Pharmacological Treatment 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 interventions that are used for the treatment of postoperative shivering is not well understood. We performed a systematic search (MEDLINE, EMBASE, Cochrane Library, hand searching, all languages, to August, 2000) for full reports of randomized comparisons of any pharmacological antishivering intervention (active) with placebo (control) in the postoperative period. Dichotomous data on absence of further shivering after treatment and adverse effects were extracted from original reports. Relative risk (RR) and number-needed-to-treat (NNT) were calculated with 95% confidence interval (CI) using a fixed effect model. Data from 20 trials (944 adults received an active intervention, 413 were controls) were analyzed. Antishivering efficacy depended on the active regimen and the length of follow-up. Efficacy with meperidine 25 mg, clonidine 150 μg, ketanserin 10 mg, and doxapram 100 mg was reported in at least three trials; all were significantly more effective than control. After 1 min, the NNT of meperidine 25 mg for no further shivering compared with placebo was 2.7 (RR, 6.8; 95% CI, 2.5–18.5). After 5 min, the NNT of meperidine 25 mg was 1.3 (RR, 9.6; 95% CI, 5.7–16), the NNT of clonidine 150 μg was 1.3 (RR, 6.8; 95% CI, 3.3–14.2), the NNT of doxapram 100 mg was 1.7 (RR 4.0; 95% CI, 2.4–6.5), and the NNT of ketanserin 10 mg was 2.3 (RR 3.1; 95% CI, 1.9–5.1). After 10 min, the NNT of meperidine 25 mg was 1.5 (RR 4.0; 95% CI, 2.5–6.2). After 15 min, the NNT of ketanserin 10 mg was 3.3 (RR 1.5; 95% CI, 1.2–1.9). Long-term outcome data were lacking. There were not enough data for alfentanil, fentanyl, morphine, nalbuphine, lidocaine, magnesium, metamizol, methylphenidate, nefopam, pentazocine, and tramadol to draw meaningful conclusions. Reporting of adverse drug reactions was sparse. Fewer than two shivering patients need to be treated with meperidine 25 mg, clonidine 150 μg, or doxapram 100 mg for one to stop shivering within 5 min who would have continued to shiver had they all received a placebo.

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Shivering is an unpleasant and frequent complication in the postoperative period (1). The origin of postoperative shivering is unclear; various mechanisms have been proposed. Shivering may happen as a thermoregulatory response to hypothermia or muscle hyperactivity with clonic or tonic patterns; and different frequencies have been reported (1). However, in the postoperative period, muscle activity may be increased even with normothermia (2), suggesting that other mechanisms than heat loss and subsequent decrease in core temperature may contribute to the development of shivering. These include uninhibited spinal reflexes, postoperative pain, decreased sympathetic activity, pyrogen release, adrenal suppression, and respiratory alkalosis (1).

In a survey on 33 clinical problems, anesthesiologists ranked postoperative shivering 8th when its frequency was considered and 21st when asked about the importance of preventing this complication (3). This suggests that most anesthesiologists do not consider shivering to be a true medical problem. However, in a shivering patient, oxygen consumption may

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increase by 200% to 500% (4,5). Also, hypothermia may trigger vasoconstriction and thus increase vascular resistance. Thus, in a patient with already limited myocardial oxygen supply because of arteriosclerosis, shivering may further compromise myocardial function. Shivering may also increase intraocular and intracranial pressure, and it may contribute to increased wound pain (1).

Numerous pharmacological interventions have been proposed for the treatment of postoperative shivering. Textbooks suggest that apart from applying radiant heat to the body surface, shivering may be treated with meperidine, clonidine, or ketanserin (1). The relative efficacy of these different molecules, however, remains unclear. The aim of this systematic review was to evaluate efficacy and harm of pharmacological interventions that are currently used for the treatment of postoperative shivering.

Methods

Inclusion and Exclusion Criteria

Relevant studies were full reports of randomized comparisons of any pharmacological antishivering intervention (active) compared with placebo or no treatment (control) in postoperative, nonventilated patients. Studies in any language were considered. Data on the efficacy of prevention of shivering or on nonpharmacological interventions were not included. We did not consider data from retrospective analyses, from studies without randomization, or from abstracts. Studies with group sizes <10 patients were excluded.

