

Original Article

The safety of high-dose rocuronium bromide in general anesthesia for spinal surgery and its effects on muscle relaxation

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Received January 26, 2021; Accepted April 12, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Purpose: This study aimed to investigate the effects of high-dose rocuronium bromide in general anesthesia for spinal surgery and analyze its safety. Methods: A total of 90 patients with spine diseases who underwent elective spinal surgery in our hospital were enrolled as study subjects, and were divided into 2-fold group (intraoperative administration of 0.6 mg/kg rocuronium bromide, n=30), 3-fold group (0.9 mg/kg rocuronium bromide, n=30) and 4-fold group (1.2 mg/kg rocuronium bromide, n=30). The effects of rocuronium bromide on muscle relaxation, the operative time and the incidence of adverse reactions were compared among the three groups. Results: The onset time of muscle relaxation in the 4-fold group was significantly lower than that in 2-fold and 3-fold groups. The duration of muscle relaxation and duration of action in the 4-fold group were significantly higher than those in the 2-fold and 3-fold groups ($P<0.05$). The satisfaction rate in the 4-fold group (100.00%) was significantly higher than that in the 2-fold group (66.67%) and the 3-fold group (86.67%) ($P<0.05$). The 4-fold group exhibited significantly higher intubating condition score at 1 min and significantly lower operative time than the 2-fold and 3-fold groups ($P<0.05$). The incidence of adverse reactions in the 4-fold group was 23.33%, slightly higher than those in the 2-fold (20.00%) and 3-fold groups (20.00%) ($P>0.05$). Conclusion: High-dose rocuronium bromide shortens the onset time of muscle relaxation in patients undergoing spinal surgery, creates better intubation conditions, has longer duration of action, and shortens the patient's operative time, without increasing adverse reactions such as skin flushing, rash, increased airway resistance and bronchospasm, laryngeal edema, etc. Meanwhile, high-dose rocuronium bromide can shorten intubation time, which is conducive to the smooth operation and reduces surgical stress injuries.

Keywords: High dose, rocuronium bromide, spinal surgery, general anesthesia, muscle relaxation, safety

Introduction

With changes in people's work patterns as well as lifestyles, sedentary and standing have led to abnormal stresses in the spine, leading to injury to the spinal nerves and spine, causing back and limb pain, numbness and movement disorders, and increasing cases of spine-related diseases, especially in the elderly population [1]. The state of muscle relaxation around the spinal skeleton should be ensured during the spinal surgery [2]. Muscle relaxants are very important adjuncts to anesthesia in surgery, providing good surgical conditions for tracheal intubation while reducing the adverse effects of prolonged deep anesthesia and expanding the surgical field [3].

According to different mechanisms of action, muscle relaxants were categorized as depolarization and non-depolarization. Depolarizing agents produce their block by binding to and activating the ACh receptor, which first causes muscle contraction, and then paralysis. They bind to the receptor and cause depolarization by opening channels, like acetylcholine. Short-term fasciculation may occur in the early stage of administration of this drug. Continuous administration may cause rapid tolerance, inducing excitatory effects instead of nerve blocking. Therefore, depolarizing agents are mainly used for complete relaxation of skeletal muscles under light anesthesia [4, 5]. Non-depolarizing agents, also known as competitive muscle relaxants, do not produce a depolariz-

ing effect when they interact with N₂ receptors on the motor endplate membrane of skeletal muscle. They compete for the same receptor with ACh, and the motor endplate membrane of skeletal muscle cannot be depolarized, resulting in skeletal muscle relaxation, and these drugs are easy to modulate, safer, and more widely used in clinical practice [6, 7].

