI). Data from 27 trials (1348 adults received an antishivering intervention; 931 were controls) were analyzed. The average incidence of shivering in controls was extremely frequent (52%). Clonidine 65–300 μg (1078 patients), meperidine 12.5–35 mg (250 patients), tramadol 35–220 mg (250 patients), and nefopam 6.5–11 mg (204 patients) were tested in at least 3 trials each. All were more effective than control. For clonidine, meperidine, and nefopam, there was some weak evidence of dose responsiveness. For small-dose clonidine (65–110 μg), the RB compared with control was 1.32 (95% CI, 1.16–1.51); for medium-dose clonidine (140–150 μg), the RB was 1.83 (95% CI, 1.47–2.27); and for large-dose clonidine (220–300 μg), the RB was 1.52 (95% CI, 1.30–1.78). For all clonidine regimens combined, the RB was 1.58 (95% CI, 1.43–1.74), with an NNT of 3.7. For all meperidine regimens combined, the RB was 1.67 (95% CI, 1.37–2.03), with an NNT of 3. For all tramadol regimens combined, the RB was 1.93 (95% CI, 1.56–2.39), with an NNT of 2.2. For all nefopam regimens combined, the RB was 2.62 (95% CI, 2.02–3.40), with an NNT of 1.7. Methylphenidate, midazolam, dolasetron, ondansetron, physostigmine, urapidil, and flumazenil were tested in no more than 3 trials each, with a limited number of patients.

Shivering may occur as an adverse effect of surgery and anesthesia. It may be associated with an increase in oxygen consumption (1), intraocular or intracranial pressure, and with wound pain (2). Thus, both the prevention of shivering and the treatment of established shivering should be regarded as clinically relevant medical interventions in the perioperative period.

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An extended version of a review on this topic is registered in the Cochrane Library.

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Methods

Relevant studies were full reports of randomized comparisons of prophylactic pharmacological, parenteral, single-dose antishivering interventions (experimental intervention) compared with placebo or no treatment (control intervention) in surgical, postoperatively nonventilated, not actively cooled adult patients. For inclusion, studies had to report dichotomous data on the presence or absence of shivering at any time after surgery. We did not consider interventions that were given via the intrathecal, epidural, or oral routes or nonpharmacological interventions. Studies in any language were considered. We did not include data from retrospective analyses or studies without randomization, from abstracts, from nonsurgical settings, or from experimental studies in volunteers. Studies with fewer than 10 patients per group were excluded. Because there is no “gold standard” antishivering intervention, we included only randomized controlled trials with a placebo (or no treatment) control group; active-controlled trials (drug-to-drug comparisons) without an inactive control group were excluded.

Two authors (PK and MRT) independently searched the MEDLINE (from 1966), EMBASE (from 1974), and CENTRAL (Cochrane) databases by using different search strategies. Free text words used were “postoperative OR postanaesthetic OR postanaesthetic,” “shivering OR shaking OR tremor,” “randomised OR randomised,” and combinations of these. The last electronic searches were on July 5, 2003. Reference lists of retrieved reports and of relevant review articles were scanned. We did not contact authors or manufacturers.

All retrieved reports were checked for inclusion by one author (PK). Those definitely not relevant were excluded at that stage. All potentially relevant reports were read by at least two authors independently to assess the adequacy of randomization and blinding and the description of withdrawals according to the validated three-item, five-point Oxford score (5). The maximum score of an included randomized controlled trial was 5, and the minimum was 1 (at least described as a randomized trial).

From relevant reports we obtained information on patients, operations, doses, routes and timing of the administration of the study drugs, and end-points. A large variety of different end-points was reported in these trials. Because of this inconsistency and to reduce the risk of interpretational bias, we extracted only dichotomous data on the complete absence of shivering. Data on adverse drug reactions were extracted when they were reported in dichotomous form. Data were extracted by one author (PK) and checked by two others (LHE and MRT). Variable doses (for instance, milligrams per kilogram of body weight) were converted to fixed doses by using the average body weights of the study populations as reported in the original trials. If these were not stated, we calculated fixed doses by assuming a body weight of 70 kg. Consensus on quality scores and extracted data was reached by discussion.

A large variety of experimental interventions were tested in these trials, and some regimens were tested in only one trial. Because no major additional information was to be expected from interventions that were tested in a limited number of patients and because undue weight would be given to those, an a priori decision was made to estimate antishivering efficacy for only those interventions that were tested in at least three trials.