Systematic Search

Two authors (PK and MRT) independently searched the MEDLINE (http://www.nlm.nih.gov), EMBASE (http://stneasy.fiz-karlsruhe.de and DataStar®) and Cochrane Controlled Trials Register (http://www.cochrane.de) databases using different search strategies. Free text words used were "postoperative OR postanesthetic OR postanaesthetic" AND "shivering OR shaking OR tremor" AND "randomized OR randomised."

The date of the last electronic search was August 11, 2000. Reference lists of retrieved reports and of relevant review articles (6,7) were screened. Locally available anesthesia journals were hand searched. The German manufacturers of pethidine (meperidine) (Aventis Pharma) and clonidine (Boehringer Ingelheim) were contacted by letter and asked for additional information, including unpublished data.

Critical Appraisal and Data Extraction

All retrieved reports were screened by one author (PK). Irrelevant data were excluded at that stage. Each potentially relevant report was then read by at least two other authors independently to assess adequacy of randomization and blinding and description of withdrawals according to the validated three-item, five-point Oxford scale (8). We assigned one point to studies described as being "randomized," and an additional point if the method of randomization was described and adequate (for instance a table of random numbers). One point was assigned when the trial was described as "double-blind," and an additional point was assigned if the method of double blinding was described and adequate (for instance, identical ampoules). Finally, reports that described the number of and reasons for withdrawals were given one point. Because we included only randomized trials, the minimum score of a valid trial was one and the maximum score was five.

Relevant efficacy data were extracted by one author (PK) and checked by another author (LHE). Numerous different efficacy endpoints were reported in these trials. To avoid unnecessary heterogeneity of the data and to reduce the risk of interpretational bias, there was a *pre hoc* decision to extract only efficacy data on complete absence of shivering after application of the study drugs. When there were repeated drug administrations at different time intervals we calculated the respective cumulative drug doses for each time interval. Variable doses (for instance, milligrams per kilogram of body weight) were extrapolated to fixed doses using the average body weight of the study populations as reported in the original trials. Consensus on both quality scores and extracted data was reached by discussion.

Meta-Analyses

As an estimate of the statistical significance of a difference between active and control, we calculated relative risks (RR) with 95% confidence intervals (CI) (9). Because all combined data were clinically and statistically homogenous ($P > 0.1$) we used a fixed effect model throughout. A statistically significant difference between active and control was assumed when the 95% CI of the RR did not include 1. As an estimate of the clinical relevance of any difference between active and control we calculated the number-needed-to-treat (NNT) (10) with 95% CI (11). Because control event rates were similar across different trials, we graphically plotted NNTs and 95% CI for individual treatments to test for relative efficacy (12). Data on adverse drug reactions were extracted when they were reported in dichotomous form, and they were analyzed as for efficacy data. Analyses were done using Excel on a Power Macintosh G3 and checked in RevMan 4.0 provided as a freeware by the Cochrane Collaboration (http://www.cochrane.org/) (13).

Results

Excluded and Included Reports

We retrieved 41 potentially relevant reports (Fig. 1). Twenty-one were later excluded; 3 evaluated the effect of a muscle relaxant in ventilated patients (14–16), 11 had no placebo or "no treatment" control (5,17–26), 5 were not randomized or the randomization process was unclear (27–31), in 1, group size was <10 patients (32), and 1 did not report on dichotomous efficacy data (33).

We eventually analyzed data from 20 randomized controlled trials published between 1984 and 2000 (34–53) (Table 1). Pharmaceutical companies did not provide relevant additional data. In those trials, 944 adults received an active intervention, and 413 controls received a placebo. The median size of active and control groups was 18 patients (range, 9–37) and 20 patients (range, 10–32), respectively. The median Oxford scale was 2.5 (range, 1–4). One report scored 1, 9 scored 2, 6 scored 3, and 4 scored 4. In five trials, efficacy data had to be extrapolated from graphs (34,39,42,49,50). There were two dose-finding studies (37,53). In one trial, patients' average body temperature was between 34°C and 35°C (41); in all other trials that reported on body temperature, it was above 35°C.