The non-depolarizing muscle relaxant rocuronium bromide has the advantages of rapid onset of action, moderate duration of action, rapid recovery, low accumulation *in vivo*, with mild effects on hemodynamic indices, and is recommended for spinal surgery [8]. The clinical application of rocuronium bromide in spinal surgery follows the minimum dose principle to reduce the complications associated with drug residues. However, small doses often have a slow onset of action and poor muscle relaxation, which cannot meet the surgical requirements [9]. To the best of our knowledge, there are no studies on the role of high-dose rocuronium bromide in spinal surgery. In this study, the effects of 2-fold, 3-fold and 4-fold ED₉₅ doses of rocuronium bromide in spinal surgery were compared, thereby providing a reference for the dose of rocuronium bromide used in spinal surgery.

Materials and methods

General information

Ninety patients with spine disorders underwent elective spine surgery in our hospital from January 2020 to December 2020 were enrolled, and were divided into 2-fold group (intraoperative administration of 0.6 mg/kg rocuronium bromide, n=30), 3-fold group (intraoperative administration of 0.9 mg/kg rocuronium bromide, n=30) and 4-fold group (intraoperative administration of 1.2 mg/kg rocuronium bromide, n=30).

Inclusion criteria: (1) patients underwent elective spinal surgery; (2) aged 18-80 years; (3) with body mass index (BMI) of 18-25 kg/m²; (4) preoperative American Society of Anesthesiologists (ASA) classification: I-II; (5) no allergy or severe adverse reactions to rocuronium; (6) agreed to participate in the study.

Exclusion criteria: (1) those with central/peripheral neurological diseases; (2) those comorbid

with cardiac, hepatic, renal and other vital organ dysfunctions; (3) those with a history of allergy to narcotic drugs and related medications; (4) those with a history of use of opioid and other analgesic drugs; (5) those with neuromuscular diseases such as myasthenia gravis and acid-base and electrolyte disturbances; (6) those with unstable hemodynamic indicators; (7) those with difficult airways; and (8) those with a history of difficult mask ventilation and tracheal intubation. This study was approved by the Ethics Committee of Yichun Peoples Hospital. The research objects and their families were informed of the study, and they signed a fully-informed consent form.

Intervention methods

Patients in all the three groups fasted for 12 h and abstained from drinking for 4 h before surgery. Before entering the operating room, blood oxygen, blood pressure and electrocardiograph (ECG) were monitored, intravenous access was established, compound sodium chloride injection was infused at a rate of 5 mL/kg/h, and imipramine 0.05 mg/kg was injected. Invasive blood pressure was monitored by radial artery puncture under local anesthesia, a muscle relaxation monitor was connected to the other upper limb to monitor the timing of muscle relaxation, propofol 2 mg/kg and sufentanil 3 ug/kg were injected for induction of anesthesia, and the muscle relaxation detector was activated when the patient had no eyelash reflex. After calibration stabilization, the dose of rocuronium bromide was administered within 5S, specifically 0.6 mg/kg for the 2-fold group, 0.9 mg/kg for the 3-fold group, and 1.2 mg/kg for the 4-fold group. Patients were extubated at the onset of the 1st convulsive response, mechanically ventilated after extubation, with PETCO₂ controlled at 35-45 mmHg. Anesthesia was maintained with propofol TCI of 3-4 ug/mL, remifentanil TCI of 3.5-4.5 ug/mL, and BIS of 45-55. Rocuronium bromide of 0.3 mg/kg/h was infused when Th recovered to 25%.

Outcome measurement

Muscle relaxation-related indices: The patients were monitored for the onset time and duration of muscle relaxation as well as the duration of action, where the onset time of muscle relaxation refers to the time from the completion of

drug infusion to the maximum suppression of Th, the duration of muscle relaxation refers to the time from the completion of drug infusion to the recovery of Th to 5% of the basal value, and the duration of action refers to the time from the completion of drug infusion to the recovery of Th to 25% of the basal value.

