



Dexmedetomidine and Postoperative Shivering, A Randomized Placebo Control Study

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ABSTRACT

Objective: *The aim of this study was to investigate the optimum dosage of dexmedetomidine for prevention of postanesthetic shivering.*

Methods: *One-hundred thirty two ASA physical status I-II patients scheduled for elective laparoscopic total hysterectomy were enrolled in this randomised, placebo-controlled study. Patients were randomly allocated to receive dexmedetomidine in four groups: group S (0.9% normal saline), group D0.5 (dexmedetomidine 0.5 µg/kg), group D0.75 (dexmedetomidine 0.75 µg/kg), group D1.0 (dexmedetomidine 1.0 µg/kg). Time to extubation and tympanic temperature during and after operation were measured. Shivering was graded (0-3 scale) upon patients arrival to the PACU and every ten minutes thereafter up to forty minutes. Sedation and first rescue analgesic time at the PACU were evaluated.*

Fewer patients required rescue analgesia in groups D0.75 and D1.0 than in group S ($P < 0.001$), and the time to rescue analgesia was longer in group D1.0 than in group S ($P < 0.001$). Modified Observer's Assessment of Alertness/Sedation (MOAA/S) at arrival in the PACU was lower in all dexmedetomidine groups than in group S ($P < 0.05$).

Conclusions: *Our results suggest that dexmedetomidine 0.75 or 1.0 µg/kg provides effective prophylaxis against postoperative shivering as well as an analgesic effect. Though potential for intraoperative requirement for atropine, sedation in the immediate recovery period and delayed extubation time with dexmedetomidine was noted, there were no major clinical impacts on the overall recovery from anesthesia.*

Keywords: *dexmedetomidine, sedation, postanesthetic shivering.*

INTRODUCTION

Postanesthetic shivering is a common complication that occurs in 5-65% of patients recovering from general anesthesia.¹⁻² It is distressing and unpleasant experience for patients. Excessive shivering can result in an increased oxygen demand up to 400% of normal and induce metabolic derangements such as hypoxemia, lactic acidosis and hypercarbia.^{1,3} Therefore, shivering may cause problems in patients with low cardiac and pulmonary reserves.⁴

Considering these undesirable consequences of shivering, measures to prevent in the postoperative period are important. Various drugs have been investigated for the prevention or treatment of postoperative shivering, including meperidine, ketamine, tramadol, doxapram and dexmedetomidine.⁵⁻⁸

Dexmedetomidine is an α_2 -agonist that decreases vasoconstriction and shivering thresholds and when administered with meperidine additively reduces the shivering threshold in healthy volunteers.⁹ Intraoperative dexmedetomidine reduces postanesthetic shivering as does meperidine after surgery.¹⁰ One bolus dose of dexmedetomidine 1 $\mu\text{g/kg}$ with or without continuous infusion was used in the previous antishivering studies.^{8,10} Dexmedetomidine also has sedative and analgesic effects in the postoperative period.⁸ Patients who received an intraoperative injection of dexmedetomidine were more sedated after surgery than those who received placebo.⁸ This can be a disadvantage particularly for patients undergoing outpatient surgery.

There has been no study regarding the optimal effective dose of dexmedetomidine for preventing postoperative shivering. Thus, the present study was conducted with the aims of identifying the dose of dexmedetomidine that provides antishivering as well as analgesic effects without significant postoperative sedation in patients undergoing elective surgery under general anesthesia.

MATERIALS AND METHODS

After obtaining written informed consents from all study patients, we enrolled 132 female patients (ASA physical status I-II, aged 18 to 60 years) who were scheduled to undergo elective laparoscopic total hysterectomy under general anesthesia. Obese patients (BMI > 27) and those with hypo- or hyperthyroidism, cardiopulmonary disease, psychological disorders, blood transfusion during surgery, an initial body temperature above 38.0 [degree celsius] or below 36.0 [degree celsius] were excluded from the study.