The active interventions were opioids (morphine, fentanyl, alfentanil, pethidine [meperidine], nalbuphine, pentazocine), other centrally acting analgesics (tramadol, metamizol, nefopam), sodium channel blocker (lidocaine), α_2-agonist (clonidine), methylphenidate, doxapram, ketanserin, and magnesium.

Time Dependency

The observation times were between 1 min and 45 min. There was a direct relationship between the length of the observation period and the percentage of control patients who shivered after application of a placebo (i.e., the control event rate) (Fig. 2). Because we have to assume that there is some relationship between the control event rate and the true underlying risk, we tested the impact of the observation period on the antishivering efficacy of active interventions. For three drugs, there was an adequate number of data for one dose to test for this potential relationship; this was with ketanserin 10 mg (36,39,45), meperidine 25 mg (42,44,46,49,51–53), and clonidine 150 μg (39,41,43,47). With all three regimens, the RR for further shivering compared with placebo decreased over time, i.e., the antishivering efficacy decreased with increasing length of the observation period (Fig. 3).

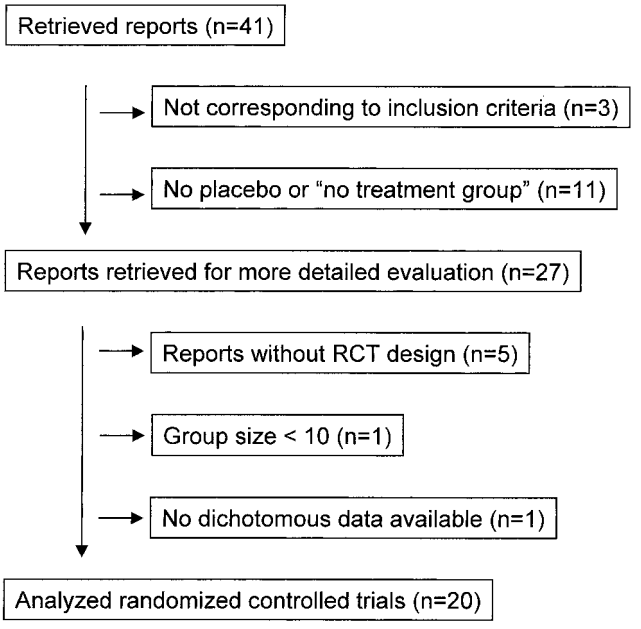

Figure 1. Flow chart of retrieved and analyzed reports.

Antishivering Efficacy

Many regimens were tested in one small trial only. Because undue weight could be given to these interventions, an arbitrary decision was made to estimate antishivering efficacy for only those interventions that were tested in at least two trials. These were meperidine 25 mg (42,44,49,51–53), clonidine 150 μg (39,41,43,47), doxapram 100 mg (48,49,53), ketanserin 10 mg (36,39,45), and alfentanil 250 μg (42,52). Because antishivering efficacy obviously depended on the length of the observation time, data pooling, and estimation of the relative efficacy of different interventions was performed only within similar observation periods (Table 2, Fig. 4). Within time periods, all combined efficacy data were statistically homogenous ($P > 0.1$).

All these interventions were statistically significantly more effective than placebo at all time points, except for ketanserin 10 mg after 30 min. Meperidine 25 mg was most often tested and performed consistently best at 1, 5, 10, and 15 min. After one min, the NNT to prevent any further shivering with meperidine 25 mg compared with placebo was approximately 3, suggesting that it acted faster than alfentanil 250 μg or doxapram 100 mg. After 5, 10, and 15 min, the NNTs for meperidine 25 mg were less than 2. Some of the other interventions came close to this; clonidine 150 μg and doxapram 100 mg, for instance, had NNTs less than 2 at 5 min but not thereafter.

