Assessment of different loading doses of dexmedetomidine hydrochloride in preventing adverse reaction after combined spinal-epidural anesthesia

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Abstract. We conducted the present study to investigate the effects of the different loading doses of dexmedetomidine hydrochloride in the prevention of adverse reactions after combined spinal-epidural anesthesia. A total of 200 patients that were admitted to the Department of Obstetrics at the Second Affiliated Hospital of Xi'an Jiaotong University hospital and treated with cesarean section through the use of combined spinal-epidural anesthesia from December, 2014 to June, 2016, were randomly divided into 4 groups. The therapeutic regimens of patients were shown as follows: group A was administered an intravenous pump of 10 ml/l physiological saline in surgery until the end of the delivery. group B was administered 0.2 μg/kg dexmedetomidine. group C was administered 0.4 μg/kg dexmedetomidine. group D was administered 0.6 μg/kg dexmedetomidine. The anesthesia plane was adjusted to the level below the T10 plane. After the onset of anesthesia, participants of each group were treated with an intravenous pump of dexmedetomidine at loading dose. After intravenous pumping for 10 min in each group during the surgery, patients were administered with an intraoperative maintenance dose of 0.2 μg/kg/h until the end of the delivery. The heart rate (HR), mean arterial pressure (MAP), Narcotrend index (NI), Ramsay sedation score and the incidence of adverse reactions at each time-point of the start of drug administration (T0), 10 min (T2), 30 min (T3), 60 min (T4), 90 min (T5) and the end of surgery (T6) were recorded. Within 24 h post-delivery, the degree of amnesia from using dexmedetomidine until the end of the delivery were followed up. Compared to group A and T0, the HRs of participants at T3-6 in groups B and C were decreased. The MAP at T1 in group D was increased. In groups B and C, the NIs were significantly decreased at T2-6, the Ramsay scores were increased at T3-6, and the differences were statistically significant (P<0.05). The follow-up within 24 h after delivery showed that the degree of anterograde amnesia from groups B to D was significantly higher than group A, with statistically significant difference (P<0.05). A combined spinal-epidural anesthesia with 0.6 μg/kg loading dose of dexmedetomidine, by intravenous pumping within 10 min before cesarean section, can achieve a satisfied sedative effect at 30 min after administration. It maintains the characteristics of intraoperative hemodynamic stability and less adverse reactions. Therefore, it is of great significance to improve the quality of cesarean section delivery.

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Introduction

With the opening of the family planning policy clinics as well as an increase of advanced maternal age, the rate of cesarean sections in China has been increasing year by year. Some reports claim that the rate of cesarean section in China is currently >40% (1). Based on this, enhancing the level of sedation in the delivery process of cesarean section is of great significance in order to improve the outcome of delivery, and to improve the comfort levels of women during cesarean delivery (2).

Cesarean section is usually performed under an intravertebral anesthesia. As a highly selective α2-adrenergic receptor agonist, dexmedetomidine has the effect of sedation, analgesia and inhibition of respiration, and also plays a preferable role in the prevention of postoperative memory loss (3-5). For patients that are accompanied by a local infection and abnormal coagulation function during the cesarean section under general anesthesia, using dexmedetomidine for during delivery can reduce the dosage of propofol and remifentanil, and obtain favorable anesthesia (6). According to previous studies, it can be seen that different loading doses of dexmedetomidine have good sedative effects in TURP (7) and lower limb fracture surgery (8). In the present study, we will further explore the sedative effects of different loading doses

of dexmedetomidine in cesarean section under combined spinal-epidural anesthesia.

Materials and methods

Clinical data. A total of 200 patients that were admitted to the Department of Obstetrics in the Second Affiliated Hospital of Xi'an Jiaotong University and treated with cesarean section using a combined spinal-epidural anesthesia from December, 2014 to June, 2016, were selected. The ASA classification of all patients was I-II, the ages ranged from 22 to 35 years, the weight was from 57 to 72 kg, the operation time was <1.5 h, and the intraoperative transfusion volume was 500-1,200 ml.

Inclusion and exclusion criteria. For inclusion into the stdy, patients had to have ASA classification I-II. The partus maturus was required. Participants that had a history of severe liver and kidney disease, severe cardiac insufficiency, nervous system disease, heart rate (HR) <50 b/min before entering the room, history of drug allergy, intraoperative blood transfusion needed and blood pressure 20% lower than basal blood pressure, were excluded. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University. Signed written informed consents were obtained from all participants before the study.