As an estimate of the statistical significance of a difference between experimental interventions and control, we calculated relative benefits (RB) as relative risks with 95% confidence intervals (CI) (6). We used a fixed-effect model throughout because heterogeneity tests lack sensitivity and because we pooled data only when they were clinically homogeneous (7). A statistically significant difference between experimental and control interventions was assumed when the 95% CI of the RB excluded 1. As an estimate of the clinical relevance of a difference, we calculated the number needed to treat (NNT) (8).

We tested for dose responsiveness by using two conservative assumptions. If one dose of an experimental intervention was not significantly different from control (i.e., if the 95% CI around the RB included 1) and if larger doses were consistently more effective than control, then we regarded this as weak evidence of dose responsiveness. Second, if the 95% CI around the RB of a smaller dose did not overlap with the point estimate of the RB of a larger dose, we regarded this as strong evidence of dose responsiveness. The incidences of shivering with experimental and control interventions were graphically plotted to explore the variability of the event rates. Data on adverse drug reactions were analyzed as for efficacy data. Analyses were performed by using Excel (Microsoft, Redmond, WA) and RevMan 4.1 (Cochrane Library software; Update Software, Oxford, UK).

Results

We screened 72 potentially relevant randomized controlled trials. Forty-five were subsequently excluded. Fourteen tested continuous, target-controlled, or repetitive drug administrations (9–22). Thirteen studied intrathecally or epidurally administered drugs (23–31), an oral premedication (32), or nonpharmacological interventions (33–35). Two studies included profoundly hypothermic patients or patients who were actively cooled (36,37); one of those (37) was published as a full report in a subsequent article (38). Two articles did not contain dichotomous data (39,40). Seven
studies were not randomized, or the randomization process was unclear (41–47). Three trials lacked an inactive control group (48–50). One used an experimental design to estimate shivering thresholds (51). In one study, patients were intubated and ventilated after surgery (52). Finally, 1 trial had group sizes <10 patients (53).

We eventually analyzed data from 27 randomized controlled trials (54–80) that were published between 1980 and 2002 (Table 1). In those, 1348 adults received an experimental intervention, and 931 patients were controls. The median group size was 30 patients (range, 10–140). The median Oxford scale was 3 (range, 2–4); 10 reports scored 1, 10 scored 2, and 7 scored 4. All trials had a placebo or a no-treatment control group; 11 (54,60,63,64,66,68–72,74) studied more than 1 experimental intervention or investigated different doses of an experimental intervention. In one trial, the experimental intervention was given by the IM route (67). In all others, drugs were given IV. All drugs were given as single-dose regimens; they could be classified as opioids (meperidine), α2-agonists (clonidine), other centrally-acting analgesics (tramadol and nefopam), serotonin antagonists (dolasetron and ondansetron), benzodiazepines (midazolam), benzodiazepine antagonists (flumazenil), α-blocking drugs (urapidil), central nervous system stimulants (methylphenidate), and cholinesterase inhibitors (physostigmine).

Of the 931 control patients, 484 were reported to shiver in the postoperative period; thus, the average control event rate was 52%. There was a large variability in control event rates; in some trials, rates were less than 20% (59,79) and in others were more than 70% (75,78). Sixteen trials (54–58,61,63,67,71–73,75,77,78,80) (59% of all) reported a 50% or more incidence of shivering in the control group. Fifteen trials (54–58,62,63,65–67,69,71,74,75,77) reported on the average core temperature of the study population. Temperatures were measured in the bladder or tympanic membrane or were esophageal, rectal, or oropharyngeal or nasopharyngeal temperatures; they varied from 34.3°C (77) to 36.5°C (57). Graphically, there was no obvious relationship between the average core temperatures and the incidence of shivering in control patients (Fig. 1). Therefore, and because we had excluded trials in which patients were profoundly hypothermic or actively cooled (36,37), we combined antishivering data across studies, independently of the average core temperatures.

Clonidine was the most frequently documented drug; it was tested in 14 trials with 978 patients (56,57,60,61,63,65,66,69–72,76,78,80). The quality and quantity of the available efficacy data allowed for three sensitivity analyses.

First, we tested the effect of the time point of clonidine administration on antishivering efficacy. In two trials, clonidine was given before induction (60,80); the combined RB compared with control was 1.29 (95% CI, 1.08–1.53). In 4 trials, clonidine was given at induction (56,61,76,78); the combined RB was 1.67 (95% CI, 1.38–2.03). In 8 trials, clonidine was given during surgery or at the end of anesthesia (57,63,65,66,69–72); the combined RB was 1.64 (95% CI, 1.40–1.68).

