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Antishivering Effect of Dexmedetomidine on Patients Undergoing Video-Assisted Thoracoscopic Wedge Resection

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Abstract

Background: Post-anesthetic shivering can cause post- surgical pain or discomfort, and create oxygen supply/demand imbalance.
Objectives: The current study aimed at evaluating the effects of Dexmedetomidine on the incidence and intensity of shivering and core temperature after general anesthesia.
Methods: The current randomized, double-blind, placebo-controlled, clinical trial was conducted at a single center (Gil Medical Center, Incheon, South Korea) from January to December 2016 with convenience sampling and simple random allocation. A total of 40 patients undergoing video-assisted thoracoscopic (VATS) wedge resection were randomly assigned to receive either 1 μg/kg of Dexmedetomidine (Dexmedetomidine group, n = 20) or normal saline (control group, n = 20) 10 minutes after skin incision. Hemodynamic variables and esophageal and tympanic temperatures were recorded five minutes after anesthetic induction, five minutes after achieving a lateral position, every five minutes after carbon dioxide insufflation to the thoracic cavity, and at the end of surgery. Incidences and intensities of post-anesthetic shivering, and postoperative pain scores were recorded.
Results: Median postoperative pain score was significantly lower in the Dexmedetomidine group than the control group (4 (0 - 5) vs. 5 (3.25 - 6) (median (interquartile range)), P = 0.004). In the post-anesthetic care unit (PACU), the incidence of shivering was significantly lower in the Dexmedetomidine group than in the control group (0/20 (0%) vs. 6/20 (30%), P = 0.020); but the incidence of hypothermia was higher in the Dexmedetomidine group than in the control group (6/20 (30%) vs. 0/20 (0%), P = 0.020).
Conclusions: A single intraoperative dose of Dexmedetomidine (1 μg/kg) may reduce postoperative shivering and pain scores, but it might also increase the incidence of postoperative hypothermia in patients undergoing Sevoflurane anesthesia for video-assisted thoracoscopic wedge resection.

Keywords: Anesthesia, Dexmedetomidine, General, Shivering, Video-Assisted Thoracoscopic Surgery

1. Background

Shivering is an involuntary clonic movement of one or more skeletal muscle groups and its incidence is reported to exceed 40% when no prophylactic strategy is adopted (1). Several risk factors of post-anesthetic shivering are reported. It was suggested that patients with the following characteristics were more susceptible to shivering in the post-anesthetic care unit (PACU): male (2), young age, undergoing endoprosthetic surgery, hypothermia (3), and more intraoperative bleeding (4).

In clinical studies, it is reported that Dexmedetomidine, a selective α_2-receptor agonist, has anti-shivering effects (5, 6). In laparotomy gynecologic surgery, a loading dose of 1 μg/kg followed by maintenance at 0.4 μg/kg/hour effectively prevented post-anesthetic shivering (5), and Dexmedetomidine of 0.5 μg/kg also reduced its severity after spinal anesthesia (6).

Video-assisted thoracoscopic surgery (VATS) is regarded as the treatment of choice for wedge resection for spontaneous pneumothorax as it has the benefits of short hospital stay and low analgesic requirements, disease recurrence risk, and low cost (7, 8). However, intrathoracic carbon dioxide insufflation during VATS can induce significant changes in pH and arterial carbon dioxide tension (9). In addition, in young male patients, ventilation/perfusion mismatch and increased shunt fraction may increase the risk of post-anesthetic shivering during one-lung ventilation for VATS, and post-anesthetic shivering increases postsurgical pain and excessive carbon dioxide production. Moreover, since oxygen consumption might be a cause of respiratory acidosis and hemodynamic instability (10-12), prevention of shivering after lung surgery is crucial.

Clinicians sometimes overlook the risk of post-anesthetic shivering due to the minimal invasiveness of VATS compared with laparotomy surgery or open thoracotomy. However, direct insufflation of cold carbon dioxide into thoracic cavity might have a negative impact on maintaining core body temperature. To date, no study addressed the effects of Dexmedetomidine on post-anesthetic shivering after VATS with carbon dioxide insufflation under general anesthesia. The current study authors hypothesized that intraoperative Dexmedetomidine might modify thermoregulation and reduce the incidence of shivering after VATS wedge resection. Thus, current study aimed at evaluating the effects of Dexmedetomidine on the incidence and intensity of shivering and on core temperature during and after VATS wedge resection under general anesthesia.