Grouping. A total of 200 patients were divided into 4 groups according to the principle of random control with 50 cases in each group. Among them, group A was a blank control group. After determining the stable plane of combined spinal-epidural anesthesia, intravenous pumping of 10 ml/l physiological saline (Yangze Pharma, Taizhou, China) was given until the end of the delivery. For group B patients, after determining the stable plane of anesthesia, 0.2 μg/kg dexmedetomidine (Yangze Pharma) was administered. For group C patients, 0.4 μg/kg dexmedetomidine was administered. For group D patients, 0.6 μg/kg of dexmedetomidine was administered. The anesthesia plane was adjusted to the level of below the T10 plane. After the onset of anesthesia, patients of each group were treated with intravenous pumping of dexmedetomidine with loading dose. After intravenous pumping for 10 min in each group during the surgery, the patients were administrated with an intraoperative maintenance dose of 0.2 μg/kg/h until the end of the delivery.

Anesthesia methods. i) The upper extremity venous access was opened, and then 130/0.4 hydroxyethyl starch sodium chloride injection at 8-10 ml/kg was administered; ii) radial artery puncture catheter was used to monitor arterial blood pressure, ECG and SpO2; iii) combined spinal-epidural puncture was selected at the L3-4 interspace, and then an epidural injection of 0.5% 10-15 mg bupivacaine and indwelling catheter were carried out; iv) the anesthesia plane was adjusted to the level of below the T10 plane and v) the Narcotrend was connected to monitor the depth of anesthesia. After subarachnoid administration for 30 min, intravenous pumping of dexmedetomidine was administered (dexmedetomidine hydrochloride injection; batch no. 12070434; specification: 200 μg: 2 ml/tube; Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China).

Table I. Narcotrend index classification.

Classification	Sub-classification	Value range	Implication
A	-	100-95	Waking state
B	B0	94-90	Light
	B1	89-85	sedation
	B3	84-80	
C	C0	79-75	Routine
	C1	74-70	sedation state
	C2	69-65	
D	D0	64-57	Routine
	D1	56-47	anesthesia state
	D2	46-37	
E	E0	36-27	Deep
	E1	26-20	anesthesia state
	E2	19-13	
F	F0	12-5	Multiple degree
	F1	4-0	of anesthesia (burst suppression)

Ramsay scoring method (9). The Ramsay scoring method is as follows: i) Dysphoria; ii) quiet cooperation; iii) drowsiness but was able to obey orders; iv) sleeping state, could be woken up; v) slow response for calling; and vi) deep sleeping, could not be woken up. Among them, (ii-iv) are considered satisfactory and (v-vi) excessive sedation.

The Narcotrend index (NI) (10) classification and implication: Table I.

Degree of amnesia: Table II.

Statistical analysis. The SPSS 19.0 software (IBM SPSS; Armonk, NY, USA) was used for statistical processing. The Chi-square test was used to analyze qualitative data. The Fisher's exact probability method was used for data from 4 tables that did not meet the conditions. Analysis of variance was used to test the comparison of quantitative data. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of the general clinical data of the selected puerperants. The general clinical data of the 200 patients that were selected for the study and treated with cesarean section were compared and analyzed; differences were not statistically significant among the groups ($P>0.05$; Table III).

Comparison of HR changes at each time-point among the different dexmedetomidine loading dose groups. The HRs of patients that were treated with different loading doses of dexmedetomidine were compared. Results demonstrated that when compared to group A and T0, the HRs of patients at T3-6 in groups B and C were decreased (Table IV).

Table II. Degree of amnesia.

Degree of amnesia	Content
No amnesia	Can correctly memorize the sound of instrument operation, medical personnel dialogue or surgical discomfort
Uncompleted amnesia	Can partially memorize things via prompting
Total amnesia	Cannot memorize things even via prompting

Table III. Comparison of the general clinical data of the selected puerperants.

Groups	Cases	Age (years)	Height (cm)	Weight (kg)
A	25	26.4±11.5	158.4±12.7	62.5±11.7
B	25	28.7±9.3	160.2±15.9	63.2±10.8
C	25	27.4±10.8	156.3±14.7	64.3±12.2
D	25	28.9±9.4	156.4±9.5	65.8±11.9
T-value	-	0.38	0.72	0.43
P-value	-	0.69	0.29	0.61

Comparison of mean arterial pressure (MAP) levels at each time-point among different groups. The MAP levels at each time-point among the different groups were compared, which showed that the MAP at T1 in group D was increased; differences were statistically significant (P<0.05; Table V).

Comparison of sedative effect. In order to compare the sedative effects of patients that were treated with cesarean section using different dexmedetomidine loading doses, the Ramsay score and NI score at each time-point were recorded and statistical analysis was conducted. Analysis showed that when compared to T0, NI score at T2 and T3 from group B to group D was significantly decreased, and at T3, the NI score in group A was significantly different from that in groups B-D, while NI scores from group D1 to group D3 were significantly lower than those in group C; differences were statistically significant (P<0.05). Compared to group A, the Ramsay score at T3 and T4 from group B to group D was significantly increased, with statistically significant difference (P<0.05). In addition, the Ramsay score in groups B-D was significantly higher than that in group A (Table VI).