Other Interventions

Regimens of fentanyl (34,46), lidocaine (34), magnesium (40), metamizol (44), methylphenidate (41), morphine (46), nalbuphine (51), nefopam (38), pentazocine

Table 1. Pharmacological Treatment of Postoperative Shivering: Analyzed Randomized Controlled Trials

Reference	Validity score (random/blinding/withdrawal)	Surgical setting	Type of anesthesia	Comparisons	Assessment of symptoms (min after application)	Temperature (°C) in each group
Pauca et al. (46)	2/2/0	Mainly intra-abdominal	General	1. Meperidine 6.25 mg every 5 min up to 25 mg	5/10/15/20	36.0 ± 0.13
				2. Morphine 0.5 mg every 5 min up to 2.5 mg		35.7 ± 0.17
				3. Fentanyl 5 μg every 5 min up to 25 μg		35.7 ± 0.17
				4. Placebo		35.6 ± 0.16
Nalda et al. (45)	1/1/0	Gynecology	General	1. Ketanserin 10 mg	5/15/30	35.6 ± 1.1
				2. Placebo		36.0 ± 1.0
Launo et al. (41)	1/2/0	General, thoracic and vascular	Inhaled, droperidol/fentanyl, propofol/fentanyl	1. Clonidine 75 μg	10/20	34.4 ± 1.3
				2. Clonidine 150 μg		34.3 ± 0.8
				3. Methylphenidate 20 mg		34.9 ± 1.1
				4. Placebo		35.1 ± 0.9
Sarma and Fry (48)	1/2/0	NA	Inhaled	1. Doxapram 100 mg	1/5	36.0 (34.2–37.5)
				2. Placebo		36.0 (34.0–38.0)
Capogna and Celleno (35)	1/1/0	Labor pain and cesarean delivery	Epidural, general	1. Clonidine 30 μg every 5 min up to 90 μg	5/10/15	n.a.
				2. Placebo	20/25/30	
Ferri et al. (38)	1/0/0	General, orthopedics, and gynecology	Balanced general	1. Nefopam 0.2 mg kg^{-1}	1/5/10	n.a.
				2. Placebo		
Joris et al. (39)	1/1/1	Abdominal, orthopedics, and urology	Balanced general	1. Clonidine 150 μg	1–30 (survival curves)	35.5 ± 0.6
				2. Ketanserin 10 mg		35.6 ± 0.8
				3. Placebo		35.6 ± 0.8
Pern et al. (47)	1/1/0	NA	Spinal or epidural	1. Clonidine 150 μg	5/10	NA
				2. Placebo		
Singh et al. (49)	1/2/0	Orthopedics and ENT	General	1. Doxapram 1.5 mg kg^{-1}	1/2/3/4/5/6/7/8/9/10	36.1 ± 0.3
				2. Meperidine 0.33 mg kg^{-1}		36.2 ± 0.4
				3. Placebo		36.2 ± 0.3
Mercadante et al. (43)	1/1/0	Labor pain	Epidural	1. Clonidine 150 μg	5	NA
				2. Meperidine 50 mg		
				3. Placebo		
Alfonsi et al. (34)	1/1/0	Orthopedics and abdominal	Balanced general	1. Meperidine 0.85 mg kg^{-1}	5/10/15	<36
				2. Fentanyl 1.7 μg kg^{-1}		
				3. Lidocaine 1 mg kg^{-1}		
				4. Placebo		
Lyons et al. (42)	1/1/0	Minor	Inhaled	1. Alfentanil 250 μg	1/5/10	36 (34.1–37.1)
				2. Meperidine 25 mg		35.9 (33.8–37.2)
				3. Placebo		36.2 (34.9–37.1)
Monso et al. (44)	1/1/0	General, orthopedics and gynecology	Balanced general	1. Meperidine 0.4 mg kg^{-1}	5/15/30/45	NA
				2. Metamizol 25 mg kg^{-1}		
				3. Placebo		
Crisinel et al. (36)	1/1/0	Elective	Balanced general	1. Ketanserin 10 mg	5/10/15/30	35.6 ± 0.2
				2. Placebo		35.5 ± 0.2
De Witte et al. (37)	1/2/1	Laparoscopy, laminectomy, discectomy	Balanced general	1. Tramadol 0.5 mg kg^{-1}	1/3/5	35.7 ± 0.4
				2. Tramadol 1 mg kg^{-1}		35.6 ± 0.5
				3. Tramadol 2 mg kg^{-1}		35.6 ± 0.5
				4. Placebo		35.7 ± 0.6
Kizilirmak et al. (40)	1/1/0	NA	General	1. Meperidine 0.5 mg kg^{-1}	20	35.6 ± 0.5
				2. Magnesium 30 mg kg^{-1}		35.6 ± 0.4
				3. Placebo		35.5 ± 0.5

Table 1. Continued.

