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Original Article

Dexmedetomidine reduces shivering during epidural anesthesia

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Abstract: Intraoperative dexmedetomidine infusion may be effective in the prevention of post general anesthetic shivering. However, there is no study has been performed under epidural anesthesia. We aimed to investigate the effect of intraoperative usage of dexmedetomidine infusion on post epidural anesthesia shivering. Sixty patients were randomly assigned to two groups. Group DEX was received dexmedetomidine at a bolus dose of 1 ug/kg for 15 min immediately after the beginning of epidural anesthesia, while the control (CON) group received the same volume normal saline. Systolic arterial blood pressure (SBP) was lower in the CON group than in the DEX group at 30 min, 40 min and 50 min after the start of anesthesia. The heart rate (HR) and temperature are lower in the DEX group than in the CON group at between 10 min and 60 min after the beginning of anesthesia. The overall incidence of shivering was lower in the DEX group than in the CON group. Intraoperative dexmedetomidine (1 ug/kg) effectively reduced the incidence of shivering during epidural anesthesia. Moreover, it produced an additional stable hemodynamic effect.

Keywords: Dexmedetomidine, shivering, epidural

Introduction

Post anesthetic shivering is relatively a common side effect of epidural anesthesia [1, 2]. Possible contributing factors to shivering are rapid loss of heat, heat redistribution from core to periphery, and decrease in vasoconstriction threshold [3]. Shivering is very stressful for patients and may interfere with monitoring of electrocardiogram, blood pressure, and pulse oxygen saturation [4]. It can significantly increase oxygen consumption, lactic acidosis, and carbon dioxide production; thus, it may induce complications in patients with coronary artery disease or other heart disease [5]. Hence, prevent shivering is the ideal option to avoid shivering-induced increase in hemodynamic and metabolic demands. Previous studies have shown that several drugs including meperidine, clonidine and tramadol, are effective in treating or preventing anesthesia-related shivering [6-9]. However, these drugs have analgesic or sedative properties, and adverse effects including hypotension, bradycardia, nausea and vomit. It has been speculated that hypothalamic Alpha 2 receptors are involved in affecting the shivering threshold [10]. Although clonidine prevents shivering after general [9] and epidural [8] anesthesia, its clinical use is limited by side effects including bradycardia, sedation, and hypotension. Dexmedetomidine, a potent Alpha 2 adrenoceptor agonist, is approximately eighttimes more selective towards the Alpha 2 receptor than clonidine. It has four times less in elimination half-life, and two times less in distribution half-life than clonidine, making dexmedetomidine more desirable for clinical use [11]. Intraoperative dexmedetomidine infusion may be effective in the prevention of post general anesthetic shivering [12]. However, there is no study has been performed to show the efficacy of intraoperative dexmedetomidine in patients under epidural anesthesia. The aim of this study was to investigate the effect of the intraoperative usage of dexmedetomidine infusion on post epidural anesthesia shivering.

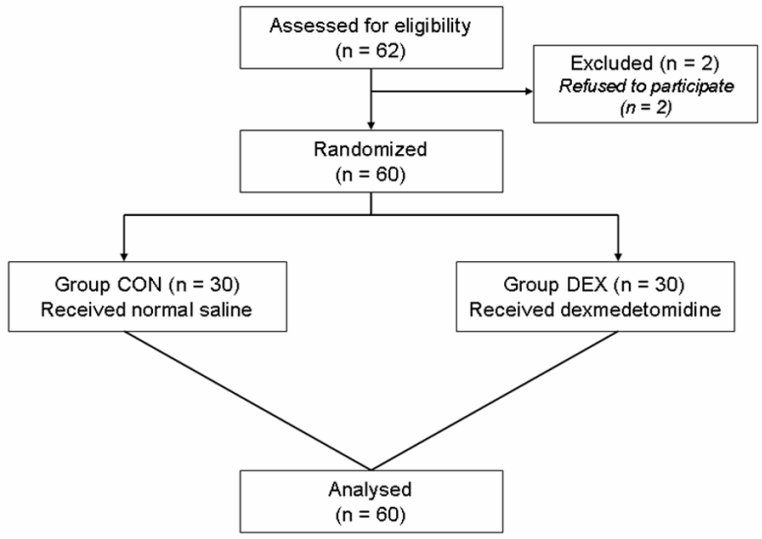

Figure 1. Consort flow chart that outline patients assignment and treatment protocols. CON = control with normal saline, DEX = dexmedetomidine (1 ug/kg).

