Comparative study: efficacy of closed-loop target controlled infusion of cisatracurium and other administration methods for spinal surgery of elderly patients

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Abstract. – OBJECTIVE: To observe the efficacy of traditional administration, continuous pump injection, and closed-loop target controlled infusion of cisatracurium to determine the optimal method of drug administration, and to establish the individualized and rational administration of muscle relaxants in elderly patients.

PATIENTS AND METHODS: A total of 150 patients who underwent spinal surgery under tracheal intubation general anesthesia in our hospital from August 2013 to April 2015 were selected. All patients were administered with general anesthesia and randomly divided into three groups: group A (n = 50) was treated under closed-loop target controlled infusion (CLTCI), group B (n = 50) was treated under muscle relaxation monitoring, and group C (n = 50) was treated under continuous pump injection. Hemodynamic changes and blood oxygen saturation of the three groups were observed, and the muscle relaxation recovery, dosage, and bleeding of the three groups were compared.

RESULTS: MAP and HR of group A were significantly lower than those of group B and group C ($p < 0.05$). There were no cases of insufficient muscle relaxation in group A, five cases in group C, and 14 cases in group B, and the differences between any two groups were statistically significant ($p < 0.05$). Regarding muscle relaxation recovery, the time (T¬¬1) of recovery from 10%-25% and 25%-75%, and the time from drug withdrawal to recovery to TOFr from 0.7-0.9 of group A were the shortest, followed by group C and group B. The differences between any two groups were statistically significant ($p < 0.05$). The total dosage of cisatracurium of group A was the least, followed by group C and group B, and differences between any two groups were statistically significant ($p < 0.05$). Moreover, the bleeding volume of group A (235.2 ± 141.3 ml) was smaller than in group B (353.1 ± 173.8 ml) and group C (316.5 ± 155.2 ml), and differences between the three groups were statistically significant ($p < 0.05$).

CONCLUSIONS: For spinal surgery of elderly patients, closed-loop target controlled infusion of cisatracurium was superior to continuous infusion and intravenous injection. The time of muscle relaxation recovery was shortened, the dosage of cisatracurium was reduced, and the number of cases of insufficient muscle relaxation was reduced.

Key Words:
Closed-loop target controlled infusion, Cisatracurium, Continuous infusion, Anesthesia.

Introduction

Muscle relaxants are essential for anesthesia[1]. The proper use of relaxants poses challenges that must be overcome. The dosage administered should not be excessive or insufficient[2]. An excessive dosage can result in complications, while an insufficient dosage can result in poor relaxation[3]. The closed-loop target-controlled infusion system is a new method that can precisely deliver anesthetics[4]. It provides the combined muscle relaxation monitoring and automatic feedback of a drug delivery system. Therefore, it is able to avoid overdose, and maintain expected muscle relaxation effects, while reducing the burden on anesthetists[4]. Cisatracurium is a new non-depolarizing muscle relaxant[5]. Its effect on the heart and blood vessels is minor, it does not cause significant histamine release, and its metabolism does

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not depend on liver and kidney function. Therefore, it is an ideal muscle relaxant for anesthesia induction and maintenance.

Given that spinal surgeries are considered to be more difficult than other types of operations, and are associated with high risk and increased blood loss. In this study, through observation of the efficacy of closed-loop target controlled infusion of cisatracurium, and by comparing it with traditional administration methods and continuous pump injection, we aimed to provide a theoretical basis for the clinical application of this system.

Patients and Methods

Patients

A total of 150 patients who underwent spinal surgery under tracheal intubation general anesthesia in our hospital from August 2013 to April 2015 were selected. All patients were administered general anesthesia, and were randomly divided into three groups: group A (n = 50) was placed under closed-loop target controlled infusion (CLTCI), group B (n = 50) was placed under muscle relaxation monitoring, and group C (n = 50) was placed under continuous pump injection. For this study, we obtained the consent of the Ethics Committee of our hospital as well as the informed consent of patients.