Reference	Validity score (random/ blinding/ withdrawal)	Surgical setting	Type of anesthesia	Comparisons	Assessment of symptoms (min after application)	Temperature (°C) in each group
Wrench et al. (52)	2/1/0	General, orthopedic, gynecology, ENT	NA	1. Meperidine 25 mg 2. Alfentanil 250 μg 3. Placebo	1–10	36.6 ± 0.8 36.3 ± 0.7 36.2 ± 0.7
Wrench et al. (53)	2/2/0	General, orthopedics, gynecology, ENT	NA	1. Doxapram 0.18–1.4 mg kg^{-1} 2. Meperidine 0.12–0.35 mg kg^{-1} 3. Placebo	5	~36.5 ± 0.8 for all active groups
Wang et al. (51)	2/1/0	General, orthopedics, gynecology	General	1. Nalbuphine 0.08 mg kg^{-1} 2. Meperidine 0.4 mg kg^{-1} 3. Placebo	5/15/30	36.5 ± 0.6 36.4 ± 0.5 36.4 ± 0.7
Terasako and Yamamoto (50)	2/2/0	General, orthopedics, plastic, ENT	General	1. Meperidine 17.5 mg 2. Pentazocine 7.5 mg 3. Placebo	2–10	35.5 ± 0.8 35.9 ± 0.9 35.8 ± 0.6

Temperatures expressed as mean ± SD or mean (range).
NA = not applicable or data not reported; ENT = ear, nose, throat.

Figure 2. Time dependency of shivering in control patients receiving a placebo. Each symbol represents one trial; symbol sizes do not take into account trial size. Data from several observation periods may come from one single trial.

(50), and tramadol (37) were tested in one trial each with a limited number of patients. No further conclusions could be drawn in addition those provided by the individual papers.

Adverse Effects

Three trials reported on nausea or vomiting with meperidine 25 mg (46), 50 mg (43) or 0.4 mg/kg (44). In those, 6 of 82 patients (7.3%) had nausea or vomited with meperidine compared with 2 of 76 (2.6%) with placebo, a difference that was not statistically significant (RR, 2.84; 95% CI, 0.60–13.5). Two trials reported on respiratory depression with meperidine (defined as "bradypnoe and pulse oximetry <85%" (34) or "bradypnoe not needing a specific treatment" (44)). Using these criteria, 2 of 48 patients (4.2%) had bradypnoe with meperidine compared with 0 of 45 with placebo, a difference that was not statistically significant (RR, 2.87; 95% CI, 0.31–26.4). Other adverse effects, reported in no more than one trial, were nausea or vomiting with fentanyl (34), and bradycardia with clonidine or ketanserin (39).

Discussion

Shivering, as nausea or vomiting, never becomes chronic and it is unlikely to kill a patient. However, in shivering postoperative patients, left ventricular systolic work index and oxygen consumption index may be increased (54). It is, therefore, encouraging that some simple and inexpensive interventions are effective in the treatment of this adverse effect of anesthesia and surgery. Two shivering patients need to be treated with meperidine 25 mg, clonidine 150 μg, or doxapram 100 mg for one to stop shivering within five minutes who would have continued to shiver had

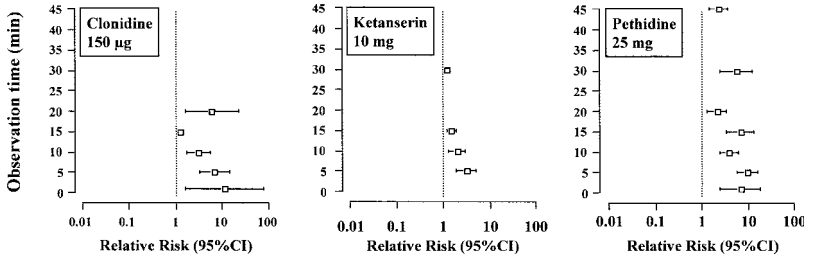

Figure 3. Relationship between the length of the observation period and the effectiveness of three antishivering regimens compared with placebo. Symbols are relative risks with 95% confidence intervals. The dotted lines represent unity (i.e., no effect).