Second, we tested the effect of trial size on the efficacy of clonidine (Fig. 2). We arbitrarily grouped trials into 3 ranges by taking the number of patients in the control groups as a measure of size. In the 6 small trials (group size, 10–20 patients), the RB was 2.00 (95% CI, 1.60–2.50) (57,61,63,66,72,80). In the 5 medium trials (30 patients), the RB was 1.62 (95% CI, 1.38–1.89) (56,65,69–71). In the 3 largest trials (50–140 patients), the RB was 1.46 (95% CI, 1.27–1.68) (60,76,78).

Third, we tested the effect of the clonidine dose on efficacy (Fig. 3). Because a large number of different doses were tested, we arbitrarily grouped regimens into 3 ranges of fixed doses: 65–110 μg, 140–150 μg, and 220–300 μg. With the smallest-dose range, RB compared with control was 1.32 (95% CI, 1.16–1.51); with the medium-dose range, the RB was 1.83 (95% CI, 1.47–2.27); and with the large-dose range, the RB was 1.61 (95% CI, 1.38–1.87).

When data from all clonidine trials were combined, the average control event rate was 52%. The RB to prevent shivering compared with control was 1.58 (95% CI, 1.43–1.74), and the NNT was 3.7 (95% CI, 3.0–4.6).

Three further drugs—meperidine, nefopam, and tramadol—were tested in at least three trials. Five trials with 250 patients tested IV meperidine (63,64,66,67,71). Shivering was reported in 40% to 57% of controls (average, 50%). The size of control groups was between 15 patients (66) and 30 patients (67,71). Tested regimens were 0.3, 0.4, and 0.5 mg/kg; 12.5 mg; and 25 mg (Table 1). When variable doses were converted to fixed doses, the tested dose range was 12.5–35 mg. There was some evidence of dose responsiveness, because doses larger than 25 mg only were consistently more effective than control (Fig. 4A). When data from all meperidine regimens were combined, the RB was 1.67 (95% CI, 1.37–2.03), and the NNT was 3.0 (95% CI, 2.3–4.5).

Five trials with 204 patients tested IV nefopam (54,72,73,75,77). Shivering was reported in 57% to 90% of controls (average, 64%). The size of the control groups was between 15 patients (73) and 30 patients (54). Tested regimens were 0.1 and 0.15 mg/kg and 10 mg (Table 1). When variable doses were converted to fixed doses, the tested dose range was 7–11 mg. All doses were more effective than control; however, there was no evidence of dose responsiveness (Fig. 4B). When data from all nefopam regimens were combined, the RB was 2.62 (95% CI, 2.02–3.40), and the NNT was 1.7 (95% CI, 1.4–2.0).
Table 1. Pharmacological Prophylaxis of Postoperative Shivering: Analyzed Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Withdrawal</th>
<th>Surgical setting</th>
<th>Type of anesthesia</th>
<th>Comparisons (No. patients)</th>
<th>Time of administration</th>
<th>Mean temperature (°C)</th>
</tr>
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<tr>
<td>Bilotta (54)</td>
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<td>Epidural/spinal</td>
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<td>Induction</td>
<td>36.3</td>
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<tr>
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<td></td>
<td></td>
<td>Dolasetron 1 mg/kg IV (25) Placebo (25)</td>
<td>End</td>
<td>36.0</td>
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<td>Bock (55)</td>
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<td>2</td>
<td>0</td>
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<td>General</td>
<td>Clonidine 150 μg IV (30) Placebo (30)</td>
<td>Induction</td>
<td>36.4</td>
</tr>
<tr>
<td>Buggy (56)</td>
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<td>2</td>
<td>0</td>
<td>Elective orthopedic limb</td>
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<td>Delaunay (57)</td>
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<td>2</td>
<td>0</td>
<td>Thyroid</td>
<td>General</td>
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<td>36.4</td>
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<td>General</td>
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<td>35.6</td>
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<td>1</td>
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<td>Wisdom teeth extraction</td>
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<td>Midazolam 50 μg/kg IV (50) Clonidine 4 μg/kg IV (14) Placebo (14)</td>
<td>Premedication</td>
<td>35.8</td>
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<tr>
<td>Frank (61)</td>
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<td>1</td>
<td>0</td>
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<td>Clonidine 4 μg/kg IV (20) Placebo (20)</td>
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<td>35.6</td>
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<td>0</td>
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<td>Clonidine 1.5 μg/kg IV (15) Meperidine 25 mg IV (21) Placebo (21)</td>
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<td>35.6</td>
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<td>0</td>
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<td>Clonidine 3 μg/kg IV (30) Placebo (30)</td>
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<td>General</td>
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<td>Study</td>
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<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo (27)</td>
<td></td>
<td>34.6</td>
</tr>
<tr>
<td>Vanderstappen (78)</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>Peripheral</td>
<td>General</td>
<td>Clonidine 2 µg/kg IV (140)</td>
<td>Induction</td>
<td>NA</td>
</tr>
<tr>
<td>Weinbroum (79)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>Inguinal hemioplasty, breast biopsy, or diagnostic arthroscopy</td>
<td>General</td>
<td>Flumazenil 1 mg IV (46 + 46 + 35)</td>
<td>End</td>
<td>NA</td>
</tr>
<tr>
<td>Yang (80)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Extracorporeal shockwave lithotripsy</td>
<td>Epidural</td>
<td>Clonidine 150 µg IV (20)</td>
<td>Premedication</td>
<td>NA</td>
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</table>