Referring to the guidelines of the American Society of Anesthesiologists[6], the inclusion criteria for the study were as follows: (1) age ranging from 60-70 years old, ASA grading from level I-II; (2) expected operative time was from 1-3 h; (3) absence of hypertension and heart and lung diseases; heart function from level I-II; (4) absence of anemia (Hb < 90 g/L) and malnutrition; liver and kidney function were mostly normal; (5) absence of chest trauma, brain injury, or stroke; or history of mental illness; (6) absence of neuromuscular diseases; history of malignant hyperthermia or drug allergy. Exclusion criteria: (1) patients who failed to meet the inclusion criteria or refused to sign the informed consent; (2) patients whose forearms could not support muscle relaxation monitoring; (3) patients with significant water, electrolyte, and acid-base balance disorders before surgery, (4) patients on drugs that can affect neuromuscular functions.

Differences in age, sex, body mass index (BMI), ASA grading, operative time, preoperative mean arterial pressure (MAP), heart rate (HR), and blood oxygen saturation (SpO_2) were not statistically significant ($p > 0.05$) (Tables I and II).

Anesthesia

An upper extremity venous transfusion pathway was established. ECG, noninvasive blood pressure, HR, pulse oxygen saturation, and surface temperature were monitored. The monitor electrode of the closed-loop target-controlled infusion system was connected to both sides of the ulnar nerves of the wrists of patients. The sensor was bound to the thumb and index finger, the temperature sensor was fixed to the thenar, and skin temperature was maintained at 32-34°C. We then began anesthesia induction using 0.05 mg/kg midazolam, 3 μg/kg fentanyl, 1.5 mg/kg diprivan, and 0.2 mg/kg cisatracurium. After the patients had lost consciousness, the scaling was calibrated to 52 mA stimulation current, 5 s interval, 2 Hz frequency, and 20 s cycle. The maintenance velocity was set at 0.33 μg/kg/min, and the dosage increment velocity was set at 5.0 μg/kg/min. The muscle relaxation depth feedback value was set at T1=12%. During surgery, measures were taken to ensure insulation, and that patient body temperature was maintained at 35.5-36.5°C. Moreover, the surface temperature was maintained at no less than 36°C, and temperature of the monitoring site was maintained at no less than 32°C. During surgery, we performed total intravenous anesthesia using 4-6 mg/kg/h diprivan, 0.05-0.1 μg/kg/min remifentanil, and discontinuous fentanyl. The fluctuation of blood pressure was maintained at less than 20% of the basal value, and maintained between 35-45 mmHg Pet CO_2 in mechanical ventilation. In group A, when T1 > 12%, the au-

Table I. Comparison of baseline parameters of the three groups of patients.

Group	Cases	Male/female	Age (years)	BMI (age/height²)	ASA grading (I/II)	Operative time (min)
A	50	27/23	65.26 ± 3.12	23.11 ± 1.13	29/21	161.2 ± 17.9
B	50	25/25	65.45 ± 3.24	23.21 ± 1.02	28/22	158.5 ± 20.5
C	50	26/24	65.48 ± 3.37	23.17 ± 1.14	30/20	162.7 ± 18.2

Table II. Comparison of hemodynamic changes and oxygen saturation in the three groups.

Groups	MAP (mmHg)		HR (beats/min)		SpO_2 (%)	
	Preoperative	Intraoperative	Preoperative	Intraoperative	Preoperative	Intraoperative
A	128.5 ± 15.4	113.1 ± 12.5	92.5 ± 18.5	71.1 ± 17.5	99.3 ± 0.4	97.4 ± 0.5
B	131.6 ± 13.3#,*	128.3 ± 16.4a,b	93.1 ± 17.9#,*	87.4 ± 18.6a,b	99.2 ± 0.3#,*	96.8 ± 0.8#,*
C	130.4 ± 15.5d	121.2 ± 16.33)	92.3 ± 16.8	80.4 ± 10.8c	98.5 ± 0.5	97.2 ± 1.0

Note: (a) Compared with group A, $p < 0.05$ t = -6.751, $p = 0.021$; (b) compared with group C, $p < 0.05$, $t = -12.976$, $p = 0.007$; (c) compared with group A, $p < 0.05$, $t = -5.956$ $p = 0.026$; #Compared with group A, $p > 0.05$ $t = -2.175$, $p = 0.125$; *Compared with group C, $p > 0.05$, $t = -2.254$, $p = 0.113$; (d) Compared with group A, $p > 0.05$, $t = -1.253$, $p = 0.184$.

