

Consciousness inhibition of intravenous dexmedetomidine in patients undergoing lower limb surgery with epidural anesthesia: A dose-response study by age group

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Abstract: Dexmedetomidine (DEX) induces a dose dependent sedation and has been widely used as an adjuvant sedative during regional anesthesia recently. We aimed to investigate the effective dose of intravenous single-dose DEX to induce consciousness inhibition in patients of different ages undergoing lower limb surgery with epidural anesthesia. Ninety-two patients were divided into three groups according to their ages. Patients aged 18-45 years, 46-64 years and 65-85 years in group Y, group M and group O, respectively. With the accomplishment of epidural anesthesia, a pre-calculated dose of DEX was infused for more than 10 minutes and the sedative state was assessed by Observer's Assessment of Alertness/Sedation (OAA/S) scale 30 minutes after the infusion. A modified Dixon's up-and-down method was applied to decided the dose of DEX for each sequential patient. The 50% effective dose (ED₅₀) of DEX in the three groups were 0.40, 0.76 and 1.03 µg/kg, respectively. The 95% effective dose (ED₉₅) in group O (0.54 µg/kg) was 45% of group Y (1.21µg/kg) and 64% of group M (0.84µg/kg). Besides, the incidence of bradycardia was more frequent with the increase of age. The present study indicated that the appropriate single-dose of DEX to induce consciousness inhibition should reduce with the increase of age in patients underling lower limb surgery with epidural anesthesia, especially in patients over 64 years old. This result may protect the old patients from excessive sedation and dose-dependent adverse reactions.

Keywords: Dexmedetomidine, spinal anesthesia, sedation, ED₅₀, ED₉₅

INTRODUCTION

Spinal anesthesia is a main anesthetic method for lower limb surgery and provides more advantages than general anesthesia (Solanki *et al*, 2013; Chery *et al*, 2014). However, patients may still suffer from discomforts such as anxiety, fear and stress (Ko *et al*, 2015). It has been proven that satisfactory sedation relieves patients' psychological and physiological discomforts, which improves patients' satisfaction during regional anesthesia (Kim *et al*, 2015; Shah *et al*, 2016). Nevertheless, excessive sedation is harmful, it can not only cause serious side effects of cardiorespiratory, but also increase the incidence of postoperative delirium in the old (Kim *et al*, 2015).

Dexmedetomidine (DEX), known as an effective alpha2-adrenergic agonist with higher receptor selectivity, has been widely used as an adjunctive sedative in patients under regional anesthesia (Hong *et al*, 2012; Senses *et al*, 2013; Song *et al*, 2013). DEX induces a dose dependent sedation by acting on the locus coeruleus without serious respiratory depression (Cooper *et al*, 2011). Besides, DEX shortens the onset time and prolongs the duration of sensory and motor block during spinal anesthesia (Kaya *et al*, 2010; Abdallah *et al*, 2013; Park *et al*, 2014). Previous

studies mainly focused on medication given as a bolus, followed by continuous infusion (Hong *et al*, 2012; Park *et al*, 2014). However, there were fewer studies investigating the intravenous single-dose administration of DEX as an adjuvant sedative during spinal anesthesia, especially in different ages groups. In our study, we aimed to investigate the effective dose and the adverse reactions of intravenous single-dose DEX to induce consciousness inhibition in patients of different ages undergoing lower limb surgery with epidural anesthesia.

MATERIALS AND METHODS

Participants

This prospective, randomized, controlled clinical study was performed from October 2016 to February 2017 at Yantai Yuhuangding Hospital, Qingdao university and was approved by the Ethical Committee of the hosital. After obtaining the written informed consents from each patient, 92 patients classified of ASA I-II and scheduled elective lower limb surgery under epidural anesthesia were enrolled. Exclusion criteria included bradycardia (HR<60 bpm), severe anemia, cardiac decompensation, infection on puncture skin, lumbar disease, coagulopathy, anaphylaxis to anesthetics, pregnancy, and history of chronic medication of sedatives and analgesics. Patients with unfavorable spinal anesthesia or a high level of

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sensory block (the peak block level over the fourth thoracic vertebra) were also excluded from the study. All the recruited subjects were divided into three groups according to their ages. Patients aged 18-45 years, 46-64 years and 65-85 years in group Y, group M and group O, respectively.