2. Methods

2.1. Ethical Considerations and Participants

The current prospective randomized, double-blind, placebo-controlled, clinical trial was conducted at Gil Medical center affiliated to Gachon University, with 1600 beds as the 3rd referral hospital (Incheon, South Korea), from January to December 2016, after obtaining approval from the ethics committee and informed consent from all the eligible subjects (Ref. IRCT 2017101236728N1). Inclusion criteria were patients aged 18 - 60 years with ASA (American Society of Anesthesiologists) grade I who were candidates for elective Video- Assisted Thoracoscopic Surgery (VATS) wedge resection due to spontaneous pneumothorax. Patients with fever (defined as tympanic temperature > 37.5°C), suspected of having any infectious diseases, history of allergic reaction to the study drug, or taking medicines for any underlying medical reason including uncontrolled hypertension, heart-block greater than first degree, respiratory insufficiency, neuromuscular disorders, history of convulsions, or thyroid disorders were excluded.

2.2. Randomization

No anticholinergic or sedative was administered for premedication. Standard electrocardiography (ECG), non-invasive blood pressure cuff, and pulse oximetry monitoring were initiated on arrival at the operating room. Patients were randomly assigned to receive either 1 μg/kg of Dexmedetomidine (the Dexmedetomidine group, n = 20) or normal saline (the control group, n = 20) without stratification, using a randomized list generated by Excel 2007 (Microsoft Office, Redmond, WA, USA). The study drugs were prepared by a senior trainee unaware of group assignments. Dexmedetomidine (Precedex®, 2 μg/mL, 50 mL) or normal saline (50 mL) were administered immediately after skin incision immediately at the trocar site and infused for 10 minutes.

2.3. Anesthesia and Clinical Settings

Anesthesia was induced with 10 μg/kg of Alfentanil, 1 mg/kg of Lidocaine, 1.5 - 2 mg/kg of Propofol, and 0.8 mg/kg of Rocuronium. After double-lumen endotracheal intubation, Sevoflurane at 1.5 - 2.5 vol% was applied to maintain a Bispectral index score (BIS) between 40 and 60. Pre-calibrated temperature sensors and monitors were applied. An esophageal stethoscope with a temperature sensor (DeRoyal Inc., Powell, TN, USA) was inserted at mid-esophagus, and tympanic membrane temperature (ThermoScan IRT 1020; Braun, Germany) was checked. All anesthetic circuits were electrically heated (Anesthesia controller and A4488 Heated and humidified anesthesia breathing circuit™, Acemedical, Seoul) and the operating room temperature was maintained at 23 - 24°C throughout general anesthesia. Intravenous fluid was not warmed, and the temperature of water circulating in the warming mattress laid on the operative table was controlled at 37°C. Mean arterial pressure, heart rate, and esophageal and tympanic temperatures were recorded five minutes after anesthesia induction (Tind), five minutes after achieving the lateral position (Tlat), and 5, 10, 15, and 20 minutes after carbon dioxide insufflation into the thoracic cavity (Td1, Td2, Td3, and Td4, respectively), and at the end of surgery (Tend). An infusion device (Accufuser, Wooyoung Meditech, Seoul) prefilled with fentanyl (600 μg, 100 mL) connected to an intravenous line with the patient in a lateral position (basal infusion rate 2 mL/hour and the intermittent bolus dose of 0.5 mL with a 15-minute lockout time) was used for patient-controlled analgesia.

Hemodynamic data and tympanic membrane temperature were recorded 10 minutes after arrival in PACU controlled at 25°C. Frequencies and intensities of post-anesthetic shivering and pain scores were recorded. Shivering was evaluated by two trained nurses unaware of group allocations and graded as follows: grade 0, no shivering; grade 1, mild fasciculation of the head and neck without voluntary limb activity; grade 2, tremors in more than one muscle group; grade 3, muscular activity over the entire body (13). Postoperative pain scores were assessed using a visual analog scale (VAS) (0 - 10 where 0 = no pain and 10 = worst pain imaginable).

2.4. Statistical Analysis

Study sample size was calculated based on the results of a previous study (14). The predicted incidences of post-

anesthetic shivering in the Dexmedetomidine and control groups were expected to be 7.5% and 37.5%, respectively. Sixteen subjects were required per group for α-error of 0.05 and a power of 80%. Considering a possible dropout rate of 20%, twenty patients were recruited per group.