tomatic pump injected cisatracurium (1 mg/ml) until T1 < 12%; in group B, when T1 > 12%, the automatic pump injected physiological saline, and 0.03 mg/kg cisatracurium was injected intravenously; in group C, continuous pump injection of 3 μg/kg/min was performed when T1 > 12%, and intravenous injection of 0.03 mg/kg cisatracurium was provided. Muscle relaxants and intravenous maintenance drugs were suspended at 20 min and 5 min, respectively, before the end of surgery. Patients were allowed to recover naturally in a resting state, and extubated by the same anesthetist after the breathing of patients recovered to a satisfactory state. The dosage of fentanyl, propofol, and remifentanil[3], as well as the bleeding volume of patients in the three groups, were recorded. We recorded the total maintenance dosage of muscle relaxants in group A and group B, the time (T_1) of recovery from 10%-25% and from 25%-75% after the final intravenous injection. In addition, we set the time from the first intravenous injection to T_1 recovery as 10% after the final intravenous injection as the maintenance time. We recorded the time of continuous infusion of cisatracurium, and the total maintenance dosage of group C. We then calculated the average maintenance dosage, recorded the time (T_1) of recovery from 10%-25% and from 25%-75% after the final pump injection. We set the time from the first pump injection to T_1 recovery as 10% after the final pump injection as the maintenance time. During surgery, patients were observed to determine whether there was skin flushing, skin rash, bronchial spasm, or signs related to histamine release. After surgery, patients were observed to determine if there was intraoperative awareness or complications related to the respiratory system.

Observational Indexes

(1) Preoperative MAP, HR, and SpO_2. (2) The time (T_1) to recovery from 10%-25% and from 25%-75%, and the time from drug withdrawal to recovery to a TOFr[4] from 0.7-0.9. (3) Total cisatracurium, dosage of cisatracurium, and total remifentanil and propofol. (4) Bleeding volume.

Statistical Analysis

A Microsoft Excel database was established, and SPSS19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Quantitative data are presented as mean ± standard deviation (X ± s); Comparisons between groups were by one-way ANOVA, followed by the Post-Hoc Test (LSD); a chi-square test was applied for categorical data. $p < 0.05$ was taken as statistically significant.

Results

Comparison of Preoperative MAP, HR, and SpO_2 in the Three Groups

The differences between the three groups in terms of preoperative hemodynamics were not statistically significant ($p > 0.05$). MAP and HR of group A were lower than those of group B and group C, and the differences were statistically significant ($p < 0.05$); in addition, MAP, HR, and SpO_2 of group C were lower than those of group B, and the differences were statistically significant ($p < 0.05$). Closed-loop target controlled infusion of cisatracurium was the most favorable method of delivery for stabilizing intraoperative hemodynamics, and reducing patient stress. It was, therefore, suitable for the successful completion of the operation.

Comparison of Muscle Relaxation Recovery in the Three Groups

The time (T_1) to recovery from 10%-25% in group A was shorter than in group B and Group C (6.45 ± 2.42 *vs.* 12.13 ± 3.09 or 6.45 ± 2.42 *vs.*

9.55 ± 4.17), and the differences were statistically significant ($p < 0.05$); in addition, the time to recovery in group C was shorter than in group B (9.55 ± 4.17 *vs.* 12.13 ± 3.09), and the difference was statistically significant ($p < 0.05$); the time (T_1) to recovery from 25%-75% in group A was shorter than in group B and Group C (15.12 ± 4.54 *vs.* 25.22 ± 5.38 or 15.12 ± 4.54 *vs.* 18.34 ± 6.30), and the differences were statistically significant ($p < 0.05$); recovery in group C was shorter than in group B (18.34 ± 6.30 *vs.* 25.22 ± 5.38), and the difference was statistically significant ($p < 0.05$); the time from drug withdrawal to recovery to a TOFr from 0.7-0.9 in group A was shorter than in group B and group C, and that of group C was shorter than that of group B, and the differences were statistically significant ($p < 0.05$). This indicated that closed-loop target controlled infusion of cisatracurium was associated with the fastest recovery (Table III).

