Clinical research on the dexmedetomidine applied for patient-controlled sedation during the lower limbs operation under combined spinal-epidural anesthesia

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Abstract: To investigate the effect and safety of dexmedetomidine applied for patient-controlled sedation under combined spinal anesthesia. 150 cases who would be implemented lower limbs operations were randomly divided into patient-controlled sedation group (Group PCS) and control group (Group C) and 75 cases for each group. The ages of patients were between 18 and 65 years old and patients were with American Society of Anesthesiologists (ASA) or level. After being implemented combined spinal anesthesia, patients of Group PCS were undergone patient-controlled sedation by using dexmedetomidine (4μg/mL) with 2mL of load quantity, 1.5ml of background infusion quantity, 0.5mL of single dose and 20s of locking time; patients of Group C were constantly infused the normal saline at the rate of 10ml/h by pump injection. HR, MAP, SpO2, Ramsay sedation scores and airway scores before the pump injection (T_0), 10 min (T_1), 3 min (T_2), 5 min (T_3), 7min (T_4) and 10min (T_5) after the pump injection, at the beginning of operations (T_6), 10min(T_7) after the operations and in the end of operations (T_8) of patients of two groups were respectively recorded. At the same time, the pressing numbers and doses of dexmedetomidine of patients of Group PCS were observed. Compared with the HR at T_0, HR in Group PCS obviously decreased between T1 and T_8 ($P<0.05$). Compared with HR in Group C, HR in Group PCS obviously slowered between T1 and T_8 ($P<0.05$). Compared with the MAP at T_0, MAP in Group PCS gradually increased between T_1 and T_3 and gradually reduced between T_5 and T_8 ($P<0.05$). MAP between T_5 and T_8 in Group PCS were significantly lower than those in Group C ($P<0.05$). Between T_3 and T_7, there were 51, 72, 74, 73, 72 patients in Group PCS whose Ramsay scores were from 3 to 4 points respectively. During the process of patient-controlled sedation of patients in Group PCS, the pressing times were 112.10±65. 79 times. The effective pressing numbers were 21.00±9. 07 times. The patient-controlled dosages were (15.12±3.19) ml; The dosages were 11.29±2.16ml when the level of sedation achieved 3 to 4 scores in Ramsay sedation scores; And the required time to achieve 3 to 4 scores in Ramsay sedation scores was 7.55±1.53 min. In the lower limbs operations, the usage of dexmedetomidine applied for patient-controlled sedation under combined spinal anesthesia can effectively approach to the personalized medicine and is effective in clinical application.

Keywords: Dexmedetomidine; Patient-controlled sedation; Combined spinal-epidural anesthesia

INTRODUCTION

Currently, Civil Service Employees Association (CSEA) as a new type way of anesthesia, having a good anesthetic effect, so it is often used in gynecology, obstetrics, and orthopedics surgery; But after the implementation of the anesthesia surgery, patients often accompanied by stress, anxiety and other negative mood. What's worse, sometimes they will feel severe pain in a temporary sense, and CSEA can not completely eliminate the visceral autonomic reflex. Therefore, the implementation of CSEA, with the corresponding of sedative drugs have the positive significance effects on ensuring the effects of operation, alleviate pain in the surgery (Yong Dai, 2015). Intra-operative sedation may effectively restrain adverse stress reactions of patients, reduce hemodynamic fluctuations and make patients feel more comfortable during the operations. As the α_2 adrenergic receptor agonist, dexmedetomidine (DEX) is used for the intra-operative sedation, which is usually reported at home and abroad (Changlu *et al*., 2011; Zijuan *et al*., 2013). Dexmedetomidine is a high selectivity α_2 adrenoceptor agonists with spontaneous breathing and has a good sedative, analgesic, inhibit sympathetic activity and so on (Liu, 2015). Zhao (2010) observed calming effect of dexmedetomidine on epidural anesthesia patient surgery. It was found that given dexmedetomidine auxiliary epidural anesthetic, with a sedative effect, and there is no inhibition on spontaneous breathing. Different doses of dexmedetomidine sedation have similar strength, but it can be extended for the duration of sedation. Cui *et al* (2015) explored the anesthesia effect of dexmedetomidine for epidural the sedative, and found that the use of dexmedetomidine given had fewer adverse reactions, and it is worthy of clinical use. But the study on dexmedetomidine used in patient-controlled sedation (PCS) is less. Therefore, the effect and safety of patient-controlled sedation with dexmedetomidine will be further

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studied (Lhlan *et al*., 2010) This article aims to observe the effect of dexmedetomidine used in patient-controlled sedation with dexmedetomidine in combined spinal anesthesia and initially discuss the safety of patient-controlled sedation with dexmedetomidine.