Comparison of adverse reactions after anesthesia. The adverse reactions after anesthesia of patients among different groups were compared. Compared to group A, the incidence of excessive sedation in the other three groups were significantly increased (P<0.05). Compared to group A, the incidence of bradycardia in groups B and C were significantly increased. Finally, the incidence of hypertension in group D was also significantly increased (Table VII).

Comparison of degree of amnesia within postoperative 24 h. The follow-up was performed within postoperative period of 24 h. Results showed that the total amnesia ratio of patients in groups B-D for delivery reached 40-80%, and there was a statistically significant difference when compared to group A (P<0.05; Table VIII).

Discussion

When considering the type of anesthesia to administer in a cesarean section, there are two aspects that need to be considered. On one hand, the patient should be treated with adequate anesthesia and on the other hand, after the delivery, the fetus will be exposed to the external atmosphere, and therefore, the anesthetic drugs must not cause respiratory depression (11). Both of these are regarded as important drug selection criterion. The combined spinal-epidural anesthesia can keep patients in a painless and sober state during the whole process of cesarean section. In addition, due to the barrier between the epidural space and the peripheral circulation, the anesthetic drugs of combined spinal-epidural anesthesia will not enter the maternal blood circulation, and thus affect the fetus. Therefore, the use of combined spinal-epidural anesthesia for cesarean section is also known as 'painless labor' (12). However, in clinical practice, it is observed that the weight, age of different patients and different levels of tolerance to anesthesia drugs can lead to complaints about the varying degrees of pain after the operation, which may affect maternal physical and mental health. The present study has confirmed that patients can obtain great sedative effect by using intravenous administration of dexmedetomidine as assistance.

In the present study, we found that when compared to group A and T0, the HRs of patients at T3-6 in groups B and C were decreased. The MAP at T1 in group D was increased. The above results indicate that dexmedetomidine played certain roles in regulating peripheral circulation. While this effect showed dose-dependent characteristics, namely the HRs of patients were related to the dose of dexmedetomidine, which presented a dose-dependent decrease. The blood pressure was manifested by a dimorphic change: The administration of a high-dose of dexmedetomidine in the early stage can directly stimulate the vascular smooth muscle α2-receptor to produce transient hypertensive response, thus leading to a transient increase of blood pressure in surgery. While the drug concentration of dexmedetomidine in blood used in clinic can cause blood pressure temporary reduction, it shows a transient reduction by the role of anti-sympathetic nerve excitation. The previous study found that after general anesthesia and determining the stability of the anesthesia plane, intravenous pumping of dexmedetomidine can improve the effects of propofol and reduce its dosage. Dexmedetomidine can play its sedative role by activating

Table IV. Comparison of heart rate changes at each time point among the different DEX loading dose groups.

Groups	Cases	T0	T1	T2	T3	T4	T5	T6
A	25	81.4±19.9	79.0±22.8	77.7±20.8	79.1±11.0	79.6±9.8	77.7±8.8	72.9±6.6
B	25	79.6±15.2	73.3±13.3	70.7±12.4	68.2±12.3[a,b]	69.2±9.5	70.3±8.2	72.8±6.8
C	25	80.7±17.5	80.6±14.5	74.1±13.3	69.4±12.6[a,b]	67.8±12.0[a,b]	67.3±10.5[a,b]	69.4±8.9[b]
D	25	82.6±12.6	79.9±9.2	75.4±8.7	65.3±10.6[a,b]	70.7±13.3[a,b]	68.8±11.3[a,b]	70.9±9.4[b]

Compared with group A, [a]P<0.05; compared with T0, [b]P<0.05.

Table V. Comparison of MAP levels at each time point among the different groups.

Groups	Cases	T0	T1	T2	T3	T4	T5	T6
A	25	88.3±11.5	86.5±10.8	86.3±11.9	89.6±11.1	87.2±7.7	87.9±6.1	86.8±5.7
B	25	91.3±9.2	95.1±12.3	89.3±11.4	83.5±10.3	89.1±11.5	89.2±10.3	88.4±11.4
C	25	87.1±10.8	87.6±10.7	87.1±15.4	85.2±14.5	82.3±11.2	85.6±9.5	86.6±7.3
D	25	91.5±12.3	99.9±12.3[a,b]	95.3±13.9	91±14.6	86.2±12.5	88.5±13.9	87.9±11.8

Compared with T0, [a]P<0.05; compared with group A, [b]P<0.05.

Table VI. Comparison of sedative effect.