Table 2. Treatment of Postoperative Shivering: Efficacy Data

Regimen	Number not shivering/total number of patients: active (%)	Number not shivering/total number of patients: control (%)	Relative risk (95% CI)	Number-needed-to-treat (NNT) (95% CI)	References
No shivering after 1 min					
Meperidine 25 mg	29/68 (43)	4/65 (6)	6.82 (2.51–18.5)	2.7 (2.0–4.3)	(42, 49, 52)
Doxapram 100 mg	16/49 (33)	4/49 (8)	4.00 (1.43–11.2)	4.1 (2.5–11)	(48, 49)
Alfentanil 250 µg	11/48 (23)	2/45 (4)	5.00 (1.18–21.2)	5.4 (3.1–19)	(42, 52)
No shivering after 5 min					
Meperidine 25 mg	133/153 (87)	13/147 (9)	9.55 (5.72–15.9)	1.3 (1.2–1.4)	(42, 44, 49, 51–53)
Clonidine 150 µg	39/45 (87)	6/49 (12)	6.82 (3.28–14.2)	1.3 (1.1–1.6)	(39, 43, 47)
Doxapram 100 mg	46/59 (78)	14/69 (20)	3.97 (2.42–6.53)	1.7 (1.4–2.3)	(48, 49, 53)
Ketanserin 10 mg	41/65 (63)	13/64 (20)	3.10 (1.88–5.13)	2.3 (1.7–3.6)	(36, 39, 45)
Alfentanil 250 µg	24/48 (50)	4/45 (9)	5.56 (2.04–15.1)	2.4 (1.7–4.0)	(42, 52)
No shivering after 10 min					
Meperidine 25 mg	62/68 (91)	15/65 (23)	3.96 (2.53–6.22)	1.5 (1.2–1.8)	(42, 49, 52)
Clonidine 150 µg	23/30 (77)	9/34 (26)	2.90 (1.60–5.25)	2.0 (1.4–3.4)	(39, 41)
Ketanserin 10 mg	33/45 (73)	16/44 (36)	2.01 (1.31–3.09)	2.7 (1.8–5.6)	(36, 39)
Alfentanil 250 µg	26/48 (54)	10/45 (22)	2.40 (1.29–4.45)	3.1 (2.0–7.5)	(42, 52)
No shivering after 15 min					
Meperidine 25 mg	57/65 (88)	8/62 (13)	6.76 (3.52–12.9)	1.3 (1.2–1.6)	(44, 51)
Ketanserin 10 mg	58/65 (89)	38/64 (59)	1.50 (1.21–1.86)	3.4 (2.3–6.4)	(36, 39, 45)
No shivering after 30 min					
Ketanserin 10 mg	42/45 (93)	36/45 (80)	1.17 (0.99–1.37)	7.5 (3.7–−227)	(36, 45)

* A negative upper limit of the 95% CI around the NNT indicates that the result is not statistically significant (the confidence interval includes zero, and thus infinity).
95% CI = 95% confidence interval.

they all received a placebo. This degree of efficacy relates to the "average" shivering adult patient in the postoperative period. Most often, shivering was diagnosed clinically; the role of body temperature remained unclear. As these trials used randomized treatment allocation, differences in body temperature (core or peripheral) were unlikely to have an effect on the overall efficacy. In none of the trials, a stratified (factorial) design with efficacy evaluation in normothermic versus hypothermic patients was applied. Average body temperatures were comparable across the studies, and no profound hypothermia was reported. We do not know, if these antishivering interventions are more (or less) effective in specific subgroups of patients, for instance in those who are hypothermic.

There were several methodological problems with this analysis. First, we had to rely on indirect comparisons (i.e., comparisons from placebo-controlled trials). This was necessary because, for shivering, as for many other clinical settings, a "gold standard" treatment is unknown. As a consequence, trialists do not know what standard comparator they should choose to test the efficacy of a new, experimental intervention. We retrieved many potentially valid randomized trials that compared an experimental intervention with a randomly chosen comparator. Combining these heterogeneous data was impossible. Active comparisons, however, may be used to test the validity of the league table of relative antishivering efficacy (Fig. 4). For instance, in a recent direct comparison, there was equivalence between meperidine 25 mg and clonidine 150 µg (55), and the league table suggested the same.