MATERIALS AND METHODS

General materials

This study was authorized by the Hospital's Ethics Committee and all the patients had signed the informed consent forms. 150 cases who had been underwent the lower limbs operations and treated by combined spinal anesthesia in our hospital from March, 2012 to March, 2013. Among the 150 patients, male patients were 98 cases and female patients were 42 cases. The ages of patients were between 18 and 65 years old. The weights of patients were between 43 and 81kg. Patients were at ASA or level. The time of operation was between 30 min and 3 hours. The difficulty of inserting tubes did not exist in any patient. And all patients were at or level with regard to cardiac functional grading evaluated by New York Heart Association (NYHA). The exclusion criteria: patients with language communication barrier, without self-controlled operational capacities, with histories of abuse of psychiatric drugs, with respiratory tract obstructions, or with sick sinus syndrome or severe sinus bradycardia. The random number table was adopted to divide patients into PCS group and Control group, and 75 cases for each group.

Methods

Before the operation, patients were underwent regular abrosia for 8h and drink-deprivation for 4h. All patients were informed the process of anesthesia and taught how to use the electronic pump of patient-controlled sedation before the operations. And none of patients was given the pre-operative sedatives. After going inside the operation room, patients were opened the peripheral venous channels as routine and infused equilibrium liquid and artificial colloidal fluid according to the requirements, and then monitored the blood pressure (BP), hemorheology (HR) and Oxygen saturation (SpO2). Next, patients were implemented combined spinal-epidural anesthesia in the intervertebral space between L3 and L4, and then infused 0.5% bupivacaine of 10~15mg (0.75% bupivacaine of 2mL plus 10% glucose of 1mL). The block level was adjusted around T10. After the block level was fixed, regular oxygen up taking was arranged at the rate of 3 L/min. Patients of Group C were arranged constant pump injection for the normal saline at the rate of 10mL/h; patients of Group PCS applied the Limei electronic pump (Rythmic Plus) for patient-controlled sedation, and the drug was dexmedetomidine (batch number: 12071234) and was mixed at the concentration of 4μg/mL. The parameters of the pharmaceutical formulation were set as 2mL of load quantity, 1.5mL of background infusion quantity, 0.5mL of single dose and 20 s of locking time. When the blood pressure of patients were lower than 90/45mm Hg, 10mg of ephedrine was given by intravenous injection; When the HR of patients decreased to 50 times/min, 0.5mg of atropine was given by intravenous injection; When the SpO2 of patients decreased and was lower than 93%, measures of awakening patients, oxygen up taking, assisted respiration or aerating by laryngeal mask were adopted.

Observation targets

The numbers of pressing or effective times (N/E) and the doses of dexmedetomidine of patients in Group PCS were observed. HR, MAP, SpO2, Ramsay sedation scores (Thorpe *et al*., 1997) and airway scores (Thorpe *et al*., 1997). Before the pump injection (T_0), 10 min (T_1), 3 min (T_2), 5 min (T_3), 7 min (T_4) and 10 min (T_5) after the pump injection, at the beginning of operations (T_6), 10 min (T_7) after the operations and in the end of operations (T_8) of patients of two groups were respectively recorded. Ramsay sedation scores: 1 minute later, after patients pressing the patient-controlled sedation device patients were conscious and anxious; 2 minutes later, patients were conscious and not anxious; 3 minutes later, patients were confused and could response to orders; 4 minutes later, patients fell asleep and could response rapidly to the external stimuli; 5 minutes later, patients fell asleep and were slow in response to the external stimuli; 6 minutes later, patients did not response to strong stimulation. Airway scores: 1 minute later, patients could speak; 2 minutes later, patients could not speak but the airways kept unobstructed; 3 minutes later, patients started to snore; 4 minutes later, patients needed intervention to help breath. If patients did not press the patient-controlled sedation device within 1 minute, it was regarded that patients had achieved proper sedation state and the Ramsay scores were between 3 and 4 scores.

STATISTIC ANALYSIS

SPSS 19.0 software was adopted to proceed the statistical analysis. The qualitative data were tested by X^2, the quantitative data were tested by *t* and the values were expressed by the mean values plus or minus the standard deviation ($\bar{\chi} \pm s$).

RESULTS

The comparison and differences of the sexes, ages, values of weight, types of operations and time of operations between the two groups had no statistical significance (See in table 1).