Patients did not receive premedication. On arrival at the preanesthetic care unit, patients were assigned randomly to one of four groups by a computer-generated randomization table: group S (saline), group D0.5 (dexmedetomidine 0.5 $\mu\text{g/kg}$), group D0.75 (dexmedetomidine 0.75 $\mu\text{g/kg}$), and group D1.0 (dexmedetomidine 1.0 $\mu\text{g/kg}$). Nurses who did not participate in this study prepared the study drugs, all of which were diluted in total volume 50 ml of normal saline.

In the operating room, routine monitors were applied, including a blood pressure cuff, electrocardiogram, pulse oximeter, and capnogram. Tym-

panic temperature was measured to determine baseline values. Anesthesia was induced with propofol 2-2.5 mg/kg and rocuronium 0.6 mg/kg. After endotracheal intubation, anesthesia was maintained with 6-8% desflurane and 50% nitrous oxide in oxygen. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide tension at 30-35 mmHg.

Operation room temperature was kept between 21-22 [degree celsius]. Patients were only covered with surgical drapes and none of the patients were actively warmed during or after anesthesia. Supplemental doses of rocuronium were administered at the discretion of the anesthesiologist. Approximately 30 minutes before the anticipated completion of surgery, an anesthesiologist who was blind to the drug and group allocation administered the study drug over 10 minutes. Any intraoperative narcotics were not administered in all patients. Local anesthetic was not infiltrated into laparoscopic incision sites. Ephedrine (10 mg i.v. bolus) was given for hypotension (systolic pressure < 80 mmHg) and atropine (0.5 mg i.v. bolus) was given for bradycardia (HR < 50 min).

Five minutes before the anticipated end of surgery, the desflurane concentration was decreased to 5 vol%. Desflurane was discontinued at the end of surgery and the lungs were ventilated with 100% oxygen. Residual neuromuscular blockade was reversed with glycopyrrolate 6 µg/kg and pyridostigmine 0.15 mg/kg. The trachea was extubated when the patient's respiratory effort was adequate. Extubation time (from termination of desflurane until extubation), duration of anesthesia and duration of surgery were noted. In the

PACU, all patients were monitored, received oxygen via a face mask and were covered with a cotton blanket. An anesthesiologist who was blind to the study drug observed the patient for shivering, sedation, first analgesic rescue time and pain score (100 mm visual analogue scale (VAS)). Shivering was assessed every 10 min over 40 min in the PACU and graded as 0 = no shivering, 1 = mild fasciculation of the face or neck, 2 = visible tremor involving more than one muscle group, 3 = gross muscular activity involving the entire body. The patients were administered meperidine 25 mg when their shivering score was 2 or higher and patients who had a pain score more than 40 mm were administered 1 µg/kg intravenous fentanyl.

Postanesthetic sedation was checked every 20 min over 40 min in the PACU and graded, using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score, as 0 = does not respond to pain, 1 = does not respond to mild prodding or shaking, 2 = responds only after mild prodding or shaking, 3 = responds only after name is called loudly and/or repeatedly, 4 = lethargic response to name spoken in normal tone, 5 = responds readily to name spoken. Recovery room temperature was kept between 22-23 [degree celsius].

STATISTICAL ANALYSIS

The number of patients required in each group was determined after a power calculation based on data from a previous investigation of dexmedetomidine and its influence on the incidence of postoperative shivering. We anticipated a difference of 35% in the incidence of shivering

between the control and treated groups as being clinically meaningful. Hence, we calculated that 28 patients were required in each group for a type I error of 0.05 and a type II error of 0.2. We increased the recruitment by 20% to compensate unexpected loss. Of the 132 recruited patients for this study, 12 patients were excluded due to transfusion or change to open abdominal hysterectomy. Of the remaining patients, 30 patients in each group received allocated interventions. All results are expressed as means (SD). Statistical analysis was performed using the SPSS (version 15.0; SPSS Inc., Chicago, IL, USA). The incidence of shivering and number of patients requiring rescue analgesia were compared among different groups

using the χ^2 test. One-way ANOVA followed by Tukey's test was used to analyze the differences among the groups in demographic profiles, temperature changes, and extubation time. The within-group data were analyzed using repeated-measures analysis of variance followed by Bonferroni's test. P value < 0.05 was considered statistically significant.