Temperatures in parentheses were extrapolated from graphs. Temperatures were measured in the bladder or the tympanic membrane or were esophageal, rectal, and oropharyngeal or nasopharyngeal. NA = not available.
Three trials with 250 patients tested IV tramadol (54,58,68). Shivering was reported in 48% to 60% of controls (average, 53%). The size of the control groups was between 20 patients (58) and 50 patients (68). Tested regimens were 0.5, 1, 2, and 3 mg/kg (Table 1). When variable doses were converted to fixed doses, the tested dose range was 35–220 mg. There was increasing efficacy with increasing doses (Fig. 4C); the RB increased consistently from 1.77 with 35 mg (0.5 mg/kg) to 2.50 with 220 mg (3 mg/kg). Corresponding NNTs decreased from 3 to 1.7. When data from all tramadol regimens were combined, the RB was 1.93 (95% CI, 1.56–2.39), and the NNT was 2.2 (95% CI, 1.8–2.8).

Three trials with more than 2 arms compared clonidine 1.5, 2, or 3 μg/kg with meperidine 0.3, 0.4, or 0.5 mg/kg (63,66,71). With all 3 clonidine regimens combined, 58 (89%) of 65 patients did not shiver; with meperidine, 55 (85%) of 65 patients did not shiver (RB, 1.06; 95% CI, 0.91–1.22). No other drug-to-drug comparisons were tested in more than two trials.

All other interventions were tested in no more than two trials and with a limited number of patients. These were midazolam (60,62), dolasetron (55,69), urapidil (70,71), methylphenidate (59), physostigmine (66), ondansetron (74), and flumazenil (79).

Reporting of adverse effects was sparse. With clonidine, hypotension and bradycardia were reported (76,78,80). With meperidine (66) and tramadol (58,68), nausea and vomiting were reported. One trial that tested nefopam reported on drowsiness (77). None of the adverse effects was significantly associated with any of the experimental interventions.

Discussion

These trials suggest that fewer than four patients have to receive prophylactic clonidine for one not to shiver after surgery. For meperidine, nefopam, and tramadol, efficacy data seemed even more convincing. The nefopam trials, for instance, suggested that fewer than two patients have to receive that drug prophylactically for one to stay free of symptoms. However, we have to assume that this extraordinary degree of efficacy is flawed. The frequent incidence of shivering in the untreated control groups suggested that these trial populations had a very high baseline risk. Two problems emerge from this. First, these study populations do not necessarily represent those whom anesthesiologists see in daily clinical practice; this challenges the external validity of the trials. Second, although the NNT represents a valuable tool to quantify the effort that is needed to achieve one successful outcome, it has to be kept in mind that absolute measurements of treatment efficacy tend to overestimate an intervention’s usefulness when control event rates are extremely frequent. To get an impression of an intervention’s performance independently of the baseline risk, it may be more sensible to express efficacy in relative terms. These prophylactic interventions, for instance, have the potential to decrease the risk of postoperative shivering by a factor of 1.5 to 2.5. Keeping this degree of relative efficacy in mind, the performance of clonidine, tramadol, nefopam, and meperidine can be extrapolated to populations with much less risk of postoperative shivering. Obviously, in populations with lower baseline risks, the absolute degree of efficacy of these drugs will be weaker, and, thus, the NNTs to prevent shivering compared with placebo will be larger.