After being arranged the patient-controlled sedation, the HR of patients in Group PCS tended to reduce within the range of 30%. Compared with the HR at T0, HR in Group PCS obviously decreased between T_1 and T_8 ($P<0.05$). Compared with HR in Group C, HR in Group PCS

obviously slowered between T_1 and T_8 ($P<0.05$) (See in fig. 1).

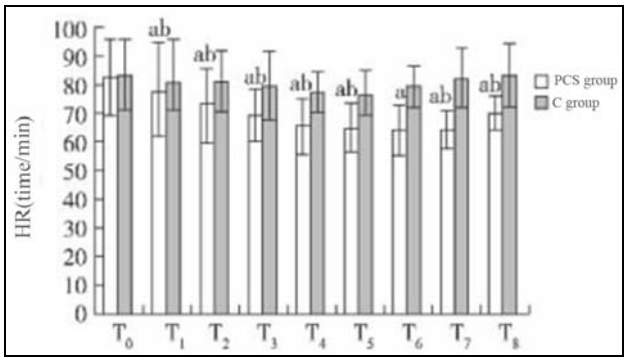

Fig. 1: Comparison between values of HR of two groups at different time-points Annotation: Compared with T_0, $^aP<0.05^a$ compared with Group C, $^bP<0.05$

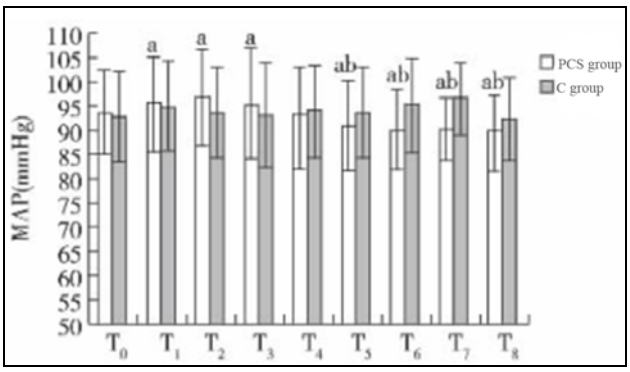

Fig. 2: Comparison between values of MAP of two groups at different time-points Annotation: Compared with T_0, $^aP<0.05^{aa}$; compared with Group C, $^bP<0.05$

After being arranged the patient-controlled sedation, the mean artery pressure (MAP) of patients in Group PCS tended to increase at first and then decrease. Compared with the MAP at T_0, MAP in Group PCS gradually increased between T_1 and T_3 and gradually reduced between T_5 and T_8 ($P<0.05$), but the descend range was less than 20%. MAP between T_5 and T_8 in Group PCS were significantly lower than those in Group C ($P<0.05$) (See in fig. 2).

Before the patient-controlled sedation with dexmedetomidine, among 75 cases in Group PCS, 64 cases got 1 score in Ramsay sedation scores; After starting the patient-controlled sedation, there respectively were 51, 72, 74, 73 and 72 patients got 3 to 4 scores in Ramsay sedation scores between T_3 and T_7. No patients ever got more than 5 scores in Ramsay sedation scores during the operations (See in fig. 3).

After being arranged the patient-controlled sedation with dexmedetomidine, the pressing numbers of patients in Group PCS were 112.10±65.79 times; the practical patient-controlled dosages were 15.12±3.19mL; The dosages were 11.29±2.16mL when the level of sedation achieved 3 to 4 socres in Ramsay sedation scores; And the required time to achieve 3 to 4 scores in Ramsay sedation scores was 7.55±1.53 min. The slope of the curve of the pressing numbers revealed that the growing rate of pressing numbers of patients in Group PCS between T_1 and T_4 was obviously greater than the growing rate between T_5 and T_8 (See in fig. 4). The accumulative total dosage for patients in Group PCS increased along with the time.

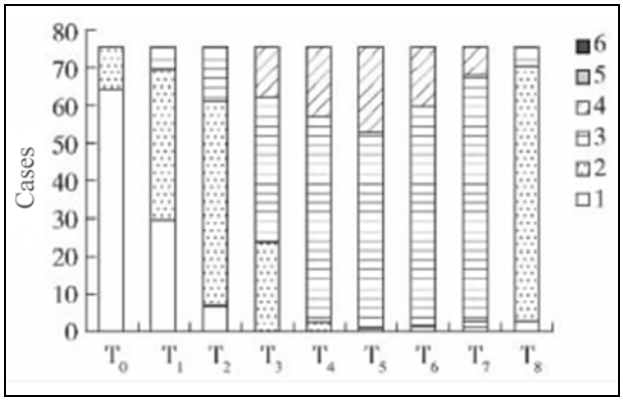

Fig. 3: The cases variation of patients in Group PCS with different sedation scores

