



Is Dexmedetomidine Effective on Postoperative Shivering in Patients Undergoing General Anesthesia for an Appendectomy? A Double-Blind, Randomized Clinical Trial

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Abstract

Background: Postoperative shivering (PS) is a mechanism to reduce heat loss and is the most frequent complication during the recovery period after general anesthesia. Shivering can lead to discomfort and is even risky in many patients; therefore, prevention is important.

Objectives: Our study aims to determine the effect of dexmedetomidine on preventing shivering after general anesthesia in appendectomy patients.

Methods: The present double-blind, randomized clinical trial divided 90 appendectomy patients into two groups. Randomization was performed using the www.random.org website from the numbers of sequence generator option. One group received 0.5 $\mu\text{g}/\text{kg}$ of dexmedetomidine before induction of general anesthesia, and another group received normal saline as a placebo. Shivering and other outcomes were checked in both groups. To find a 50% reduction of this incidence, based on alpha error of 5% and beta error of 20%, the sample size of 45 people was determined for each group. A P-value ≤ 0.05 was considered statistically significant.

Results: In total, 63 (70%) patients were male, and 27 (30%) were female. There were no significant differences between the two groups in terms of age ($P = 0.412$), weight ($P = 0.460$), temperature of serum for fluid therapy ($P = 0.315$), fluid volume ($P = 0.736$), perioperative body temperature ($P = 0.418$), preoperative body temperature ($P = 0.540$), and room temperature ($P = 0.310$). The severity of shivering was significantly lower in the dexmedetomidine group (60%) than in the placebo group ($P < 0.001$). There was no significant difference according to gender and severity of shivering between the two groups ($P > 0.05$).

Conclusions: This study suggests that the administration of dexmedetomidine can prevent postoperative shivering.

Keywords: Dexmedetomidine, Shivering, Appendectomy, General Anesthesia

1. Background

Postoperative shivering (PS) is the most frequent complication during the recovery period after general anesthesia (1). Postoperative shivering reduces heat loss by involuntary skeletal muscle contractions and peripheral vasoconstriction. By preservation of heat, shivering causes more oxygen consumption, energy expenditure, production of carbon dioxide, increase in cardiac output, and elevation in intraocular pressure, can lead to lactic acidosis, tachycardia, and disturbs oxygen saturation monitoring, electrocardiogram (ECG), and blood pressure. It may cause difficulties in the recovery from general anesthesia, particularly in patients

with cardiac and pulmonary problems. Shivering is an unpleasant experience, being able to bother more than surgical pain in some cases (2-5); however, the exact treatment and prophylactic medications need to be clarified (2). Shivering is a remarkable cause of distress after general anesthesia. Unfortunately, numerous studies aimed at developing the best way of prophylaxis for postanesthetic shivering have not identified a gold-standard pharmacologic agent (6-8).

Dexmedetomidine is a strong alpha-2 receptor agonist with sedative and also amnesia properties. It has been reported previously in several clinical studies that intrathecal or intravenous dexmedetomidine may prevent

shivering (3, 9-11), but this effect remains controversial and has not been clearly explained. Although debatable, the prophylactic effect of dexmedetomidine on PS has been evaluated (3, 8, 12).

Prevention of PS has a tremendous effect on patient satisfaction and the reduction of complications caused by shivering. As mentioned previously, not only the efficacy of different agents previously used for preventing PS is unobvious, but the administration strategies and other potential complications are also unclear. In this study, we intend to evaluate the effect of dexmedetomidine on shivering appendectomy patients.

Postoperative shivering, as a heat loss reduction function, is considered the most frequent complication after general anesthesia. Shivering can lead to an inappropriate or even dangerous situation in patients and, therefore, should be considered.

2. Objectives

In this study, we intend to evaluate the preventive effect of dexmedetomidine on reducing shivering after appendectomy in patients undergoing general anesthesia.

3. Methods

The present research was a double-blind, randomized controlled trial approved by the Institutional Clinical Research Ethics Committee (Kurdistan University of Medical Sciences), and patients participated in this study with full knowledge and signed informed consent. Also, this study was registered at the Iranian Registry of Clinical Trials ([IRCT20120801010471N4](https://www.clinicaltrials.gov/ct2/show/study?term=IRCT20120801010471N4)) and Ethics Committee (IR.MUK.REC.1395.385). Ninety patients underwent general anesthesia for appendectomy with inclusion criteria, including the American Society of Anesthesiologists (ASA) classifications 1 and 2 and an age range of 15-65 years. Exclusion criteria included peritonitis, malignant hyperthermia, epilepsy, anaphylaxis, cardiac disease, vascular disease, dyspnea, diabetes mellitus, renal failure, liver disease, psychiatric disorders, addiction, and alcohol consumption.