Methods

Patients

The institutional review board of the Tongling People's Hospital approved this study. Written informed consent was obtained from all patients. Between January 2015 and August 2015 at Tongling People's Hospital, 62 patients aged 24~65 yr and ASA (American Society of Anesthesiologists) physical status I or II, scheduled for lower limb and hypogastric operation under epidural anesthesia were enrolled. No premedication was given. Patients with known contraindications to dexmedetomidine, history of neurological, ischemic heart disease, uncontrolled hypertension and diabetes mellitus were excluded.

Protocol

Epidural anesthesia was induced at the lumbar vertebrate 1-2 interspaces, with 0.75% ropivacaine 13-15 ml. Sensory block height was determined by loss of temperature discrimination and by pinprick testing every 5 min during the first 30 minutes of epidural anesthesia. Immediately before epidural anesthesia, 60 patients were randomly assigned into dexmedetomidine (DEX, Nhwa Pharma, Jiangsu, China) and control (CON) group, 30 patients per group. Patients in the DEX group received 1.0 μg/kg dexmedetomidine diluted in 50 ml of normal saline over 15 min. Patients in the CON group received the equal amount of NS infusion.

Patients were supplemented with oxygen 5 L/min by face mask and conventional fluid infusion of 12 ml/kg/h of Lactated Ringer's Solution, and connected to a monitor to record ECG, blood pressure, heart rate, temperature and pulse oxygen saturation were recorded during the anesthesia. Patients wore a light cotton shirt, and were covered with a light blanket. The operating room temperature was 21-23°C, with a room humidity of nearly 60%. Patients who were administered atropine or ephedrine intraoperatively because of bradycardia (< 50 bpm) and hypotension were also recordedby attending anesthesiologists.

The incidence of shivering was determined for the first 60 min of anesthesia. The severity ofshivering was classified into 1 of 5 grades namely, 0 = no shivering; 1 = 1 or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause but without 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 entire body. The shivering assessment was performed in the operating room by an attending anesthesiologist, who was blinded to the treatment allocation.

Statistical analysis

The number of patients required in each group was determined by a pilot study. A study population of at least 24 patients for each group was needed to produce statistical power ≥ 90%, with $\alpha = 0.05$ (two-tailed), based on the incidence of shivering 80% in the control group and 20% in the dexmedetomidine group. In this study, 62 patients were totally enrolled to increase power. Statistical analysis was performed using the SPSS 11.0 program (SPSS

Table 1. Patient characteristics and operation details

	CON	DEX
Gender (M/F)	12/18	17/13
Age (years)	50 ± 2	52 ± 1
Weight (kg)	65 ± 2	66 ± 2
Height (cm)	163 ± 1	167 ± 1
ASA grade (I/II)	17/13	19/11
Site of surgery		
Lower limb	11	12
Lower abdominal	14	11
Ureter and bladder	4	6
Perineum	1	1
Duration of surgery (min)	90 ± 7	89 ± 4
Duration of anesthesia (min)	111 ± 7	108 ± 4

Categorical variables were presented as numbers, quantitative variables were shown as means and standard error of mean (SEM). ASA = American Society of Anesthesiologists. CON = control with normal saline, DEX = dexmedetomidine (1 ug/kg).

Inc., Chicago, IL, USA). Parametric data were analyzed by using independent *t*-test. Non-parametric data were analyzed by using the Mann-Whitney U test. The χ^2 test was used to evaluate categorical variables. All data are presented as mean ± standard error of mean (SEM), or the number of patients. A *P* value of < 0.05 was considered statistically significant.

Results

A total of 62 patients were assessed for eligibility. Then, 2 patients refused to participate in this study. Therefore, 60 patients were subsequently randomly assigned to control group (CON) and dexmedetomidine group (DEX, 1 ug/kg). All patients completed this study (**Figure 1**). There were no significant differences in patient characteristics and operative procedures between groups (**Table 1**).

Systolic arterial blood pressure (SBP) was lower in the CON group than in the DEX group at 30 min, 40 min and 50 min after the start of anesthesia. However, diastolic arterial blood pressure (DBP) is similar between two groups during the first hour of anesthesia. The heart rate (HR) and temperature are lower in the DEX group than in the CON group at between 10 min and 60 min after the beginning of anesthesia (**Figure 2**). There were no significant differences with respect to pulse oxygen saturations between the two groups.

The overall incidence of shivering was lower in the DEX group than in the CON group (**Table 2**). Grade 4 shivering was not noted in any of the patients in the DEX group (**Table 2**).