OBESERVATION

Patient characteristics, duration of surgery, duration of anesthesia and temperatures of operating and recovery rooms were similar among the four groups (P > 0.05, Table Table11).

Table 1. (Patient characteristics and perioperative data)

	Group S(n=30)	Group D 0.5 (n=30)	Group D 0.75(n=30)	Group D 1.0(n=30)
Age(yr)	45.6(5.3)	46.5(7.3)	45.7(4.2)	45.4(5.1)
Weight(kg)	58.3(7.3)	56.4(7.2)	58.2(7.0)	55.5(6.2)
Height(cm)	160(4)	157(4)	159(4)	158(5)
ASA grade(1/2)	23/7	26/4	28/2	27/3
Duration of surgery(min)	109(22)	111(27)	106(28)	105(24)
Duration of anaesthesia(min)	86(20)	89(26)	85(26)	86(22)
OR temprature(c)	21.2(0.5)	21.2(0)	21.1(0.6)	21.2(0.5)
Recovery room temp.(c)	22.3(0.3)	22.2(0.4)	22.4(0.3)	22.2(0.4)
Extubation time(min)	3.1(0.9)	3.8(1.2)	4.1*(1.0)	4.6*(1.3)
Patients receiving atropine	0	3	6*	5*
patient receiving ephedrine	0	1	2	2

Values are mean (SD) *P<0.05 compared with group S. t P <0.05 compared with D 0.5

The number of patients receiving ephedrine during the operation was not different among the four groups. However, significantly more patients in the groups D0.75 and 1.0 µg/kg needed atropine to treat intraoperative bradycardia compared to the placebo group (Table 1).

Extubation time was longer in groups D0.75 and D1.0 as compared to group S ($P < 0.05$, Table1).

Tympanic temperature after induction of anesthesia was comparable in all the groups; However, tympanic temperature at 40 minutes postoperatively in the recovery room was found to be significantly higher in group S than in the other dexmedetomidine groups ($P < 0.05$, Table 2)

Table 2. Tympanic temperature (degree celsius).

	Group S(n=30)	Group D 0.5 (n=30)	Group D 0.75(n=30)	Group D 1.0(n=30)
After induction (baseline)	37.0(0.2)	37.0(0.2)	37.0(0.2)	37.0(0.2)
Before drug administtrain	36.2(0.3)*	36.1(0.3)*	36.1(0.4)*	36.3(0.3*)
After extubation	36.0(0.3)*	35.7(0.4)*	35.8(0.4)*	35.9(0.3)*
Postoperative 0 min.	36.0(0.4)*	35.7(0.4)*	35.8(0.4)*	35.9(0.3)*
Postoperative 20 min.	36.1(0.4)*	35.7(0.4)*	35.7(0.4)*	35.9(0.4)*
Postoperative 40 min.	36.1(0.4)*	35.8(0.4)*	35.7(0.3)*	35.8(0.4)*

Values are mean (SD) * $P < 0.05$ compared with baseline t $P < 0.05$ compared group S

Table3 shows the grades of shivering in the four groups. The number of patients experiencing shivering was the highest in group S where 19 out

of 30 (63%) patients shivered. On the other hand, 12 (40%), 4 (13%) and 5 (17%) patients shivered in groups D0.5, D0.75 and D1.0 respectively.

Table 3. The grades of shivering in various groups.

Grades	Group S(n=30)	Group D 0.5 (n=30)	Group D 0.75(n=30)	Group D 1.0(n=30)
0	11(37)	18(60)	26*(86)	25*(83)
1	9(30)	6(20)	2+(7)	5(17)
2	10(33)	6(20)	2+(7)	0+(0)
3	0(0)	0(0)	0(0)	0(0)

Values are number of patients (proportion). * $P < 0.001$ compared with group S. † $P < 0.05$ compared with group D0.5. ‡ $P < 0.05$ compared with group S.