Before the start of the study, the study participation conditions were explained to the patients. Their questions were answered, and there was a possibility of withdrawing from the study if they did not intend to participate in the study. They were ensured that their information would be kept confidential and analyzed with codes and anonymously. Those willing to participate in the study were asked to read and sign the written informed consent. Medicines were prepared by the anesthesiologist in

invisible syringes, and the blind anesthesiologist injected the drugs.

In this study, the response rate of PS was a general anesthetic method as a qualitative variable with five levels (zero to four). Ninety selective patients participated in this study. Our sample size was calculated to be 45 patients in each group, considering a significance level of 95%, a test power of 90%, and an effect size of 0.85. We started our study in 2017-04-21 and ended it in 2018-05-03.

Randomization of patients was performed using the www.random.org website from the numbers of sequence generator option; numbers 1 to 15 were randomly placed in groups A and B. In this way, the grouping of the first 15 eligible patients was determined; for example, in randomization, number 14 in column B means that the 14th disease eligible to enter the study will be placed in group B, etc. Randomization was carried out again for the next 15 patients. This process continued until we reached the desired sample size.

The included patients were randomly assigned to the dexmedetomidine and placebo groups. Random allocation and provision of anesthetic medicines were performed by an anesthetist who did not interfere with the procedure and outcome measurements.

We studied patients referring to Besat Hospital in the city of Sanandaj for surgery with one and two physical statuses regarding the division of the ASA using a randomized method. The questionnaire was completed by a medical student under a research associate's anesthesiologist, both blind.

The anesthetic induction procedure was quite similar in both groups. Before induction of anesthesia, fluid therapy was performed with a ringer at a rate of 7cc/kg within 5-7 minutes. Pre-oxygenation was performed with 5 liters of oxygen using anesthetic masks for all patients. First, fentanyl 2 μ /kg was prescribed as premedication, and 5 mg/kg of sodium thiopental and 1.5 mg/kg of succinylcholine were later prescribed as the anesthetic agent. Maintenance of anesthesia in both groups included the minimum alveolar concentration (MAC) of isoflurane and oxygen+N₂O mixture of equal amounts (3 Lit/min). All patients underwent synchronized intermittent mode of ventilation (SIMV) with a tidal volume of about 6 mL/kg, a frequency rate of 12 to 14 per minute, and a positive end-expiratory pressure (PEEP) of 3. The intraoperative fluid (4 cc/ kg/ h) was injected as maintenance fluid plus maintenance fluid + 3cc/kg per cc of blood loss. Hemorrhage was measured based on the blood mass of sterile gases together with the amount of blood loss in the suction. The temperature of all ringer fluids was the same and supplied by the common room for maintenance of the operating room sera. The room temperature was 25 - 28° C,

and a serum was selected to measure the temperature on a daily basis randomly. Fentanyl $1\mu/\text{kg}$ was injected as the opioid, based on the BIS criteria. Atracurium $0.2\text{ mg}/\text{kg}$ was injected as the intraoperative relaxant. The control group received 10 cc of distilled sterilized intravenously within 10 - 20 minutes before anesthetic induction.

In the intervention group, $0.5\ \mu/\text{kg}$ of dexmedetomidine was injected intravenously 20 minutes before extubation for 10 minutes ($1\mu/\text{kg}$ diluted in 10 mL of sterile distilled water). The control group received 10 cc of distilled sterilized intravenously within 10 - 20 minutes before extubation. Patients' body temperature and noninvasive blood pressure (NIBP) are measured at the baseline. Also, common monitoring included ECG (Lead II), pulse oximetry, NIBP, and capnography for all patients.

The severity of shivering was evaluated based on the visual analog scale (VAS) criteria as the primary outcome.

The scale used was as follows:

0 = No shivering;

1 = Observation of one or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis without other causes, and no visible muscular activity;

2 = Visible muscular activity confined to 1 muscle group;

3 = Visible muscular activity in more than 1 muscle group;

4 = Gross muscular activity involving the whole body.

Shivering was evaluated immediately and then at 5, 15, 30, and 60 minutes after general anesthesia. The shivering rate was evaluated based on the following criteria. Meperidine (25 mg) was injected intravenously in case of a shivering score greater than 2. The room temperature was maintained at 22°C during the anesthesia, no heating system was used for patients, and all surgical procedures were performed in the general surgery room.

In this study, the hypotension was defined as $\text{MAP} \leq 60\text{mmHg}$ or more than 20% reduction in the baseline rate. In the event of hypotension, 5 mg of ephedrine was prescribed intravenously. Atropine was injected intravenously ($0.2\text{ mg}/\text{kg}$) to the patient in case of bradycardia (heart rate less than 50) or more than 20% reduction in heart rate compared to the baseline rate.