In addition, the outcomes of patients were evaluated according to the muscle relaxation satisfaction criteria [10], where very satisfactory (scored 5) indicated an clear operative field with an adequate operating space and no muscle contractions; satisfactory (scored 4) indicated an clear operative field with a good operating space and little or occasional muscle contractions; fair (scored 3) indicated an extensive operative field but with regular muscle contractions; poor (scored 2) indicated a suitable operative field but the operation was severely hampered by the presence of persistent muscle contractions; very poor (scored 1) indicated that the surgeon was unable to work because the patient was choking or a suitable operative field was unavailable due to insufficient muscle relaxation.

Intubation-related indicators

The intubation condition, intubation condition score at 1 min, and operative time were assessed. Among them, the intubation condition was scored according to the following criteria [11]: 3: completely relaxed jaw, no resistance of the lens, open field at vocal cord, no activity, no limb movement and no choking during intubation; 2: slightly contracted jaw, no resistance of the lens, vocal cord in the middle and with activity, and slight limb movement and choking; 1: stiff jaw, completely resistant lens, tightly closed vocal cord, and severe limb movement and choking. Intubation time refers to the time from the start to the completion of intubation. Operative time refers to the average time from the start of anesthesia to the end of surgery.

Comparison of the incidence of adverse reactions

The incidence of various types of adverse reactions including skin flushing, rash, increased airway resistance, bronchospasm, laryngeal edema during the intervention were recorded among the three groups.

Statistical methods

SPSS22.0 was used to analyze the data collected in the study, where the measurement data were expressed as mean \pm standard deviation (mean \pm SD). The t-test was used for differences between groups for data meeting normal distribution or with even variance. Approximate t-test was applied for data with uneven variance. F-test was used to compare the differences between multiple groups. Chi-square test was used for differences in count data between groups. Graphpad Prism 8.0 was adopted to make statistical charts. $P < 0.05$ was considered as statistically significant difference [12].

Results

Comparison of baseline data

The baseline data, including the ratio of gender, mean age, mean BMI, ASA classification, etc., showed no significant difference among the three groups ($P > 0.05$), suggesting that the three groups were comparable (**Table 1**).

Comparison of muscle relaxation

The onset time of muscle relaxation in the 4-fold group were significantly lower than those in the 2-fold and 3-fold groups ($P < 0.05$), while the duration of muscle relaxation and duration of action in the 4-fold group were significantly higher than those in the 2-fold and 3-fold groups ($P < 0.05$) (**Table 2; Figure 1**). With the increase of rocuronium bromide dose, the patients' satisfaction with muscle relaxation also showed an increasing trend, reaching 100% in the 4-fold group, which was significantly higher than that in the 2-fold group (66.67%) and the 3-fold group (86.67%) ($P < 0.05$) (**Table 3**).

Comparison of intubation-related indices

The intubation time exhibited no significant difference among the three groups ($P > 0.05$), while in the 1 min intubation condition score of the 4-fold group was significantly higher than the 2-fold and 3-fold groups, and the operative time in the 4-fold group was significantly lower than that in the 2-fold and 3-fold groups ($P < 0.05$) (**Table 4; Figure 2**).

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Table 1. Comparison of baseline data (mean \pm SD)/[n (%)]

General information		2-fold group (n=30)	3-fold group (n=30)	4-fold group (n=30)	F	P
Sex	Male	16 (53.33)	17 (56.67)	14 (46.67)	1.021	0.652
	Female	14 (46.67)	13 (43.33)	16 (53.33)		
Average age (years)		43.29 \pm 3.22	44.01 \pm 2.98	43.28 \pm 2.91	0.569	0.568
Average BMI (kg/m ²)		21.98 \pm 2.11	22.01 \pm 2.01	22.01 \pm 1.98	0.002	0.998
ASA Classification	I	17 (56.67)	18 (60.00)	17 (56.67)	0.891	0.434
	II	13 (43.33)	12 (40.00)	13 (43.33)		
Airway Classification	I	20 (66.67)	21 (70.00)	19 (63.33)	0.987	0.401
	II	10 (33.33)	9 (30.00)	11 (36.67)		