Data were analyzed with SPSS version 18.0 (SPSS Inc., Chicago, I.L., U.S.A.) and results were expressed as mean ± standard deviation (SD), number of patients, or medians (interquartile ranges). The Kolmogorov-Smirnov test was performed to test data normality. The independent t test or the chi-square test, as appropriate, was used to determine the significance of intergroup differences. Non-normally distributed data were analyzed using the Kruskal-Wallis test with Bonferroni correction. Longitudinal changes in hemodynamic and temperature variables were analyzed using repeated-measures ANOVA. Agreement between two observers to evaluate post-anesthetic shivering was analyzed using the Kappa statistics. Data in PACU were compensated using bootstrap method and described as 95% confidence intervals (CI) of mean difference. Group variables were compared using one-way ANOVA with Bonferroni correction. Statistical significance was accepted for P value < 0.05.

3. Results

Twenty patients per group were enrolled in the current prospective randomized study. Patients' demographics and peri-operative data are presented in Table 1. No significant intergroup difference was noted for anesthesia time. However, mean extubation time was significantly higher in the Dexmedetomidine group than in the control group (P = 0.006).

Table 1. Patients Characteristics (N = 20)[a]

Variables	Control	Dexmedetomidine	P Value
Age, y	31 ± 14	27 ± 12	0.430
Gender, M/F	18/2	16/4	0.661
Weight, kg	60 ± 7	59 ± 8	0.684
Height, cm	173 ± 7	171 ± 7	0.361
Body surface area, m^2	1.69 ± 0.11	1.67 ± 0.13	0.538
Anesthesia time, min	77 ± 18	81 ± 17	0.482
Operation time, min	43 ± 16	37 ± 10	0.144
CO_2 insufflation time, min	26 ± 11	23 ± 10	0.325
Extubation time, min	8.7 ± 3.3	13.0 ± 3.3	0.006

[a]Values are expressed as mean ± SD or numbers.

Intraoperative changes in the mean arterial pressure, heart rate, and esophageal and tympanic temperatures are illustrated in Figure 1. Longitudinal changes in the mean arterial pressure (MAP) and heart rate (HR) were similar in the Dexmedetomidine and control groups (P = 0.687 and 0.500, respectively). MAP and HR were significantly lower in the Dexmedetomidine group than the control group immediately after surgery (Tend) (P = 0.003 and 0.021, respectively). Changes in esophageal and tympanic temperatures over time were similar in the two groups (P = 0.251 and 0.990, respectively). Group esophageal and tympanic membrane temperatures were similar at all time points. Compared to the baseline value (Tind), esophageal temperature significantly decreased at Td2, Td3, Td4, and Tend in the control group (P = 0.021, 0.002, < 0.001 and < 0.001, respectively) and at Td4 and Tend in the Dexmedetomidine group (P = 0.014 and < 0.001, respectively). Tympanic membrane temperature significantly decreased at Td1, Td2, Td3, Td4, and Tend in the control group (P = 0.001 at Td1, all others P < 0.001) and at Tlat, Td1, Td2, Td3, Td4, and Tend in the Dexmedetomidine group (P = 0.015 at T1at, 0.001 at Td1, all others P < 0.001, respectively) compared with Tind.

Data recorded in PACU are summarized in Table 2. MAP and HR were significantly lower in the Dexmedetomidine group than the control group (P = 0.002 and 0.002, respectively). Postoperative pain score (median (interquartile range)) in the PACU was significantly lower in the Dexmedetomidine group (4 (0 - 5) vs. 5 (3.25 - 6), P = 0.004). Furthermore, the incidence of post-anesthetic shivering was significantly higher in the control group than the Dexmedetomidine group (P = 0.020, Kappa coefficient (95% CI) = 0.907 (0.780 - 1.000), and two patients in this group experienced grade 3 post-anesthetic shivering. However, the incidence of hypothermia (< 36.0°C) was significantly lower in the control group than the Dexmedetomidine group (P = 0.020). None of the 40 study subjects experienced oversedation (defined as a Ramsay sedation score of > 4).