Comparison of Dosage, Bleeding Volume, and Total Occurrence of Muscle Relaxation Insufficiency in he Three Groups

The total dosage of cisatracurium used was least in the group A, followed by the group C and the group B, and differences between any two groups were statistically significant ($p < 0.05$). The bleeding volume in group A (235.2 ± 141.3 ml) was smaller than in both group B (353.1 ± 173.8 ml) and group C (316.5 ± 155.2 ml), and the differences between the three groups were statistically significant ($p < 0.05$), indicating that closed-loop target controlled infusion of cisatracurium had the highest efficiency, thereby greatly reducing drug-induced injury of the liver and kidney. Regarding muscle relaxation, no patients in group A experienced insufficient muscle relaxation. Insufficient muscle relaxation occurred in five patients in group C, and in 14 patients in group B, and the differences between any two groups were statistically significant ($p < 0.05$), indicating that the effect of closed-loop target controlled infusion of cisatracurium was the most stable and effective (Table IV).

Discussion

Muscle relaxants are a major class of drugs used for general anesthesia in modern clinical medicine. Traditionally, drugs are initially administered as a loading dosage, which is supplemented according to clinical reactions, such as autonomous respiration, airway pressure changes, and body movement. Such methods can lead to markedly increased blood drug concentration, increased drug excretion over time, and large fluctuations of plasma drug concentration. Moreover, this method is unfavorable for controlling muscle relaxation recovery time, and might result in higher risks of postoperative residual curarization[7]. The results from group B (traditional drug delivery) in our study confirmed this observation. The second drug delivery method, continuous intravenous infusion, is considered to be a relatively ideal method of drug delivery that can maintain a relatively constant plasma drug concentration, and stabilize and maintain neuromuscular junction blockade. Moreover, it can maintain a satisfactory level of muscle relaxation, and allow for adjustment of the infusion rate according to the results of muscle relaxation monitoring to maintain the level of muscle relaxation within a given narrow range. This avoids deficiency or accumulation of muscle relaxants, and reduces complications. Therefore, compared with traditional drug delivery methods, the continuous intravenous infusion is superior in terms of both convenience and controllability. However, under continuous intravenous infusion, the dosage of muscle relaxants required for main-

Table III. Comparison of muscle relaxation recovery in the three groups.

Groups	T¬¬1 recovery from 10%-25% (min)	T¬¬1 recovery from 25%-75% (min)	Drug withdrawal to recovery to TOFr (min)	
			70%	90%
A	6.45 ± 2.42	15.12 ± 4.54	27.51 ± 7.12	36.89 ± 1.23
B	12.13 ± 3.09$^{(1,2)}$	25.22 ± 5.38$^{(1,2)}$	33.46 ± 3.21$^{(1,2))}$	45.68 ± 3.61$^{(1,2)}$
C	9.55 ± 4.17$^{(3)}$	18.34 ± 6.30$^{(3)}$	29.34 ± 2.41$^{(3)}$	41.09 ± 2.04$^{(3)}$

Note: (1) Compared with group A, $p < 0.05$, $t = -9.312$ $p = 0.013$; (2) Compared with group C, t =-5.854, $p = 0.028$; (3) Compared with group A, $p < 0.05$, $t = -6.231$, $p = 0.025$.

Table IV. Dosage and bleeding volume in the three groups.

Groups	Bleeding volume (ml)	Total cisatracurium (mg)	Cisatracurium dosage (ug/kg.min)	Total remifentanil (mg)	Total propofol (mg)	Total cases of muscle relaxation insufficiency during surgery
A	235.2 ± 141.3	15.2 ± 3.56	1.19 ± 0.99	0.89 ± 0.20	906.3 ± 11.3	0
B	353.1 ± 173.8(1,2)	23.45 ± 4.34(1,2)	1.89 ± 0.57(1,2)	1.20 ± 0.12	1013.2 ± 22.3(1,2)	14(1,2)
C	316.5 ± 155.2(3)	19.22 ±4.31(3)	1.49 ± 0.44(3)	1.01 ± 0.16	960.1 ± 20.8(3)	5(3)

Note: (1) Compared with group A, $p < 0.05$ $t = -12.315$, $p = 0.008$; (2) Compared with group C, $p < 0.05$ $t = -4.695$, $p = 0.038$; (3) compared with group A, $p < 0.05$, $t = -10.953$, $p = 0.045$.

taining the target muscle relaxation effect must be adjusted. Otherwise, this can result in excessive accumulation of drugs[8-10].