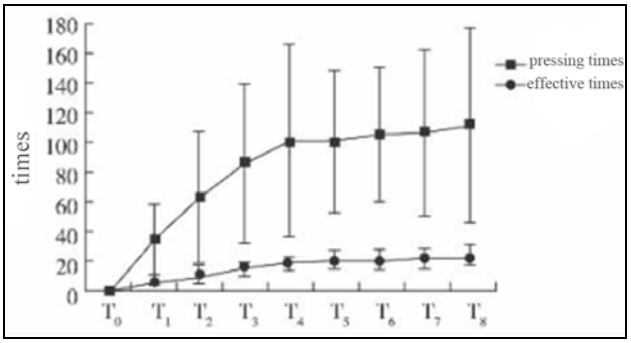

Fig. 4: The variation of pressing times and effective times of patients in Group PCS

After being arranged the patient-controlled sedation with dexmedetomidine, the scores of Ramsay sedation scores and the scores of Airway scores of 75 patients in Group PCS gradually increased and basically recovered to level before the patient-controlled sedation before the end of operations. 2 cases got the highest scores of 5 scores in Ramsay sedation scores, 3 cases got the highest scores of 4 scores in Airway scores. And patients got better after being awaken or up taking oxygen. The Ramsay scores and Airway scores of patients in Group PCS presented linear dependence, and y equaled 0.581x plus or minus 0.458, r equaled 0.7622.

It was analyzed that the relationship between HR and accumulative total dosages, pressing numbers and effective times presented linear dependence, and the correlation indexes were respectively 0. 8813, 0.9100, 0.8183; The multiple linear regression analysis was

Table 1: The comparison of general data between the two groups

Group	Cases	Male/Femal (cases)	Ages	Weight (Kg)	Knee arthroscopy operation (Cases)	Knee prosthesis (Cases)	Hip replacement (Cases)	Operation time (min)
Group PCS	75	50/25	51.2±12.9	59.8±9.9	29	24	22	110.2±27.8
Group C	75	48/27	51.7±12.3	60.3±10.5	31	25	19	109.4±27.1

Table 2: The multiple linear regression of HR during the process of patient-controlled sedation

Variable	Regression coefficient	Standard error	*t*	*P*	Standardized partial regression coefficient
Accumulative total dosages (ml)	6.113	0.722	8.469	0.000	4.340
Pressing numbers (times)	0.110	0.049	2.263	0.073	0.658
Effective times (times)	-4.739	0.593	-7.997	0.000	-5.909

adopted to analyze the influence of accumulative total dosages, pressing numbers and effective times on HR. The results revealed that the effective pressing times had the largest impact on HR, the accumulative total dosages had the second largest impact on HR, and the pressing numbers had the lowest impact on HR (See in table 2).

One patient among patients of Group PCS appeared xerostomia during the operation and self-recovered without any treatment; One patient got the lowest SpO_2 value of 92%, which was caused by respiratory tract obstruction after falling asleep. And the SpO_2 value of that patient rose to 100% by means of being awaken, and the SpO_2 values of other patients remained between 96% and 100%; The HR values of 16 patients (21.33%) were lower than 60 times/min but all of them were above 50 times/min, and all 16 patients did not occur severe adverse complications.

DISCUSSION

During the operations of non-general anesthesia, patients had nervous, anxious and other bad stress reactions to varying degrees, which was regarded as one of the main reasons that caused the periprocedural complications and was regarded to be correlated to the postoperative delirium (Guofang *et al*., 2012). Intra-operative conscious sedation to the patients could effectively stabilize haemodynamics, restrain the over excitation of sympathetic nerves and make patients feel more comfortable and help complete the operations successfully. Dexmedetomidine had sedative, hypnotic, antianxiety and antalgic functions and had no respiratory inhibition effects, which could effectively restrain the intra-operative bad stress reactions (Cheung *et al*., 2011; YinZhou *et al*., 2011). In the past, anesthetists usually calculated the drug administration dosages according to the weight of patients, which frequently easily caused the intra-operative sedative deficiency or excessive sedation due to the individual differences of patients.