4. Discussion

In the current prospective study, a single infusion of Dexmedetomidine (1 μg/kg) significantly reduced the frequency and severity of post-anesthetic shivering and pain scores, and stabilized hemodynamics in the PACU setting, but increased the risks of postoperative hypothermia and delayed awakening after VATS wedge resection under general anesthesia. To the authors' best knowledge, it was the first study, which proved the anti-shivering property of Dexmedetomidine in the case of VATS with cold carbon dioxide insufflation into the thoracic cavity.

The current study found a lower incidence of post-anesthetic shivering in the Dexmedetomidine group than in the placebo control group (0/20 (0%) vs. 6/20 (30%),

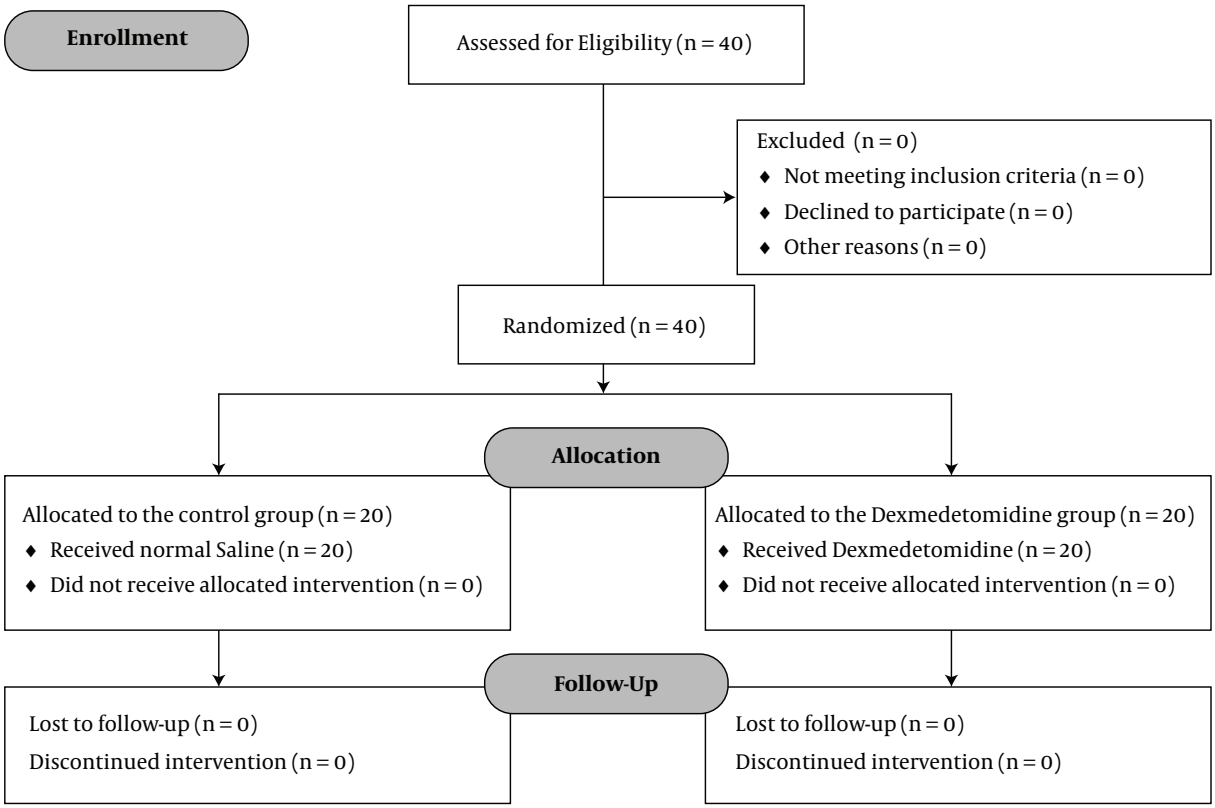

Figure 1. Flow diagram of patient allocations

Table 2. Post-anesthesia Care Unit Data (N = 20)[a,b]

Variable	Control	Dexmedetomidine	P Value	95% CI of MD
MAP, mmHg	93 ± 8	82 ± 12	0.003	-7.28 - 14.29
HR, beats/min	80 ± 9	70 ± 9	0.003	4.50 - 17.75
Pain score, NRS	5 (3.25 - 6)	4 (0 - 5)	0.027	-3.15 - -0.20
Body temperature, °C	36.4	36.2	0.082	-0.018 - 0.435
Hypothermia, No.	0	6	0.019	0.10 - 0.50
35.5 - 35.9, °C	0	5		
35.0 - 35.4, °C	0	1		
≤ 35.0, °C	0	0		
Shivering, No	6	0	0.022	-0.25 - 0.00
Grade 1	2	0		
2	2	0		
3	2	0		