Table 2. Comparison of muscle relaxation effects among the three groups (mean \pm SD)

Group	Number of cases	Onset time (min)	Duration of muscle relaxation (min)	Clinical duration of action (min)
2-fold group	30	1.72 \pm 0.11	33.19 \pm 2.12	35.18 \pm 2.22
3-fold group	30	1.53 \pm 0.09	36.21 \pm 2.91	37.32 \pm 3.01
4-fold group	30	1.23 \pm 0.11	40.12 \pm 2.32	41.98 \pm 2.41
t1	-	7.322	4.594	3.134
P1	-	<0.001	<0.001	0.003
t2	-	17.252	12.078	11.367
P2	-	<0.001	<0.001	<0.001
t3	-	11.561	5.754	6.619
P3	-	<0.001	<0.001	<0.001

Note: P1: 2-fold vs. 3-fold groups, P2: the 2-fold vs. 4-fold groups, and P3: 3-fold vs. 4-fold groups.

Comparison of incidence of adverse reactions

No significant difference was found among the three groups in terms of incidence of adverse reactions ($P>0.05$) (Table 5).

Discussion

During the spinal surgery, wake-up test is often performed, which places relatively high demands on anesthesia [13, 14]. Muscle relaxants should have no accumulation, rapid onset of action, no adverse cardiovascular effects, short duration, rapid recovery, no histamine release, no pharmacological activity of metabolites, and pharmacological effects that can be antagonized by anticholinesterase agents [15]. The non-depolarizing agents are classified into two types [16], namely, benzylisoquinolines and aminosteroids. Benzylisoquinolines, with the exception of atracurium and cis-atracurium, is eliminated mostly via renal excretion and can cause release of histamine [17]. Aminosteroid myorelaxants generally have no histamine-

releasing effects and minimal cardiovascular effects, and its disadvantage is that its metabolism and clearance significantly depend on hepatic and renal function [18]. The aminosteroid non-depolarizing agents has a structure similar to that of vecuronium and pancuronium. Rocuronium does not have the acetylcholine-like structure on the A-ring of the pancuronium steroid nucleus, but it has a D-ring acetylcholine-like structure suitable for binding to receptors at the neuromuscular junction, making it a rapid onset of action and the

fastest-acting agent of all non-depolarizing myorelaxants [19].

The results in this study showed that the 4-fold group exhibited significantly shorter onset time and significantly longer duration of action than the 2-fold and 3-fold groups, suggesting that the increase in dose significantly improved the muscle relaxation and prolonged the duration of muscle relaxation. By comparing 120 patients undergoing gynecological surgery in randomized groups, it was found that the onset time could be significantly altered by increasing the administered dose of rocuronium bromide, with (226 \pm 57) s for 1 dose of rocuronium bromide compared to (80 \pm 25) s for 3 doses, which is similar to the results of this study [20]. A study also indicated that the increase of administration of rocuronium bromide significantly prolonged the duration of action from (19.54 \pm 5.27) min to (25.36 \pm 7.69) min [21]. We speculated that rocuronium bromide contains ED95 of 0.3 mg/kg. When the dose of rocuronium bromide is sufficient to produce complete