The number of patients receiving atropine during the operation was similar between the two groups. However, less patients of the DEX group obviously needed ephedrine to treat intraoperative hypotension compared to CON group (**Figure 3**).

Discussion

In this double blind randomized controlled study, the results indicated that intraoperative dexmedetomidine at a single dose of 1 ug/kg over 15 minutes, significantly reduced the incidence and severity of shivering in patients undergoing epidural anesthesia. Furthermore, dexmedetomidine also provided stable hemodynamics to epidural anesthesia during surgery.

Plenty of studies have focused on shivering under neuraxial anesthesia, but the specific mechanism has not been well established [1, 2]. It has been shown that central thermoregulation likely contribute to the shivering under epidural anesthesia [12]. There are several drugs like meperidine, clonidine and tramadol, have been suggested to reduce the incidence of shivering anesthesia-related shivering [6-9]. Initial studies suggested that the prevention of shivering of meperidine and tramadol is owed to their interaction with opioid receptors [6, 13, 14]. Subsequently, animal studies demonstrated that the suppression of shivering of meperidine could not be reversed by naloxone, but abolished by atipamezole, a Alpha 2 receptor antagonist [15, 16]. Hocker *et al.* [17] found that Alpha 2A subtype plays an important role in the mediation of thermoregulatory effects caused by meperidine in mice. This can be explained that meperidine binds to various receptors including opioid receptors, Alpha 2 receptors and so on [18]. However, meperidine and tramadol have the side effect of respiration depression in clinic. Jeon *et al.* [19] showed that intravenous infusion of clonidine 1 ug/kg significantly reduced the incidence of post spinal anesthesia shivering. Although intrathecal administration of clonidine could prolong anesthesia maintainence time, it failed to prevent post spinal anesthesia shivering. Other studies have shown that intravenous clonidine was an

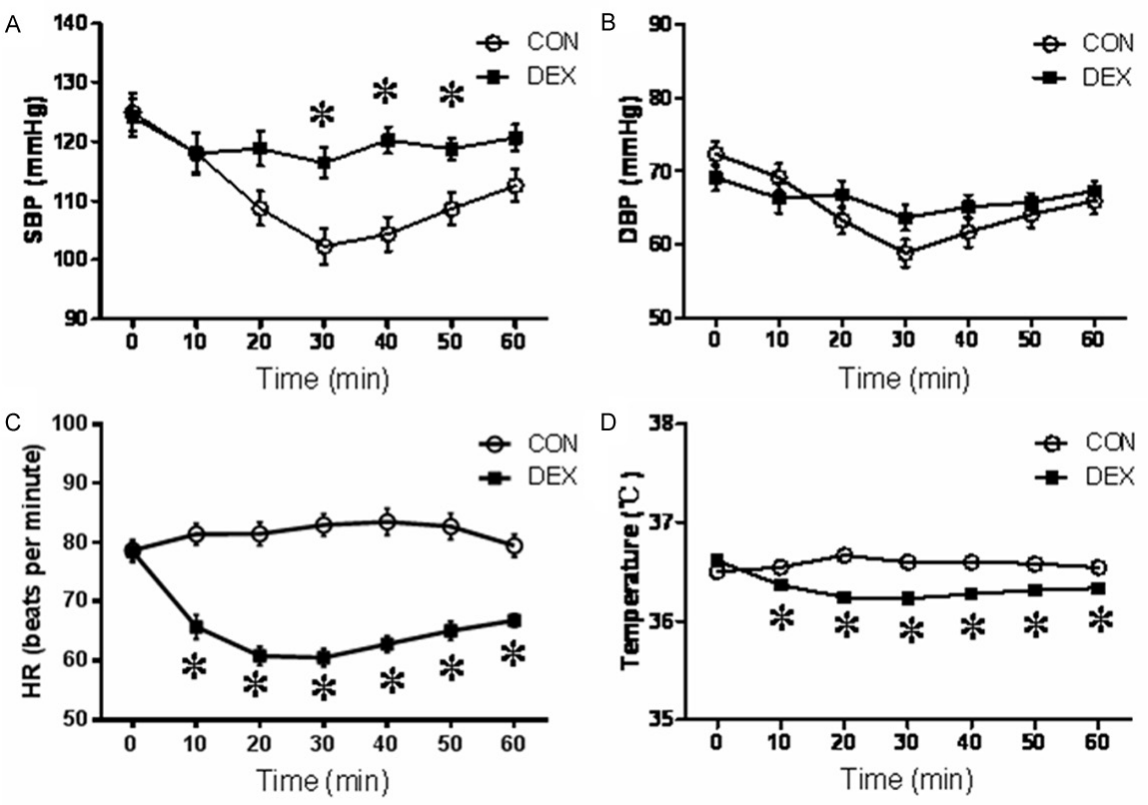

Figure 2. Hemodynamics and temperature changes during epidural anesthesia. Values were shown as means and standard error of mean (SEM). SBP = systolic arterial blood pressure, DBP = diastolic arterial blood pressure, HR = heart rate. CON = control with normal saline, DEX = dexmedetomidine (1 ug/kg). *$P < 0.05$ compared with group CON.

