

# The effectiveness of meperidine and doxapram in relieving postoperative shivering: A randomized clinical trial

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ABSTRACT

**Background:** Various medications with different efficacy and safety are used to relieve postoperative shivering. The present study aimed to determine the effectiveness and speed of treatment of shivering after general anesthesia with meperidine and doxapram.

**Methods:** This randomized double-blinded clinical trial was performed on patients with ASA I-II and aged 20 years and 60 years with shivering during the first 10 minutes of recovery after general anesthesia following routine orthopedic or urology surgery. Patients were randomly assigned to receive meperidine (25 mg, intravenously) or doxapram (0.7 mg/kg, intravenously) in recovery and the shivering score was recorded every minute for 10 minutes.

**Results:** In the two groups receiving doxapram and meperidine, the mean time of shivering relief (shivering score less than 1) was 4.54 minutes  $\pm$  2.04 minutes and 4.50 minutes  $\pm$  2.08 minutes, respectively with no difference ( $p=0.945$ ). In both groups a significant decrease in the shivering score was observed during ten minutes, but there was no difference between the trend of changes in mean pain score in the two groups ( $p=0.489$ ).

**Conclusion:** Doxapram at a dose of 0.7 mg/kg is as effective as 25 mg of meperidine in controlling shivering after general anesthesia.

**Keywords:** shivering, doxapram, meperidine, general anesthesia

## INTRODUCTION

Postoperative hypothermia and shivering are relatively common complications after surgery that can lead to other complications such as increased oxygen requirement, cellular metabolism, cardiac output, peripheral vascular resistance, CO<sub>2</sub> production as well as elevated intraocular pressure and intracranial pressure and also deterioration of pain at the surgical suture site due to skin stretching and lactic acidosis [1, 2]. Some of these complications, especially in patients with cardiac ischemia, can lead to worsening of the patient's condition. Therefore, timely prevention and treatment of this complication is one of the important issues in anesthesia. Regulation of shivering threshold and vasoconstriction is mediated by mechanisms such as norepinephrine, dopamine, acetylcholine, prostaglandin E1, and 5-hydroxytryptamine. Therefore, it seems that drugs that act on these mediators can also be useful in controlling shivering [3].

One of the most effective drugs in controlling chills after surgery is meperidine. Although its mechanism is unclear, it may have a direct effect on the temperature regulation center or on opioid receptors [4, 5]. In some sources fentanyl is also recommended for the treatment of shivering after general anesthesia [6]. Given the side effects of narcotics such as reduced ventilation, itching, nausea and vomiting, and the unique complication of meperidine (tachycardia), it makes sense to find an effective drug as an alternative to treating postoperative shivering.

Doxapram is a potent respiratory stimulant that, in addition to treating chills, also has a respiratory support effect that increases respiration as a result of direct stimulation of the respiratory center in the medulla oblongata and indirect effects on chemical receptors in the carotid artery and aortic arch [7]. Doxapram reduces shivering by stimulating the release of dopamine and affecting the chemical receptors of carotid bodies [8]. Doxapram allows the body to reach its lowest temperature tolerance level before shivering. Although lowering the temperature justifies the effect of medication and treatment of postoperative shivering, the exact mechanism of doxapram's effect on postoperative shivering is unclear.

Due to the fact that meperidine is a very available drug and has been used in the past as a treatment for shivering after anesthesia and its anti-shivering effects have been proven, it is used as the most common treatment for shivering after surgery [9]. However, due to its side effects, using the alternatives with maximum efficacy

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and higher safety is highly recommended [10]. Due to the proven effects of doxapram in the treatment of shivering after anesthesia and the fact that this drug has bronchodilator effects by increasing the central nervous system and increasing the number of breaths (unlike meperidine) can be a good alternative. The present study aimed to determine the effectiveness and speed of treatment of shivering after general anesthesia with meperidine and doxapram.