Clonidine has been tested in more trials than any other drug; therefore, sensitivity analyses could be...
performed to study the effect of dose and timing of administration. For best efficacy, clonidine should be administered no earlier than at induction, and doses should be larger than 140/\textmu g. Similar analyses could not be performed for the other drugs because of a lack of relevant data.

Our analysis has some limitations; most are related to the original trials. First, for none of the tested molecules is the biological basis for their antishivering effect fully understood. Some may alter the shivering threshold. This has been demonstrated for meperidine (81) and clonidine (82). Second, we were unable to identify predictive factors for postoperative shivering. We had to rely on the incidence of shivering with clonidine and with control (placebo); each symbol represents one trial, and the area of the symbol is proportional to the trial size.

Figure 3. Prevention of shivering with small-, medium-, and large-close clonidine. Dose ranges were chosen post hoc. Forest plots show a relative benefit with 95% confidence interval (CI) for absence of shivering with clonidine compared with control (placebo). Event rate scatters show incidences of shivering with clonidine and with control (placebo); each symbol represents one trial, and the area of the symbol is proportional to the trial size.

from meta-analyses of indirect comparisons are similar to those that include direct drug-to-drug comparisons (83). Data from three placebo-controlled trials that directly compared clonidine with meperidine confirmed the results from the indirect comparisons (63,66,71). Fourth, most trials were of limited size; 5 trials only included 30 or more patients per group (60,68,76,78,79); 4 of those tested clonidine. With clonidine, there was strong evidence that trial size affected antishivering efficacy; small trials overestimated treatment effect compared with larger trials. None of the other drugs was tested in trials of comparable size. When all trials were considered independent of size, the relative benefit for antishivering efficacy with nefopam was 2.62 (NNT, 1.7), and with clonidine it was 1.58 (NNT, 3.7). This indirect comparison suggests that nefopam was more effective than clonidine. Nefopam trials, however, had on average much smaller group sizes. When data from a subgroup of small clonidine trials were combined in a sensitivity analysis, the relative risk point estimate improved to 2.0 (NNT, 2.2) and thus came close to the values for nefopam.
This example strongly suggests that trial size should not be ignored when efficacy is estimated on the basis of data from indirect (placebo-controlled) comparisons. Fifth, the methodological quality of most trials was unsatisfactory. Twenty reports had a quality score of 2 or less on the five-point Oxford scale. Low quality scores also have been associated with biased estimates of efficacy. We were unable to conduct the necessary sensitivity analyses to confirm this because there were not enough high-quality trials. Finally, reporting of harm was sparse. A single dose of meperidine 30 mg or of nefopam 10 mg is unlikely to induce clinically relevant adverse effects. However, with clonidine 150 μg, we would expect bradycardia or hypotension in most patients. Lack of reporting of adverse effects does not mean that none occurred.

In conclusion, prophylaxis of postoperative shivering with simple pharmacological interventions is possible and clinically effective if the risk of developing postoperative shivering is very high. This begs the question of whether shivering should be prevented or if shivering patients should be treated. Treatment of established shivering was also shown to be very effective (4); indeed, NNTs to stop further shivering with meperidine or clonidine in a shivering patient were even less than for prophylaxis. However, in the treatment trials, observation periods were very short, often <10 minutes (4); thus, we do not know how these drugs perform long-term as a therapy of established shivering. With prophylaxis, many patients will receive a drug without actually needing it. These patients are unnecessarily exposed to adverse drug reactions. The fact that intraoperative body warming and maintaining core temperature per se have a major effect on the incidence of postoperative shivering (84) further puts into question the usefulness of pharmacological shivering prophylaxis. There may be a special case for selected patients with compromised cardiac oxygen supply; in these patients, it may be worthwhile to give an antishivering drug prophylactically, and clonidine may be the most rational choice, because in addition to its antishivering effect, it has a favorable effect on cardiac outcome (85). Finally, more knowledge about predictive factors for postoperative shivering is likely to further ameliorate the clinical management of patients at risk and, it is hoped, improve outcomes.

Figure 4. Prevention of shivering with meperidine (A), nefopam (B), and tramadol (C). Regimens are fixed doses and variable doses (as used in the included trials) in parentheses. Forest plots show relative benefit with 95% confidence interval (CI) for the absence of shivering with experimental interventions compared with control (placebo). Event rate scatters show the incidence of shivering with active treatment (experimental interventions) and with control (placebo); each symbol represents one trial, and the area of the symbol is proportional to trial size. *Trials with two active arms; placebo patients were counted only once.
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References