Data were entered into SPSS V.23 after data collection and checked for missing data. Descriptive statistics, including mean, standard deviation, and frequency, were used to describe the results. The variables were compared between the two groups using the chi-square and Fisher's exact tests for categorical variables and the Student's *t*-test and Mann-Whitney U test for parametric and nonparametric variables, respectively. Also, repeated

measures analysis of variance (ANOVA) was used to evaluate parameters over time. The significance level was considered < 0.05 in all tests.

4. Results

A total of 90 patients were enrolled in our study, with 63 (70%) males and 27 (30%) females. The gender difference was not significant in the two groups ($P = 0.818$). The mean \pm SD on age in all participants was 19.38 ± 3.24 (age range = 18 to 56). The mean age was not significant in patients and the control group ($P = 0.412$).

There were no significant differences between the two groups in terms of the weight, temperature of serum for fluid therapy, fluid volume, perioperative body temperature, preoperative body temperature, and room temperature (Table 1).

The severity of shivering was significantly lower in the dexmedetomidine group (60%) than in the placebo group ($P < 0.001$). Also, other criteria for shivering in both groups of patients are shown in Table 2.

Table 3 shows no significant differences according to gender/surgical history and the severity of shivering between the two groups ($P > 0.05$). Also, no significant relationship was found between age, perioperative fluid volume, preoperative body temperature/perioperative body temperature, and the severity of shivering in any of the study groups (Table 4).

5. Discussion

Different medications reduce body temperature. General anesthesia or deep sedation can lead to the complete elimination of shivering. Previous studies have shown that using α_2 agonists such as dexmedetomidine can reduce shivering and be a simple drug intervention; however, it is not suitable for patients with acute ischemia or stroke (13). The results of our study were similar to the results of these articles, revealing a statistically significant difference between the dexmedetomidine and control groups ($P = 0.0001$).

Shivering is a state of changing continuously and without intended contraction of the skeletal muscle, with potentially increasing discomfort in patients (14).

A meta-analysis refers to using dexmedetomidine as an anti-shivering agent, aiming to determine the factors that might influence its effectiveness. Based on the data of the relevant trials, we found that $0.5\ \mu\text{g}/\text{kg}$ of dexmedetomidine sufficiently and effectively prevented PS (3). These data support the results of our study.

The present study examined the effects of one of the α_2 -agonist variants (dexmedetomidine) in reducing

Table 1. Comparing Qualitative Demographic Values and Preoperative Features Between the Study's Two Groups ^{a,b}

Variables	Dexmedetomidine Group	Placebo Group	P-Value
Gender			0.818
Male	32 (71.1)	31 (68.8)	
Female	13 (28.8)	14 (31.1)	
Surgical history			0.829
Positive	18 (45)	17 (37.8)	
Negative	27 (60)	28 (62.8)	
Complications			-
Positive	0 (0)	0 (0)	
Negative	45 (100)	45 (100)	
Age	19.08 ± 3.62	19.44 ± 3.1	0.412
Weight	55.97 ± 15.58	57.51 ± 13.85	0.460
Systolic blood pressure	144.35 ± 21.50	141.77 ± 21.1	0.935
Diastolic blood pressure	86.46 ± 18.41	84.53 ± 14.86	0.589
Body's temperature	37.41 ± 0.89	37.22 ± 0.67	0.975
Surgery time (min)	75.23 ± 12.65	69.74 ± 10.64	0.0473
Preoperative fluid volume	287.14 ± 69.03	279.01 ± 78.96	0.623
Perioperative fluid volume	542.9 ± 136.99	532.93 ± 139.34	0.736
Temperature of serum for fluid therapy	28.8 ± 32.1	24 ± 0	0.315
Preoperative body temperature	37.64 ± 1.53	37.76 ± 0.45	0.540
Perioperative body temperature	36.6 ± 0.42	36.54 ± 0.43	0.418
Room temperature	25 ± 2	24.9 ± 0.14	0.310

^a Frequency and analysis of variance tests were used.^b Values are presented as No. (%) or mean ± SD.**Table 2.** Comparing the Severity of Shivering Between the Study Groups ^a

Severity of Shivering	Placebo Group	Dexmedetomidine Group	P-Value
No shivering (0)	0 (0)	(60) 27	< 0.001
Idiopathic partial cyanosis of extremities/hair stiffening (1)	6 (13.3)	13 (28.9)	
Muscular shaking in a single group of muscles (2)	5 (11.1)	1 (2.2)	
Muscular shaking in more than one group of muscles (3)	15 (33.3)	2 (4.4)	
Muscular shaking visible in the whole body (4)	19 (42.5)	2 (4.4)	
Total	45	45	

^a Values are presented as No. (%).

shivering after general anesthesia in appendectomy surgery. The present study showed a significant relationship between the use of dexmedetomidine and a reduction in shivering rate. This finding was consistent with the new meta-analysis's data on the use of dexmedetomidine (0.5 µg/kg) (3, 6). In another study, tramadol was used as an anti-shivering drug, but its complications were greater than those of

dexmedetomidine (15).