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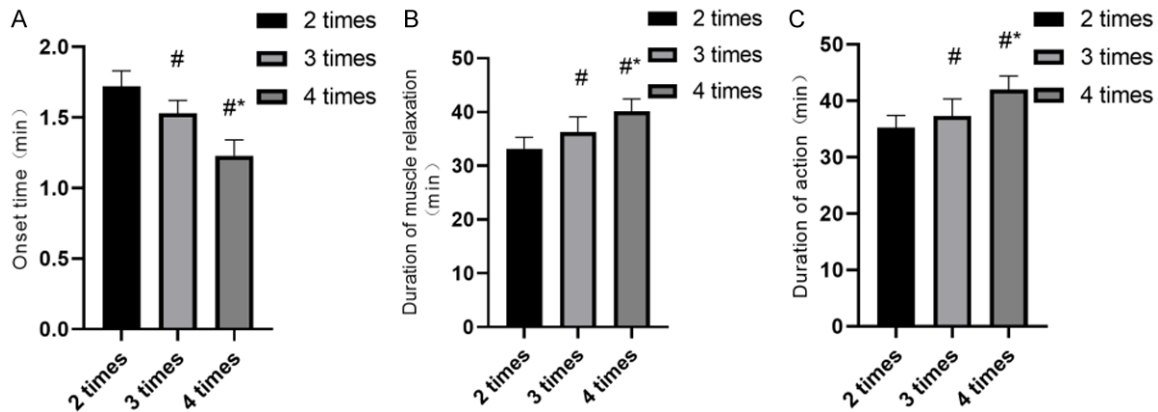


Figure 1. Comparison of muscle relaxation among the three groups of patients. The onset time of muscle relaxation (A) in the 4-fold group were significantly lower than those in the 2-fold and 3-fold groups ($P < 0.05$), while the duration of muscle relaxation (B) and duration of action (C) in the 4-fold group were significantly higher than those in the 2-fold and 3-fold groups ($P < 0.05$). # $P < 0.05$ vs. 2-fold group; * $P < 0.05$ vs. 3-fold group.

Table 3. Comparison of the percentage of patients' satisfaction with muscle relaxation (%)

Group	Number of cases	Very Satisfied	Satisfied	Fair	Poor + Very Poor	Satisfaction rate
2-fold group	30	9	11	8	2	20 (66.67)
3-fold group	30	20	6	4	0	26 (86.67)
4-fold group	30	28	2	0	0	30 (100.00)
χ^2_1	-	-	-	-	-	3.354
P_1	-	-	-	-	-	0.067
χ^2_2	-	-	-	-	-	12.0
P_2	-	-	-	-	-	0.001
χ^2_3	-	-	-	-	-	4.286
P_3	-	-	-	-	-	0.038

Note: P_1 : 2-fold vs. 3-fold groups, P_2 : the 2-fold vs. 4-fold groups, and P_3 : 3-fold vs. 4-fold groups.

Table 4. Comparison of intubation indexes (mean \pm SD)

Group	Number of cases	Intubation time (s)	1 min intubation condition (score)	Operative time (min)
2-fold group	30	20.19 \pm 2.33	1.76 \pm 0.31	120.28 \pm 19.28
3-fold group	30	19.98 \pm 2.21	2.21 \pm 0.08	110.28 \pm 14.34
4-fold group	30	20.11 \pm 2.41	2.87 \pm 0.11	98.28 \pm 10.29
t_1	-	0.358	7.699	2.279
P_1	-	0.722	<0.001	0.026
t_2	-	0.131	18.483	5.514
P_2	-	0.896	<0.001	<0.001
t_3	-	0.218	26.578	3.724
P_3	-	0.828	<0.001	<0.001

Note: P_1 : 2-fold vs. 3-fold groups, P_2 : the 2-fold vs. 4-fold groups, and P_3 : 3-fold vs. 4-fold groups.

range (1-fold to 3-fold ED95), while the onset time of action does not be shortened with increasing dose of less than or close to 1-fold ED95. A retrospective study showed that the onset of action of rocuronium bromide with 2-fold ED95 was approximately (86 \pm 10) s. When a dose of 3-fold ED95 was given, its onset time would be halved, with a corresponding increase in its clinical duration [22]. The reason may be that the rapid onset of rocuronium bromide is related to the dose administered, and its rapid onset may be related to its lower potency strength, that is, low potency strength achieves muscle relaxation by increasing the molecules of the muscle relaxants in the blood, which leads to an increase in the concentration gradient at both sides of the biofilm and a correspondingly shorter onset of action [23, 24], which is also evidenced by the fact that the satisfaction rate in the 4-fold group was significantly higher than that in the 2-fold and 3-fold groups in this study.