Spinal anesthesia

All the patients were preoperative fasting for 6-8 hours and no premedication was given. After arriving at the operation room, standard monitors were applied, consisting of mean arterial pressure (MAP), heart rate (HR), electrocardiogram (ECG) as well as blood oxygen saturation (SpO₂) and the bispectral index (BIS). Nasal catheter oxygen inhalation with the flow rate of 2-3 L/min. Before the performance of epidural anesthesia, Ringer's solution was intravenously administered. Lumbar puncture was performed on L2-L3 interspace in the lateral decubitus position using a 25-gauge quincke spinal needle. After confirming the epidural space, 2% lidocaine with the dose of 3 ml was administered to epidural space over 10 s, and an epidural catheter was put into epidural space for 3 - 4 cm. The pin-prick test was used to assess the sensory block level every 2 minutes until there were no differences in four consecutive tests and make sure that the peak block level was under T10 by injecting ropivacaine discontinuously. The level of motor block was defined by a modified Bromage Scale (0=no paralysis; 1 = unable to raise extended leg; 2 = unable to flex knee; 3 = unable to flex ankle) (Bromage, 1965).

When the epidural anesthesia was accomplished, patients were asked to close their eyes and wore disposable noise free earplugs to keep quiet for a few seconds and then the initial BIS value were recorded. Subsequently, a pre-calculated amount of DEX was administered by an infusion pump for more than 10 minutes and a modified Dixon's up-and-down method (Dawes *et al*, 2014) was applied to decide the dosage of DEX for next patient according to the last patient's sedative score. The DEX was diluted to 4 µg/ml with 0.9% normal saline.

The degree of sedative state was evaluated by using the Observer's Assessment of Alertness/Sedation (OAA/S) scale (Stylianou and Flournoy, 2002) (1- does not respond to mild prodding or shaking; 2- responds to mild prodding or shaking; 3- responds only after name is spoken loudly or repeatedly; 4 -lethargic response to name spoken in normal tone; 5 -responds readily to name spoken in normal tone) 30 minutes after the administration of DEX. The consciousness inhibition was defined as OAA/S=2 or OAA/S=3 and bispectral index score (BIS)45-55. The initial dose of DEX in the first patient was 1 µg/kg, if recorded consciousness inhibition which was defined as positive, the dose of DEX for next patient then decreased 0.05µg/kg, on the contrary, the dose of DEX increased 0.05µg/kg, until 7 turning points (negative to positive) were observed and then terminated the study.

MAP, HR and SpO₂ were recorded and analyzed at the following time: before infusion of DEX(T0), 5, 10, 15, 20, 25 and 30 min after infusion of DEX (T1-T6) and at the end of surgery (T7). Hypotension was defined as MAP below 60 mmHg or the blood pressure declining more than 30% compared to baseline values, while bradycardia was HR less than 60 bpm and respiratory depression was SpO₂ under 90%. Hypotension was treated immediately with intravenous ephedrine 0.1mg/kg, while bradycardia was treated with intravenous atropine 0.01mg/kg and respiratory depression was treated with oxygen inhalation via face mask.

STATISTICAL ANALYSIS

All of the data in the study were analyzed with SPSS for Windows Version 16.0. All quantitative data are expressed as mean ± standard deviation (SD). Age, weight, height, BMI, duration of operation and duration of anesthesia were analyzed with one-way ANOVA and level of motor block were compared by Kruskal Wallis test. In each group, MAP changes were compared to baseline values using one-way ANOVA, while HR using Friedman test. Chi-square test was used to analyze the incidence of bradycardia and hypotension. Probit analysis was used to calculate the 50% effective dose (ED₅₀), the 95% effective dose (ED₉₀) and the 95% CI of DEX. Origin 85 software was used to plot the diagram of sequential test method and dose-effect relationship. All data with *P*<0.05 were considered to be significant.

RESULTS

Demographic Characteristics

Eighty six patients completed this study, and six patients were excluded from this study because of bradycardia (1 in group M, 2 in group O), unfavorable spinal anesthesia (1 in group M) or delayed surgery (1 in group M, 1 in group O). There were no significant differences of the three groups (*P*<0.05) as regard to demographic and surgery/anesthesia-related variables including height, weight, BMI, surgery/anesthesia time and motor block level, except for age (*P*>0.05) (table 1).