## MATERIALS AND METHODS

### Study population

This randomized double-blinded clinical trial was performed on patients with ASA I-II and aged 20 years and 60 years old who were admitted to Firoozgar Hospital in Tehran and had shivering during the first 10 minutes of recovery after general anesthesia following routine orthopedic or urology surgery. The inclusion criteria were:

- Occurrence of shivering during the first 10 minutes of recovery,
- Lack of blood transfusion during surgery,
- Under general anesthesia with propofol used for maintenance anesthesia,
- Lack of response to surface warming in recovery,
- Satisfaction with participation in the study, and
- Shivering score greater than or equal to one.

In this regard, those with the following criteria were excluded from the study:

- Hypersensitivity and prohibition of meperidine use (history of lung disease, seizures, drug allergies, use of TCA and MAOI, increased ICP, severe renal disease and hypothyroidism),
- Sensitivity and prohibition of doxapram (mechanical obstruction of airways, neuromuscular diseases, nomothorax, acute asthma attack, pulmonary fibrosis and restrictive lung disease), history of opioid use, hemodynamic instability during recovery, and failure to respond to initial dose of medications.

### Study interventions and assessments

After the approval of this project in the ethics committee of the Iran University of Medical Sciences, patients entered the study according to the inclusion criteria. Patients who are candidates for orthopedic or urology surgery underwent general anesthesia by the same method. In recovery, after obtaining the informed consent of the patients, they entered our study and the shivering score was measured upon arrival. For patients with shivering scores of 1 and 2, surface warming methods were used to treat chills (for 3 minutes with blanket and Covidien warmer at 38°C) and by heating the skin surface, the patient's temperature tried to be raised. In case of failure in complete control of shivering and a shiver score greater than or equal to one, while maintaining the warmer, the patient was included in the study. Patients were then randomly (using the block randomization method) divided into two groups receiving meperidine (25 mg, intravenously) or doxapram (0.7 mg/kg, intravenously), both of which were

distilled water in syringes 10 cc by similar anesthesia technician. The shivering score was recorded every minute for 10 minutes by an anesthesia assistant who was unaware of the type of injected drug. If the initial shivering score scaled 3 or 4, the patient was immediately admitted to the study and treated with warmer. It is worth mentioning that for all patients, the operating room temperature was maintained at 20°C to 22°C and serums stored at room temperature were used for injections. The present study was a double-blind clinical trial meaning that the evaluator and the patient were unaware of the type of intervention. The score of shivering was determined based on the following criteria: zero (without shivering), one (cyanosis or peripheral vasoconstriction), two (shivering and obvious movements in one group of muscles), three (shivering and clear vibrating movements in more than one group of muscles) and four (complete and severe shivering throughout the body). Finally, the change in shivering score, time to reach zero shivering score and finally the frequency of success in improving shivering were determined and compared in the two groups. In addition, written consent was obtained from patients to use the information obtained from them for a research project while respecting privacy and non-disclosure of personal details.

### Statistical analysis

For statistical analysis, results were presented as mean  $\pm$  Standard Deviation (SD) for quantitative variables and were summarized by frequency (%) for categorical variables. Continuous variables were compared using t-test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. The Chi-Square test or Fisher's exact test were used to compare the categorical variables. p-values  $\leq 0.05$  were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used.

## RESULTS

Of 120 patients enrolled, 9 had ASA score higher than 2 and were excluded from the study. Other factors that excluded patients from the study included age over 60 years and under 20 years (n=10), other surgeries (n=30), and surgeries over 4 hours (n=2), responded to warming (n=15). Finally, 54 patients were included in the study. According to the study by Singh et al, the rate of lack of shivering relief after doxapram and meperidine was found to be 10% and 50% respectively. Considering the confidence coefficient of 0.05 and study power of 90% (beta coefficient error of 0.10), the number of samples required for the present trial was estimated to be 27 in each group. Based on randomization, these patients were classified into two groups of 27 patients receiving meperidine or doxapram. In the two groups receiving meperidine and doxapram, 2 and 1 patients faced with the impossibility of continuing follow-up and 1 and 2 patients also withdrew from the study respectively. Finally, in each group, 24 people were analyzed (Figure 1). Patients were evaluated for shivering scores within 10 minutes after the intervention and cases of shivering control failures were identified in the groups.