Abbreviations: HR, Heart Rate; MAP, Mean Arterial Pressure; MD, Mean Difference; PACU, Post-anesthetic Care Unit; PAS, Anesthetic Shivering; NRS, Numeric Rating Scale (0 - 10); 95% CI, 95% Confidence Interval.
[a] Values are mean ± SD, numbers of patients, or medians (interquartile ranges).
[b] Grade 0, no visual shivering; grade 1, mild fasciculations of face or/and neck in the absence of voluntary limb activity; grade 2, visible tremors involving more than one muscle group; grade 3, visible muscular activity over the entire body with bed shaking.

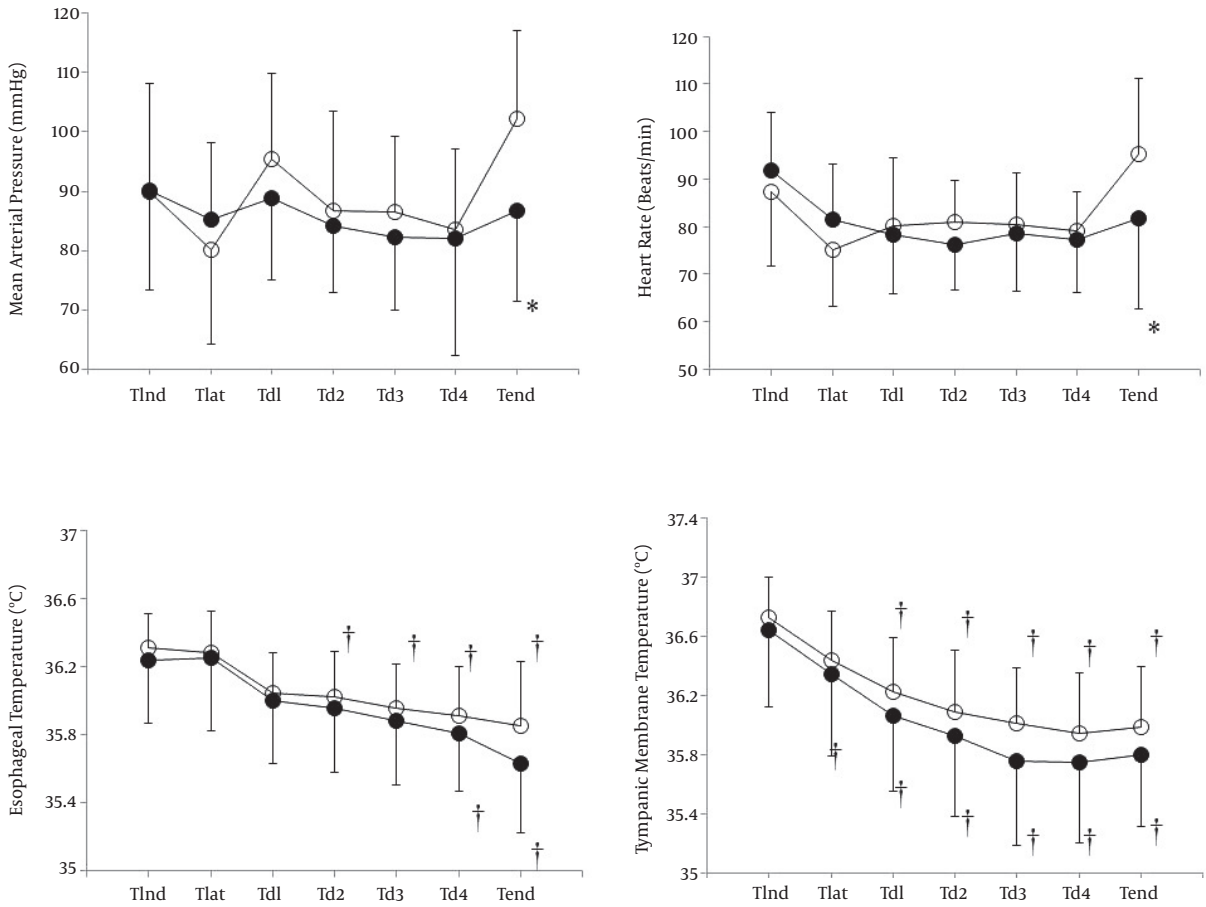

Figure 2. Intraoperative changes in mean arterial pressure, heart rate, and tympanic and esophageal temperatures. Tind, 5 minutes after anesthesia induction; Tlat, 5 minutes after lateral positioning; Td1, Td2, Td3 and Td4, 5, 10, 15, and 20 minutes, respectively after carbon dioxide insufflation to the thoracic cavity; Tend, at the end of surgery.