The ED₅₀ and ED₉₅ of the Single-dose DEX to Induce Consciousness Inhibition in Different Groups

The ED₅₀ of the single-dose DEX to induce consciousness inhibition were 1.03 µg/kg (95% CI 0.92-1.74µg/kg) in group Y, 0.76µg/kg (95% CI 0.72-0.80µg/kg) in group M and 0.40 µg/kg (95% CI 0.32-0.45µg/kg) in group O, respectively. The ED₉₅ of the three groups were 1.21µg/kg (95% CI 1.10-2.93µg/kg), 0.84µg/kg (95% CI 0.80-1.15µg/kg) and 0.54µg/kg (95% CI 0.46-1.62 µg/kg), respectively. The ED₅₀ of single-dose DEX in elderly patients was 39% that of younger patients and 53 % that of middle-aged patients and the ED₉₅ of single-dose DEX in elderly patients was 45% that of younger patients and

64% that of middle-aged patients. Besides, both the ED_{50} and the ED_{95} were significantly decreased ($P < 0.05$) with the increase of age (fig. 1 and table 2).

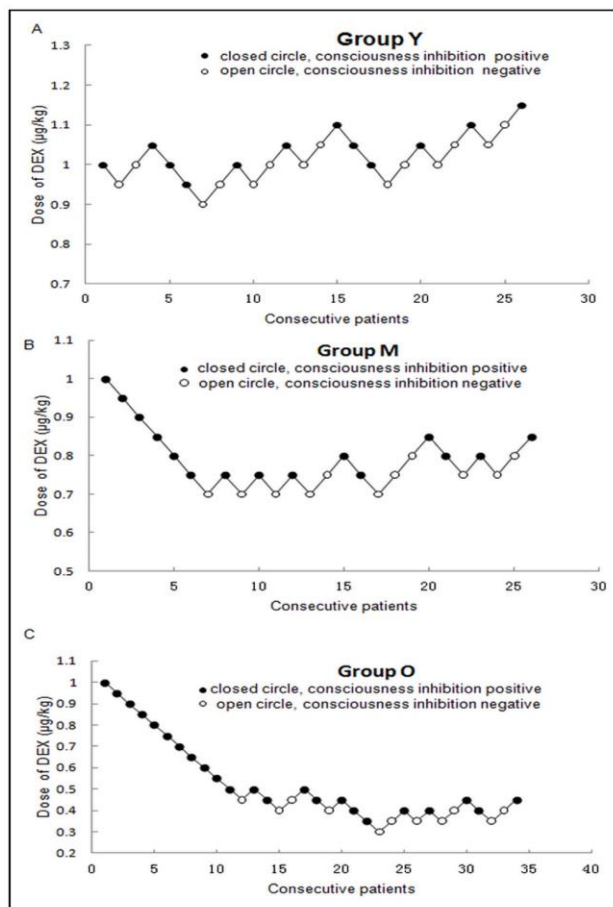


Fig. 1: The sequences sedation state of three groups

The regression equation of the single-dose dex to induce consciousness inhibition in different groups

The regression equation fitted by Probit regression analysis of the three groups were Probit (P_Y) = $-0.2716 + 23.64492 * \lg(\text{dosage})$, Probit (P_M) = $4.51128 + 37.84799 * \lg(\text{dosage})$, Probit (P_O) = $5.0417 + 12.48739 * \lg(\text{dosage})$, respectively.

Adverse reactions

In each group, both the HR and MAP gradually decreased after the DEX infusion compared to the baseline ($P < 0.05$) (table 3). The HR and MAP of group O decreased significantly more than that of group Y ($P < 0.05$). The incidence of bradycardia was more frequent in group O when compared to group Y (14/34 vs 3/26) ($P < 0.0167$), while there were no differences between group O and M (5/26). No hypotension or respiratory depression has been observed.

DISCUSSION

In this study, we determined the ED_{50} and ED_{95} of intravenous single-dose DEX to induce consciousness

inhibition in patients of different ages undergoing lower limb surgery with epidural anesthesia, and found that both the ED_{50} and the ED_{95} were significantly decreased with the increase of age. In addition, bradycardia was more frequent in patients over 64 years old when compared to the younger.