Although continuous infusion can greatly improve the stability of the concentration of muscle relaxants, many factors such as the complexity of autonomic regulation (adaptability), the variability of physiological systems, the nonlinearity of pharmacokinetics, the different stress responses of each physiological subsystem to anesthesia, and the individual differences can cause the control of anesthesia to become more complicated. Therefore, it has become important to study and explore the theory of automatic control of anesthesia. TCI has two classifications: open-loop and closed-loop. Open-loop has no feedback device. Anesthesiologists must set a target concentration according to clinical needs, and must adjust the maintenance anesthesia according to the state of the patient. Closed-loop muscle relaxation infusion system injection (CLARIS-I) is a new technology that combines muscle relaxation monitoring and automatic feedback injection on the basis of target controlled infusion[11]. The closed-loop control system can precisely deliver drugs to improve the quality of drug application. It is a drug delivery method that provides feedback, and controls the injection rate of a micro pump. This, in turn, adjusts the anesthetic depth according to the effects of former instructions, thereby automatically regulating drug delivery according to the feedback signals, and directly controls the anesthetic effects. At present, the TCI system is most commonly used for diprivan administration. Compared with manual drug delivery, this technology not only optimizes the drug delivery scheme, but also reduces the burden on anesthetists[12]. It has been gradually applied in clinical anesthesia in our country.

There is an increasing number of elderly patients (> 60 years) in our country. As people grow older, their physiological and organ functions change. These changes inevitably result in changes in drug pharmacokinetics and pharmacodynamics. Elderly patients are more vulnerable to residual muscle relaxants, especially those with liver and kidney dysfunction. Postoperative residual muscle relaxants can: (1) increase the risks of hypoxia and hypercapnia; (2) reduce the sensitivity of chemical sensors to hypoxia; (3) increase the risks of counter flow and aspiration because of unrecovered upper esophageal and pharyngeal muscle functions[13]; and (4) increase the risks of postoperative pulmonary complications. Therefore, for elderly patients, the depth of anesthesia should be adjusted during surgery, and extubation should occur as soon as possible after surgery[14-17]. Cisatracurium, a new non-depolarizing muscle relaxant belonging to the family of benzylisoquinolines, has several advantages. It has extensive clinical indications, rapid-onset, medium duration, fast recovery, and causes minimal effects on the cardiovascular system. In addition, it does not cause histamine release or accumulation, and its metabolic product is free from muscle relaxation effects. It is, therefore, more favorable for use in elderly patients[18]. The results of our study confirmed this observation.

Closed-loop target controlled infusion of cisatracurium can achieve satisfactory muscle relaxation during surgery, support timely tracheal catheter withdrawal after surgery[19], avoid the occurrence of residual effects of muscle relaxation, and achieve the rationalized and individualized application of muscle relaxation drugs. In our work, patients in group A experienced no muscle relaxation insufficiency. At present, TOF is the most widely used method for muscle relaxation monitoring in clinical practice. TOF value can precisely reflect the degree of muscle relaxation, and has been widely used clinically for assessing the degree of intraoperative muscle relaxation and postoperative residual muscle relaxation. TOFr from 0.15-0.25 can satisfy the requirements of most operations. TOFr > 0.9 indicates that muscle relaxation is completely recovered, and can meet the criteria for safe extubation[20].

Conclusions

For spinal surgery in elderly patients, closed-loop target controlled infusion of cisatracurium was superior to continuous infusion and intravenous injection. Its required dosage for muscle relaxation recovery was lower, the dosage of cisatracurium was reduced, and the number of cases of insufficient muscle relaxation was reduced.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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