In this study, the patient-controlled sedation with dexmedetomidine adopted the drug administration dose pattern of loading doses plus background doses plus single doses plus locking time. The parameters were set more less for the sake of remaining spaces for autonomous control for the patients and decreasing individual differences, which was in favour of realizing the individual drug administration. The above viewpoint was similar with the viewpoint of Mazanikov *et al* in their study on patient-controlled sedation. Mazanikov set the parameters of PCS pump without any loading doses, background doses and locking time only with the single doses, which meant that the parameters were completely set by patients autonomously pressing the hand shanks. Within 7min after using dexmedetomidine for patient-controlled sedation, the blood pressure of patients in Group PCS gradually increased within the range of base value of 30% and then gradually decreased; At the end of operation, the values of MAP were obviously lower than the base value, but the descending range was less than 20%. The HR value of patients in Group PCS gradually decreased after the begining of patient-controlled sedation with dexmedetomidine and the descend ranges were within 30%. Therefore, this study claimed that the influence of patient-controlled sedation with dexmedetomidine on the bidirectional curve of blood pressure and HR values was similar with the phenomenon generated by regular drug administration patterns, and Group C did not occur this phenomenon (Mazanikov *et al*., 2011). The increasing or descending ranges of HR and blood pressure of patients in Group PCS were within 30%, and no patients occurred servely adverse reactions and no patients needed special interventions; Compared with Group C, the differences of oxyhemoglobin saturation between the two groups had no statistical significance, which meant that patient-controlled sedation with dexmedetomidine under combined spinal anesthesia was relatively safe. The study of Liu, *et al* claimed that patient-controlled sedation was safe, easy to operate and

convenient to manage, and even could be managed by preofessional nurses as long as the nurses could recognize the hypoventilation and other complications caused by excessive sedation and be prepared for salvaging patients (Liu *et al*., 2009).

5min, 7min and 10min after the patient-controlled sedation with dexmedetomidine, there were respectively 51, 72 and 74 patients in Group PCS achieved proper sedative state (Ramsay sedation scores were between 3 an 4 scores), and 10min after the begining of the operations, there still were 72 patients remained the proper sedative state, which indicated that the usage of dexmedetomidine in patient-controlled sedation was effective. During the patient-controlled sedation, the pressing numbers, the required time to achieve proper sedative state and the required doses of dexmedetomidine of patients in Group PCS were respectively between 17 and 317 times, 3 and 10min, 9 and 25ml. The differences between the minimum value and the maximum value were larger, which indicated that the individual differences in the respects of the quantity demanded for the sedation were larger. This study adopted dexmedetomidine for patient-controlled sedation and set smaller parameters, which better settled this kind of problem, realized the individual drug administration and effectively avoided the contradiction between the sedative deficiency and excessive sedation. The above-mentioned viewpoint was similar with the viewpoint of Stonell (2006) in the study of patient-controlled sedation with propofol. Stonell claimed that patient-controlled sedation was more advantageous than the traditional drug administration patterns, could realize the individual drug administration and prevent the sedatve deficiency and excessive sedation. Within 7min after the patient-controlled sedation with dexmedetomidine, the pressing numbers for PCS pump of patients fast increased, which indicated that patients needed sedation most during those periods.

There were no clear conclusion about the onset time of dexmedetomidine, and it was regarded that the dosages and the rate drug administration correlated to the onset time at present. In this study, 2mL (8μg) of loading capacity was given at the first time, and the drug administration rate of the electronic pump was faster so that the required time to achieve proper sedation was narrowed down (Stonell *et al*., 2006). The average time to achieve proper sedation of patients in Group PCS was 7.55±1.53min, which indicated that the patient-controlled sedation with dexmedetomidine remained the patient-controlled space and avoided long-term non-sedative state. This result may correlate to the reason that the distribution half-life period of dexmedetomidine was 6 min (Kukoyi *et al*., 2013).

According to the specification of dexmedetomidine, the adverse reactions with occurrence rate of more than 2% included xerostomia, hypotension and bradycardia. Riker claimed that 42% patients occurred bradycardia (HR<60 times/min) when were injected $1.4\mu g \cdot kg^{-1} \cdot h^{-1}$ of dexmedetomidine by venous pump and only 5% patients were in need of intervention treatment (Riker *et al*., 2009). In this study, patients in patient-controlled sedation with dexmedetomidine with occurrence rate of HR values of less than 60 times/min was 21.33%, which was lower than the research result of Riker. And all the HR values were more than 50 times/min, and no patients were in need of intervention treatment due to the hypotension and bradycardia.

CONCLUSION

In conclusion, in the operations under the combined spinal-epidural anesthesia, the individual differences for the required sedation degrees were larger, and the onset of dexmedetomidine was slow. The patient-controlled sedation autonomously pressed and proceeded the drug administration according to the condition of each patient, which could effectively realize the individual drug administration and avoid the sedative deficiency and effective sedation. With the parameters of 2 ml of loading capacity, 1.5 ml/h of background doses, 0. 5 ml of single dosages, and 20s of locking time, the patient-controlled sedation with dexmedetomidine was relatively safe and effective but still in need of massive researches to further evaluate.

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