It is well known that DEX is a highly selective α_2 adrenergic receptor agonist, which induces sedation effects with specific properties (Nelson *et al*, 2003). Patients sedated with DEX remain cooperative and can be easily aroused by language stimulation and then feel into sleep quickly when the stimulation disappears, which is similar to natural Non-Rapid Eye Movement Sleep (Rampil, 1998). As a consequence, it is not wise to use the traditional sedation scoring systems based on clinical observation or a single sedation scoring system to evaluate sedation induced by DEX. BIS has been widely used as a quantitative parameter to evaluate anesthesia and sedation levels. Kasuya *et al* (Kasuya *et al*, 2009) demonstrated that BIS combined with sedation scales can work well for evaluating sedation level when DEX was used. Furthermore, they found that the BIS values at the level OAA/S score equal 2 were about 20 points less in DEX when compared to propofol. In our study, we combined BIS with OAA/S score to evaluate the sedation state, which improved the accuracy of sedation assessment. In addition, the fast distribution phase half-life of DEX was 6 min after infusion and peak time was about 25 to 30 minutes. In consideration that repeated stimulation of incomplete sedated patients during sedation scoring will interfere sedation state (Ebert *et al*, 2000), we only chose 30 minutes after infusion to evaluate the sedation state.

DEX has been widely used as an adjunctive sedative during regional anesthesia due to its potential effects, including decreases intraoperative anesthetic requirements, improves postoperative analgesia, as well as shortens the onset time and prolongs the duration of sensory and motor block (Zhang *et al*, 2016). It can be used as a bolus with the loading dose of $1.0 \mu\text{g/kg}$ and followed by continuous infusion with the dose of $0.2\text{--}0.7 \mu\text{g/kg/h}$ as the dispensatory recommend (Korea Pharmaceutical Information C, 2014). However, excessive sedation has been frequently reported in previous studies when the recommend dosage of DEX was used, especially in elder patients. Park and his colleagues reported that excessive sedation (with Ramsay score of 5/6) occurred in 46% and 60% of patients aged more than 60 years, respectively, when administering DEX with the dosage of $0.5 \mu\text{g/kg}$ and $1 \mu\text{g/kg}$. In another study, there was no excessive sedation cases which assessed by OAA/S has been observed when $0.5 \mu\text{g/kg}$ of DEX was used in middle-age patients for lower extremity surgery under spinal anesthesia (Jung *et al*, 2013). Therefore, it is necessary to determine the appropriate dose of DEX to induce consciousness inhibition. Besides, DEX results in hemodynamic

Table 1: Clinical characteristics of patients of the three groups (mean \pm SD).

	Group Y (n=26)	Group M (n=26)	Group O (n=34)	P values
Age (y)	33.38 \pm 7.16	54.69 \pm 5.61	73.65 \pm 5.72	<0.01
Height (m)	1.70 \pm 0.11	1.68 \pm 0.10	1.68 \pm 0.92	0.643
Weight (kg)	64.35 \pm 10.45	63.78 \pm 9.80	63.69 \pm 9.00	0.962
BMI (kg/m ²)	22.00 \pm 1.39	22.47 \pm 1.23	22.35 \pm 1.53	0.450
Duration of surgery (min)	108.88 \pm 9.53	108.00 \pm 10.29	108.88 \pm 9.56	0.816
Duration of anesthesia (min)	118.73 \pm 9.59	120.12 \pm 10.25	120.29 \pm 10.01	0.931
Level of motor block	2.81 \pm 0.40	2.92 \pm 0.27	2.85 \pm 0.35	0.484

Table 2: ED₅₀ and ED₉₅ of the three groups

	Group Y (n=26)	Group M (n=26)	Group O (n=34)
ED ₅₀ (ug/kg)	1.03	0.76	0.40
95%CI (ug/kg)	0.92-1.74	0.72-0.80	0.32-0.45
ED ₉₅ (ug/kg)	1.21	0.84	0.54
95%CI (ug/kg)	1.10-2.93	0.80-1.15	0.46-1.62

Table 3: Hemodynamic data (mean \pm SD)