As shown in table 1, the two groups of interventions were similar in baseline characteristics including gender, mean age and types of surgeries. In the two groups receiving doxapram and meperidine, the mean time of shivering relief (shivering score less than 1) was

4.54 minutes ± 2.04 minutes and 4.50 minutes ± 2.08 minutes, respectively, which did not show a significant difference between the two groups (p=0.945). As indicated in figure 2, the trend of changes in shivering score in both groups was examined and it was found that firstly in both groups a significant decrease in the pointed score was observed during ten minutes, but there was no difference between the trend of changes in mean pain score in the

two groups (p=0.489). In total, in the two groups of doxapram and meperidine, the success rate in the treatment of shivering after surgery was 21 (87.5%) and 23 (95.8%), respectively, which did not show a significant difference between the two groups (p=0.672). Therefore, 3 cases from the first group and 1 case from the second group were injected with a supplementary dose of the drug (15 mg of meperidine).]

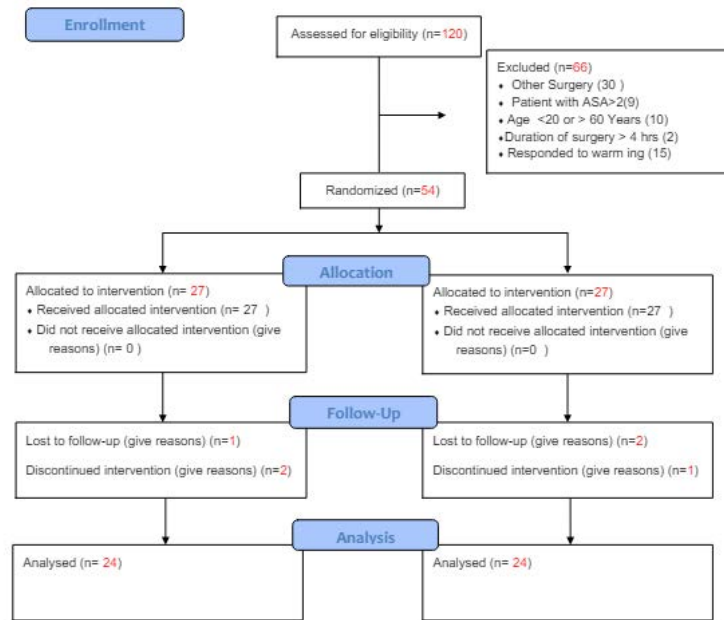


Fig. 1. The consort of selecting the participants for interventions

Tab. 1. Baseline characteristics in two interventional groups

Characteristics	Meperidine Group	Doxapram Group	p-value
Male gender, %	16 (66.7)	13 (54.2)	0.376
Mean age, year	43.38 ± 17.72	45.54 ± 17.53	0.672
Type of surgery, %	-	-	0.871
Orthopedics	17 (70.8)	16 (66.7)	-
Urology	7 (29.2)	8 (33.3)	-

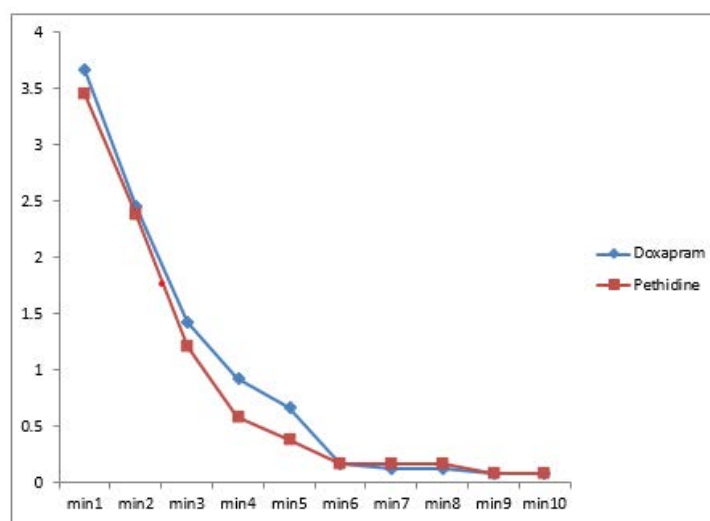


Fig. 2. The trend of the changes in shivering score in the two groups receiving meperidine or doxapram