P = 0.020). Previous clinical studies demonstrated the anti-shivering effect of Dexmedetomidine in patients undergoing various surgeries under general anesthesia (5, 6, 14-16). Talke et al., (17) reported that since Dexmedetomidine dose-dependently decreases vasoconstriction and shivering thresholds, but does not affect the sweating threshold, it markedly widens the tolerable temperature range without triggering thermoregulatory defense (17) and suggested that Dexmedetomidine might promote hypothermia in typical hospital environments and that it might constitute an effective treatment for shivering (17). Their result was consistent with the current study result that Dexmedetomidine infusion group decreased the incidence of shivering (30% vs. 0%, P = 0.020), despite the higher incidence of hypothermia compared to the placebo group in the PACU.

Though the mechanism responsible for the anti-shivering property of Dexmedetomidine is not estab-

lished, it is known that central α_2-receptor activation in the hypothalamus hinders metabolic activity and reduces heat generation (18), and inhibits shivering-associated thermogenesis by suppressing the sympathetic activity of brown adipose tissue (19). Furthermore, it is also reported that central α_2-receptor activation inhibits norepinephrine-induced firing activity on the dorsal raphe nucleus and decreases central thermo-sensitivity (20), and that the suppressive effects of Dexmedetomidine on serotonergic activity in the locus ceruleus, nucleus tractus solitarii, and raphe dorsalis contribute to its anti-shivering effect (21, 22).

Dexmedetomidine might also promote hemodynamic stability during and after anesthetic emergence. Previous clinical studies on facial surgery and craniotomy reported that Dexmedetomidine reduced hypertension and tachycardia after surgery (23, 24). These observations were consistent with the current study findings, as hemodynamics were more stable during the emergence or in the PACU in the Dexmedetomidine group than the control group. Dexmedetomidine centrally decreases norepinephrine release by activating pre-synaptic α_2-receptor, and inhibits sympathetic outflow from postsynaptic receptors, which suppresses sympathetic activation and stabilizes hemodynamic profiles (25).

In the current study, patients of the Dexmedetomidine group had lower PACU pain scores than those of the control group. A recent clinical meta-analysis showed that Dexmedetomidine reduced postoperative pain and opioid consumptions without respiratory suppression (26, 27). It is reported that analgesic effect of Dexmedetomidine is due to its inhibitions of the conductions of Aδ- and C-nociceptive sensory fibers, and of the pain-specific sodium channel (28, 29).

The current study had some limitations that warrant mention. First, only the core body temperatures were monitored, that is esophageal and tympanic temperatures. However, general anesthesia dose-dependently reduces core body temperature and impairs the cold defense mechanism, and thus, leads to core-to-peripheral heat transfer (30). Therefore, monitoring of skin temperature and calculation of core-to-peripheral temperature gradients would have helped the study. Second, patients that underwent VATS wedge resection due to spontaneous pneumothorax were included, and the cohort was primarily composed of relatively young and male patients, which are the major independent risk factors of post-anesthetic shivering (2, 3). Also, since the study managed the enrolled patients according to the management manual of a single institute, the obtained results could not be generalized merely to other centers, which may have different anesthetic or surgical conditions. Lastly, although the incidence of shivering was calculated, the sample size was too small to elucidate the anti-shivering property of Dexmedetomidine. Further studies with larger sample sizes might be needed to generalize results with greater precision and power.

In conclusion, intraoperative Dexmedetomidine administered by infusion at 1 μg/kg reduced post-anesthetic shivering and pain effectively in a PACU setting and provided stable hemodynamics during and after emergence. On the other hand, it appeared to increase the risks of postoperative hypothermia and delayed awakening from general anesthesia in patients undergoing VATS wedge resection for spontaneous pneumothorax.

Footnote

Conflict of Interest: The authors declared no conflict of interest.

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