		T0	T1	T2	T3	T4	T5	T6	T7
HR (bpm)	Group Y (n=26)	74.0 \pm 9.1	72.4 \pm 9.0	71.2 \pm 8.9	68.8 \pm 9.0	69.2 \pm 8.3	68.7 \pm 8.3	69.8 \pm 8.7	70.2 \pm 8.4
	Group M (n=26)	76.2 \pm 8.9	74.5 \pm 9.3	72.0 \pm 9.8	70.5 \pm 9.8	70.2 \pm 10.6	70.2 \pm 10.6	70.3 \pm 9.8	70.7 \pm 9.0
	Group O (n=34)	77.9 \pm 7.6	74.7 \pm 8.4	71.6 \pm 10.2	70.0 \pm 12.9*	68.0 \pm 12.6*	68.0 \pm 12.3*	68.7 \pm 11.0*	69.9 \pm 10.0*
MAP (mmHg)	Group Y (n=26)	86.7 \pm 8.0	86.0 \pm 8.2	84.8 \pm 8.0	82.3 \pm 8.5	82.0 \pm 8.4	81.4 \pm 8.1	81.0 \pm 7.0	83.7 \pm 6.7
	Group M (n=26)	88.8 \pm 9.4	87.2 \pm 8.8	85.2 \pm 8.6	81.1 \pm 8.1	81.0 \pm 8.2	80.5 \pm 6.7	80.7 \pm 6.7	84.8 \pm 7.0
	Group O (n=34)	90.6 \pm 8.0	87.2 \pm 7.5	84.0 \pm 7.0	76.2 \pm 6.9*	75.5 \pm 6.6*	75.0 \pm 6.4*	74.4 \pm 5.7*	77.7 \pm 5.4*

Note: T0: before infusion of DEX; T1-T6: 5, 10, 15, 20, 25 and 30 min after infusion of DEX; T7: at the end of surgery.

*P<0.05 compared with T0.

instability, such as hypertension, hypotension and bradycardia, especially after a loading dose (Ren *et al*, 2015). In our study we found that both the MAP and HR declined under the baseline after the DEX infusion, especially in group O, and bradycardia was more frequent in the old. These evidences indicated that dose-dependent adverse reactions were more serious in the old, and the present study may provide some clinical guidance in the application of DEX. However, the application of tourniquets during lower limb surgery may have some effects on MAP, leading to this result not extrapolated to all kinds of surgeries.

Kim *et al* defined the adequate sedation as OAA/S scale 4/3, and they found that the ED₅₀ of DEX was 0.25 μ g/kg in patients aged 65 to 78 years old and 0.35 μ g/kg in patients aged 45 to 64 years old, and the ED₉₅ was 33% lower in the elderly patients in comparison with the younger (0.38 μ g/kg vs 0.57 μ g/kg). They suggested that when used for the elderly patients, they should reduce the dosage of DEX one third of the recommend dose for young patients, which was consistent with our results. The possible explanations for our results are as followed. First

of all, elderly patients may be more sensitive and less consumption of sedative could achieve desired sedation. Besides, clinical study has confirmed that the elimination half-life was prolonged as regard to pharmacokinetics of DEX in elderly patient (Iirola *et al*, 2012). In addition, spinal anesthesia itself has an effect on sedation status. On the one hand, spinal anesthesia acts as sedatives and induces slight sedation (Gentili *et al*, 1998; Pollock *et al*, 2000). According to Jabalamel (Jabalamel *et al*, 2012), the BIS score decreases during surgery with spinal anesthesia and the maximal effect occurred at 30 and 45 minutes after spinal anesthesia. On the other hand, spinal anesthesia elevates sensitivity of sedatives and several studies have reported that spinal anesthesia with bupivacaine reduced requirement of midazolam and propofol (Tverskoy *et al*, 1994; Tverskoy *et al*, 1996). Therefore, the required dose of DEX decreased, which explaining the low ED₅₀ and ED₉₅ for consciousness inhibition in our study.

CONCLUSION

This study indicated that the appropriate single-dose of DEX to induce consciousness inhibition reduced with the

increase of age in patients undergoing lower limb surgery with epidural anesthesia, especially in patients over 64 years old. And our findings concluded that the appropriate single-dose of DEX may protect the old patients from excessive sedation and dose-dependent adverse reactions.

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