More patients in group S experienced significant shivering requiring treatment compared to groups D0.75 and D1.0 ($P < 0.05$, $P < 0.001$, Table 4). No patients in group D1.0 and two

patients in group D0.75 required meperidine, while ten patients in group S needed treatment for their shivering episodes.

Table 4 Grades of shivering according to requirement of treatment.

Grades	Group S(n=30)	Group D 0.5 (n=30)	Group D 0.75(n=30)	Group D 1.0(n=30)
0 or 1 (not requiring treatment)	20	24	28*	30
2 or 3 (requiring treatment)	10	6	2*	0

$P < 0.05$ compared with group S. † $P < 0.001$ compared with group S.

Table 5 shows the number of patients requiring rescue analgesia at some point during the study period. More patients in group S required rescue analgesia compared to group D0.75 and D1.0 ($P < 0.001$, Table 5). Time to rescue analgesia in group

D1.0 was significantly longer than that in group S ($P < 0.001$) and the time to rescue analgesia was the shortest in group S and the longest in group D1.0 (Table 5).

Table 5 Analgesic requirements.

	Group S(n=30)	Group D 0.5 (n=30)	Group D 0.75(n=30)	Group D 1.0(n=30)
Time to rescue analgesia; min.	17.0 (7.4)	22.0 (7.5)	22.0 (7.7)	28.5 (7.7)*
Patients requiring rescue analgesia ; no.(%)	28 (93)	23 (76)	15 (50)*	13 (43)*†

Values are mean (SD) or number of patients (proportion). * $P < 0.001$ compared with group S. † $P < 0.05$ compared with group D0.5.

The MOAA/S was significantly lower in the dexmedetomidine groups compared with the

saline group on arrival in the recovery room ($P < 0.05$, Table 6) but there were no significant

differences among the groups at 20 min and 40

min after arrival in the PACU.

Table 6 Postoperative MOAA/S.

	MOAA/S			
	Group S(n=30)	Group D 0.5 (n=30)	Group D 0.75(n=30)	Group D 1.0(n=30)
Arrival at PACU	4.4 (0.6)	3.6* (1.0)	3.2† (1.2)	3.2† (1.2)
20 min after arrival				
at PACU	5 (0)	5 (0)	4.9 (0.2)	4.9 (0.4)
40 min after arrival				
at PACU	5 (0)	5 (0)	5 (0)	5 (0)

Values are mean (SD). * P < 0.05 compared with group S. † P < 0.001 compared with group S.

DISCUSSION

In this study, we found that dexmedetomidine 0.75 or 1.0 µg/kg significantly reduced the incidence and severity of postoperative shivering compared with saline or dexmedetomidine 0.5 µg/kg.

Shivering is a frequent and undesirable complication of anesthesia during the postoperative period. Due to undesirable effects such as hypoxia, lactic acidosis, and increased intraocular pressure, postanesthetic shivering needs to be prevented.^{1,3,11}

Dexmedetomidine is a potent α₂-adrenoceptor agonist with an eight times higher affinity for the α₂-adrenoceptor than clonidine. Dexmedetomidine at a dose of 1 µg/kg has been shown to be useful for prevention of postanesthetic shivering. Elvan et al. compared a

loading dose of 1 µg/kg and continuous infusion of 0.4 µg/kg/hr of dexmedetomidine with placebo for preventing postanesthetic shivering.⁸ In that study, the shivering incidence was 18% with dexmedetomidine and 53% with placebo. Our results are comparable to those with shivering noted in 14% and 17% of patients in the dexmedetomidine 0.75 µg/kg and 1.0 µg/kg groups respectively and 63% in the placebo group. The incidence of shivering in the dexmedetomidine 0.5 µg/kg group was 40%, which was lower than that in the placebo group but the difference was not significant. Bicer et al. reported that intraoperative intravenous dexmedetomidine 1.0 µg/kg reduces postanesthetic shivering with effects comparable to those of meperidine 0.5 mg/kg.¹⁰ Incidences of postanesthetic shivering in the meperidine and

dexmedetomidine group were 10% and 15%, respectively, compared with 55% in the placebo group. Meanwhile, Blaine Easley et al. reported that dexmedetomidine 0.5 µg/kg was effective for treatment of postanesthetic shivering in children.¹² In the present study we aimed to find the optimal dose for prophylaxis of postanesthetic shivering by comparing dexmedetomidine in doses of 0.5, 0.75 and 1.0 µg/kg in adults undergoing surgical procedure under general anesthesia.