Our results suggest that 0.5 µg/kg of dexmedetomidine provides effective prophylaxis against PS and has an analgesic effect. Though the potential for intraoperative requirement for atropine, sedation in the immediate recovery period, and delayed extubating time with dexmedetomidine were noted, there were no major clinical impacts on the overall recovery from anesthesia

Table 3. Comparing the Severity of Shivering According to Gender and Surgical History Between the Study Groups^a

Groups and Variables	Severity of Shivering					P-Value
	0	1	2	3	4	
Placebo Group						
Gender						0.815
Male	0 (0)	5 (11.1)	3 (6.6)	10 (22.2)	14 (31.1)	
Female	0 (0)	1 (2.2)	2 (4.4)	5 (11.1)	5 (11.1)	
Dexmedetomidine Group						
Gender						0.220
Male	20 (44.4)	7 (15.5)	0(0)	2 (2.2)	2 (2.2)	
Female	7 (15.5)	6 (13.3)	1 (2.2)	0(0)	0(0)	
Negative	17 (37.7)	9 (20)	0(0)	1 (2.2)	1 (2.2)	

^a Values are presented as No. (%).

Table 4. Comparing the Severity of Shivering According to Age, Perioperative Fluid Volume, Preoperative Body Temperature, and Perioperative Body Temperature Between the Study Groups^a

Groups	Variables	Severity of Shivering					P-Value
		0	1	2	3	4	
Placebo group	Age	18.3 ± 3.5	18.8 ± 2.6	20.2 ± 4.3	18.3 ± 3.3	19 ± 3.6	0.542
Dexmedetomidine group		19.5 ± 3.4	19 ± 3.4	23 ± 11.1	20 ± 4.2	19 ± 1.1	0.807
Placebo group	Perioperative fluid volume	0 ± 0	547 ± 170	474 ± 125	595 ± 152	494 ± 109	0.138
Dexmedetomidine group		535 ± 155	551 ± 112	586 ± 59	584 ± 50	527 ± 121	0.981
Placebo group	Preoperative body temperature	0 ± 0	37.5 ± 0.5	38 ± 0.3	37.2 ± 0.42	38 ± 0.37	0.591
Dexmedetomidine group		37.7 ± 0.44	37.7 ± 0.52	38 ± 0.4	37.5 ± 0.7	38 ± 0	0.834
Placebo group	Perioperative body temperature	0 ± 0	36.4 ± 0.037	36.4 ± 0.41	36.5 ± 0.45	36.6 ± 0.45	0.704
Dexmedetomidine group		36.6 ± 0.41	36 ± 0	36.5 ± 0.7	36.5 ± 0.5	36.7 ± 0.42	0.625

^a Values are presented as mean ± SD.

(16).

The administration of prophylactic intravenous dexmedetomidine reduces the incidence of shivering in patients undergoing general anesthesia (8).

Although the results of our study revealed no significant difference between the control and intervention groups regarding the severity of shivering according to gender ($P > 0.05$), other studies did not assess the relevance between these two items.

Our study supported that dexmedetomidine could reduce shivering in general anesthesia, but it does not affect the severity of shivering. This result is in concordance with other studies (3, 8, 11, 15).

In our study, no significant relationship was found between gender, education level, and marital status (P -value < 0.05). An interesting point in our study was that although the use of dexmedetomidine reduced the amount of shivering in general anesthesia, it was not

effective on the severity of shivering, and there was no difference between the intervention and control groups in this regard. One of the benefits of our study was the use of dexmedetomidine in emergency surgeries. Although regional methods such as spinal and epidural are used in appendectomy surgery in many cases, in our age group, the use of these methods is sometimes associated with restrictions such as dissatisfaction among patients or their parents. Therefore, this study could be the basis for further studies in emergency cases.

5.1. Conclusions

In conclusion, the use of dexmedetomidine reduced shivering after appendectomy; however, dexmedetomidine did not affect the severity of PS. More studies are required in this area, particularly on regional anesthetic techniques.

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Footnotes

Authors' Contribution: M. M. and B. A.: Conceiving and designing the evaluation and drafting the manuscript; M. A. M.: Participating in designing the evaluation, performing parts of the statistical analysis, and helping draft the manuscript; M. A. M. and M. M.: Re-evaluating the clinical data, revising the manuscript, and performing the statistical analysis; S. S.: Collecting and interpreting the clinical data and revising the manuscript. All authors read and approved the final manuscript.

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