Index	Groups	T0	T1	T2	T3	T4	T5	T6
NI score	A	99.2±11.4	99.9±16.8	98.7±14.7	98.4±13.5	98.3±10.9	99.2±10.8	99.4±11.2
	B	98.4±18.5	97.8±23.4	88.9±17.8	80.3±21.2[a,b]	92.4±17.3	98.4±11.6	98.5±20.4
	C	99.3±0.4	95.5±31.1	83.4±16.2[a]	69.8±12.0[a,b]	74.2±18.2[a,b]	76.1±16.1[a,b]	81.3±14[a,b]
	D	98.4±21.7	93.3±23.4	81.1±23.5[a,b]	65.3±15.4[a,b]	67.1±15.8[a,b]	74.8±13.5[a,b]	78.2±17.8[a,b]
Ramsay score	A	2.1±0.4	2.4±0.3	2.5±0.2	2.1±0.3	2.2±0.8	2.7±0.5	2.3±0.4
	B	2.2±0.3	2.0±0.8	2.0±0.6	2.6±0.5[a,b]	2.5±0.6[a,b]	2.1±0.3	2.0±0.7
	C	2.0±0.3	2.6±0.5	2.2±0.6	3.3±0.7[a,b]	3.2±0.5[a,b]	2.6±0.5[a,b]	2.6±0.7[a,b]
	D	2.0±0.3	2.0±0.4	2.2±0.3	4.4±0.4[a,b]	4.2±0.6[a,b]	2.9±0.6[a,b]	3.0±0.4[a,b]

Compared with T0, [a]P<0.05; compared with group C, [b]P<0.05.

Table VII. Adverse reactions of the selected patients.

Groups	Hypertension	Hypotension	Bradycardia	Excessive sedation
A	2 (8)	0 (0)	0 (0)	0 (0)[b]
B	0 (0)	0 (0)	1 (4)	0 (0)[b]
C	1 (4)	4 (16)	4 (16)[a]	1 (4)[b]
D	4 (16)[a]	2 (8)	7 (28)[a]	4 (16)

Compared with group A, [a]P<0.05; compared with group D, [b]P<0.05. The value in brackets is the incidence.

Table VIII. Comparison of degree of amnesia within post-operative 24 h.

Groups	Cases	No amnesia	Total amnesia	Uncompleted amnesia
A	25	18 (72)	2 (8)	0 (0)
B	25	3 (12)[a]	9 (36)[a]	8 (32)[a]
C	25	2 (8)[a]	6 (24)[a]	12 (48)[a]
D	25	0 (0)[a]	4 (16)[a]	16 (64)[a]

Compared with group C, [a]P<0.05.

the α2-adrenergic receptor in the locus, which has certain dose-dependence (13-17). In the present study, we found that in most of the patients, excessive sedation is caused by dexmedetomidine loading dose reaching 0.6 μg/kg, which indicates that the larger the dose of dexmedetomidine used, the stronger the sedative effect caused by dexmedetomidine

would be. Therefore, it can be concluded that the dose of dexmedetomidine should be controlled within the range of 0.6 μg/kg during the process of delivery.

Previous studies mention that the NI and Ramsay scales are currently used for monitoring the depth of anesthesia and intraoperative evaluation. However, the advantage of the NI scale is that it can monitor the changes of consciousness level of patients during anesthesia in real time (18,19). In the present study, we found that in groups B and C, NIs were significantly decreased at T2-6, the Ramsay scores were increased at T3-6, and the differences were statistically significant ($P<0.05$). The follow-up within 24 h post-delivery showed that the degree of anterograde amnesia from group B to group D was significantly higher than group A, with a statistically significant difference ($P<0.05$). The anterograde amnesia referred to the experience and adverse memory of patients, which was lost after anesthesia. Namely, they could not recall the experience during a period of time after memory loss (20). Our study indicates that the supplementary application of dexmedetomidine in anesthesia can make the anterograde amnesia rate during cesarean section reach >40%, and with the increase in dosage, the proportion of this type of anterograde amnesia gradually increases.

Through the analysis of adverse reactions, we found that the changes of blood pressure and decreased HR were the main adverse reactions after the use of dexmedetomidine. Therefore, in the process of using dexmedetomidine-assisted anesthesia, the general condition and medical history of patients should be deeply evaluated, especially for women with diseases of the circulatory system. Dexmedetomidine should be carefully used to prevent cardiovascular complications that threaten the safety of the mother and infant.

In conclusion, we suggest that the combined spinal-epidural anesthesia should be administered with the use of 0.6 μg/kg loading dose of dexmedetomidine, by intravenous pumping within 10 min before the cesarean section, which can achieve satisfactory sedative effect at 30 min after administration, and with the characteristics of maintaining intraoperative hemodynamic stability, less adverse reactions, and in general, improve the quality of cesarean section delivery.

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