Intraoperative hypothermia is the major risk factor for post-anesthetic shivering, but shivering can occur in patients who are normothermic at the end of the surgery.^{13,14} In our study, tympanic temperatures in the operation room started to decrease after induction and were lower than the baseline temperatures in all groups. In the recovery room, patients in the dexmedetomidine groups were hypothermic and their body temperatures were mostly lower than those of patients in the saline group, who were normothermic. However, the incidence and severity of shivering patients were significantly greater in saline group. Dexmedetomidine has been reported to reduce the core temperature and our results are consistent with this findings.¹⁵ We were unable to find relationship between the tympanic temperature values and postanesthetic shivering.

Nausea and vomiting are common after general anesthesia. Nausea is also one of the adverse effects of dexmedetomidine. However, there are also studies showing no difference of dexmedetomidine compared with placebo for nausea.⁸ In our study, the nausea and vomiting incidence did not differ among the four groups.

Bradycardia is one of the known hemodynamic effects of dexmedetomidine. In our study, three, six and five patients in the groups of dexmedetomidine 0.5, 0.75, and 1.0 µg/kg received atropine respectively. The use of atropine for bradycardia should be considered here because anticholinergic premedication increases the incidence of post anesthetic shivering by increasing vasoconstriction and shivering thresholds.¹⁶ Although more patients in the dexmedetomidine group received atropine compared to placebo group, fewer patients shivered.

Dexmedetomidine has sedative and analgesia-sparing effects via central actions in the locus coeruleus and in the dorsal horn of the spinal cord, respectively.¹⁷

Bicer et al. demonstrated that patients who received dexmedetomidine demonstrated a prolonged extubation time and higher sedation scores compared with placebo patients.¹⁰ The present study showed that extubation time was prolonged significantly in the dexmedetomidine 0.75 and 1.0 µg/kg groups. This prolonged extubation time, which appeared to be dose dependent, was longest in the dexmedetomidine 1.0 µg/kg group and shortest in the dexmedetomidine 0.5 µg/kg group. Extubation time in the dexmedetomidine 0.5 µg/kg group was longer than that in the saline group but the difference was not significant.

The patients in dexmedetomidine groups in our study had lower MOAA/S postoperative sedation scores upon arrival in the recovery room compared with the saline group. But beginning 20 minutes after arrival at the PACU, the sedation scores were not different among the groups.

Considering the analgesic effect, dexmedetomidine 0.5 µg/kg was not as effective as dexmedetomidine 0.75 or 1.0 µg/kg. The effect of dexmedetomidine 1.0 µg/kg on analgesia was more consistent than other dexmedetomidine groups. The lowest patients required rescue analgesia in the dexmedetomidine 1.0 µg/kg group and the time to rescue analgesic was the longest in this group.

There are some limitations in our study. First, the sample population consisted only young adult female patients who were relatively healthy. It needs to be determined whether the present findings can be generalized to other age groups and the male sex. Second, administration of meperidine can influence to analgesic rescue during postoperative period but we made no attempt to assess it. However, the number of patients who received analgesic rescue was the most in the saline group. The time to rescue analgesia in the saline group was the shortest among the four groups. Therefore, in our study, it doesn't seem like meperidine affected analgesic rescue significantly.

CONCLUSION

We conclude that dexmedetomidine possesses good antishivering properties as well as an analgesic effect at a dose of 0.75 or 1.0 µg/kg. Though sedation in the immediate recovery period and delayed extubation time with dexmedetomidine appeared, they did not have any major clinical impacts on the overall recovery from anesthesia.

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