effective prevention and therapeutics for post epidural anesthesia shivering [20]. But prevention of shivering by using clonidine may be limited by its side effects such as hypotension or bradycardia. Dexmedetomidine, a potent Alpha 2 adrenoceptor agonist, is approximately eight-times more selective towards the Alpha 2 receptor than clonidine. It has four times less in elimination half-life, and two times less in distribution half-life than clonidine, showing dexmedetomidine more desirable for clinical use [11]. Intraoperative dexmedetomidine infusion may be effective in the prevention of post general anesthetic shivering [12]. Recently, Callaway *et al.* [10] found that bolus infusion of dexmedetomidine 1 ug/kg reduced shivering during mild hypothermia in waking volunteers by decreasing the threshold temperature for shivering. This effect could last more than 90 minutes, and there is no respiration depression only with a slight blood pressure reduction and moderate sedation.

The mechanism by which dexmedetomidine reduces shivering has not been clearly stated. Since, the Alpha 2 receptors are widely existed in the hypothalamus, and hypothalamic Alpha 2 receptors are likely involved in affecting the shivering threshold [10]. The main cause of this effect possibly is that dexmedetomidine may interfere in central processing and downgrade the central thermoregulatory threshold for shivering.

Consistent with previous studies, dexmedetomidine decreases heart rate and also maintains hemodynamic stability [21, 22]. In this study, less people need ephedrine treatment in dexmedetomidine group. It suggested that dexmedetomidine effectively prevent hypotension due to epidural anesthesia. It also decreased oxygen demand by reducing heart rate to an optimal value.

There are several limitations to this study. Firstly, although we selected a defined criteria of shivering, this data was merelyrecorded by human observation of the occurrence of shivering. Therefore, it might need further works to

Table 2. Incidence of shivering during epidural anesthesia

Group	Grade of shivering				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
CON	6 (20)	6 (20)	7 (23.3)	5 (16.7)	6 (20)
DEX	23 (76.7)*	5 (16.7)	1 (3.3)	1 (3.3)	0 (0)

CON = control with normal saline, DEX = dexmedetomidine (1 ug/kg). *P < 0.05 compared with group CON.

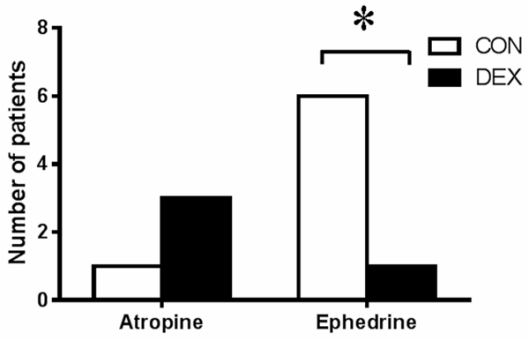

Figure 3. Number of patients needed to be treated with atropine and ephedrine during epidural anesthesia. CON = control with normal saline, DEX = dexmedetomidine (1 ug/kg). *P < 0.05 compared with group CON.

determine whether this single use of dexmedetomidineactually reduced the incidence of shivering. Secondly, this is only a single-center study. Thus, a multiple-center study would be better to determine this effect. Lastly, it would be better that if patients received a supplementary warm pad may provide an additional effect.

In conclusion, we demonstrated intraoperative dexmedetomidine (1 ug/kg) over 15 minutes at the beginning of the anesthesia, effectively reduced the incidence of shivering during epidural anesthesia without other severe complications. Moreover, it also produced an additional stable hemodynamic effect to epidural anesthesia.

Acknowledgements

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Authors' contribution

J.H.,M.Z., and Y.L. contributed to the conception and design. J.H., M.Z., and J.C. did the data collection. J.H., L.C., and Y.L. did the analysis and interpretation. J.H.,C.D., and Y.L. did the writing, critical revision of the article. All authors reviewed and approved the final manuscript.

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