Second, as in previous similar analyses (56,57), we had to choose a dichotomous efficacy end point to overcome the large variability of the different reported end points. The only way to reduce both the risk of interpretation bias and heterogeneity of the data was to define a clearly dichotomous hurdle of efficacy, for

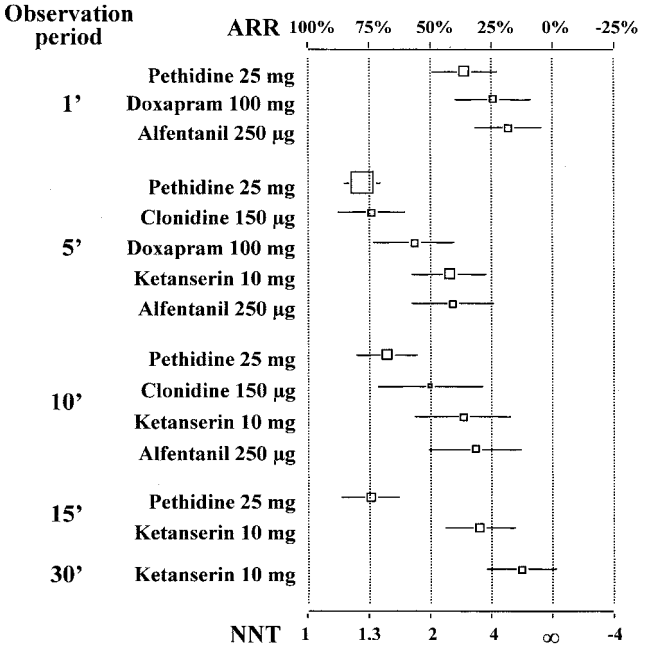

Figure 4. League table of antishivering effectiveness. Each symbol represents the meta-analysis of at least two trials. Symbol sizes are proportional to the number of analyzed patients. Horizontal bars are 95% confidence intervals. ARR = absolute risk reduction; NNT = number needed to treat; ∞ = infinity = absolute risk reduction equals zero.

instance, absence of any shivering after treatment. Such a hurdle may be unnecessarily high; a treatment that does not stop shivering but that alleviates symptoms to a great extent may be clinically useful. However, a dichotomous end point allows combination of data from independent trials, and thus increases power.

Third, when analyzing the control event rates (i.e., the incidence of shivering in placebo patients) it became obvious that the length of the observation period was a factor (Fig. 3). In such circumstances it was invalid to combine efficacy data that originated from different observation times. The relative efficacy of the different experimental interventions was, therefore, compared within similar observation periods only, and indeed the data within these periods were statistically homogenous. Because observation times were inconsistently reported and because many interventions were tested in no more than 1 trial each, only 5 regimens could be compared: meperidine 25 mg, doxapram 100 mg, clonidine 150 µg, ketanserin 10 mg, and alfentanil 250 µg after 5 minutes. One drug only was tested up to 30 minutes; this was ketanserin 10 mg, and it was not significantly different from placebo. Thus, the information on the relative efficacy of these drugs remains limited.

Reporting of adverse drug reactions was sparse. The problem then is that we do not know if adverse drug reactions did not occur, or if they were not reported. Typically opioid-related side effects, such as nausea, vomiting or respiratory depression, seemed to be rare with relatively small and single doses of morphine, fentanyl, alfentanil, meperidine, nalbuphine, or pentazocine. The absence of bradycardia and hypotension with clonidine up to 150 µg is less obvious; it may be cautious to titrate the clonidine.

The fact that simple regimens such as meperidine 25 mg are very effective in treating shivering patients begs the question as to whether more trials to investigate the efficacy of yet other drugs that may have some antishivering efficacy are actually needed. However, there were some weaknesses in almost all these trials; this may justify the definition of a research agenda. For instance, there was a lack of data on long-term outcome. Many trials stopped observations after only 5 or 10 minutes. Such short observation periods may not be long enough to identify the true efficacy of these interventions and their long-term effect on patients. Also, data on the efficacy of these drugs in children are lacking. Finally, because the time course plays a crucial role in this setting, it seems reasonable to report the time to the first treatment application to allow for meaningful comparisons between studies.

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