## DISCUSSION

In our study, it was found that doxapram at a dose of 0.7 mg/kg is as effective as 25 mg of meperidine in controlling shivering after anesthesia. The occurrence of postoperative shivering due to

general anesthesia not only causes patient dissatisfaction but also exacerbates the postoperative complications, especially hemodynamic instability in the patient. Various non-pharmacological and pharmacological methods have been used to relieve shivering after surgery. The first group has had a limited effect on the improve-

ment of shivering and among the second group; its use has been limited due to the side effects of drugs. Therefore, the use of drug methods with the highest effectiveness and at the same time the highest level of safety has always been considered by experts. In this regard, the use of opioid drug agonists such as meperidine has been commonly considered, but due to some side effects, trying to use them with the lowest dose has been effective. In addition to these drugs, some drugs such as drugs related to the dopaminergic system (such as doxapram) have also been considered. In the present study, we evaluated the clinical efficacy of doxapram and meperidine in relieving chills after routine surgery. However, it should be noted that fixed doses of 25 mg of meperidine and 0.7 mg/kg of doxapram were considered for the present trial, respectively, while studies have shown that different doses of the drug have different efficiencies while maintaining optimal safety. However, considering that the doses used were among the usual and standard doses for these drugs, it can still be claimed that the effectiveness of these two drugs in relieving shivering after surgery is similar. This will be even more important when meperidine, because it is a subset of opioid drugs, can be associated with some potential side effects such as respiratory depression or hemodynamic changes that do not occur following doxapram and thus the latter drug is more recommended than meperidine. Another important point was that the time to achieve complete relief of shivering in both groups was about four minutes, in this regard, the similarity in the effectiveness of the two drugs in timely relief of shivering was quite observed.

Various studies have reached various conclusions about the effectiveness of the two drugs studied in relieving postoperative shivering, which was mainly due to differences in the doses used by these drugs. Of course, the conditions of the clinical trial and the conditions of entry and exit of the study, especially the number of samples entering it, were also involved in this difference. Based on a study by Wrench et al, different doses of the two drugs including 10 doses of doxapram (from 0.18 mg/kg to 1.4 mg/kg) and five doses of meperidine (from 0.12 mg/kg to 0.35 mg/kg) were randomly evaluated. The analysis showed that, first, the postoperative

cessation of shivering in the doxapram group was completely independent of the injectable dose of the drug. The lowest dose used for doxapram in relieving chills (0.18 mg/kg) was more effective than placebo. For meperidine, the efficacy of the drug was dose-dependent and its efficacy was fully confirmed with a maximum dose of 0.35 mg/kg. Finally, both drugs were quite successful in relieving chills and had similar effects, but because doxapram was effective at the lowest dose, it was preferable to meperidine. In the study of Shrestha et al, doxapram (1.5 mg/kg) was compared with meperidine (0.35 mg/kg), but there was no significant difference between doxapram and normal saline in reducing postoperative shivering. The frequency of postoperative shivering recovery in meperidine, doxapram and saline was 80%, 60% and 20%, respectively, which was again consistent with our study. In a study by Singh et al, doxapram at a dose of 1.5 mg/kg and meperidine at a dose of 0.33 mg/kg were compared, indicating that both meperidine and doxapram were successful in controlling chills within 2 minutes to 3 minutes after injection. Of course, our time to relieve chills was a little longer than his study [11-13]. Therefore, considering the optimal effective dose of both drugs, it is still highly recommended to use both drugs, and of course, due to the greater respiratory support of doxapram, this drug is preferred over meperidine as an opioid drug. However, the main limitation of our study was the small sample size and considering only a fixed dose for two drugs, which is recommended in subsequent intervention studies of a larger sample volume, compared with placebo (as normal saline) and different doses of drugs.

## CONCLUSION

Finally, it can be concluded that both meperidine (25 mg) and doxapram (0.7 mg/kg) are effective in relieving postoperative shivering. Both drugs will be able to completely eliminate shivering after surgery within about four minutes of administration. Due to the fact that doxapram has fewer side effects, it can be a better alternative to meperidine in the treatment of shivering after anesthesia.

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