neuromuscular blockade, the onset of action accelerates with increasing dose in a limited

The results of this study also showed that patients in the 4-fold group had significantly

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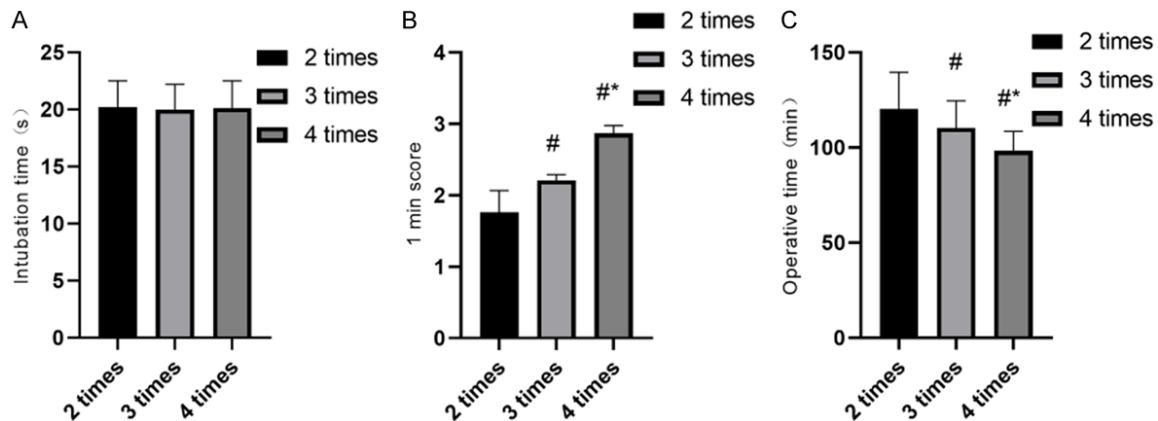


Figure 2. Comparison of intubation indicators among the three groups of patients. The intubation time (A) exhibited no significant difference among the three groups ($P>0.05$), while in the 1 min intubation condition score (B) of the 4-fold group was significantly higher than the 2-fold and 3-fold groups, and the operative time (C) in the 4-fold group was significantly lower than that in the 2-fold and 3-fold groups ($P<0.05$). # $P<0.05$ vs. 2-fold group. * $P<0.05$ vs. 3-fold group.

Table 5. Comparison of incidence of adverse reactions [n (%)]

Group	Number of cases	Skin reactions	Increased airway resistance	Bronchospasm	Laryngeal edema	Total incidence
2-fold group	30	1	3	2	1	7 (23.33)
3-fold group	30	2	2	1	1	6 (20.00)
4-fold group	30	4	1	1	0	6 (20.00)
X^2_1	-	-	-	-	-	0.098
P_1	-	-	-	-	-	0.754
X^2_2	-	-	-	-	-	0.098
P_2	-	-	-	-	-	0.754
X^2_3	-	-	-	-	-	0.0
P_3	-	-	-	-	-	1.0

higher 1 min intubation condition scores and significantly lower operative time than the 2-fold and 3-fold groups. A study of effects of three doses of rocuronium bromide on intubation time showed that 90.91% of patients in group III with 0.9 mg/kg rocuronium had excellent tracheal intubation conditions at 1 min and 95.45% by 2 min, while group I with 0.3 mg/kg had 0.00% excellent at 1 min and 18.18% at 2 min, with significant differences between groups [25]. The results of another randomized controlled trial conducted on 92 patients showed that patients in the high-dose rocuronium bromide group had shorter operative time than those in the low-dose group, all of which were similar to the results of this study, suggesting that high-dose rocuronium bromide significantly improved intubation indices and accelerated the intubation process [26]. Finally, we found that high-dose did not increase the incidence of postop-

erative adverse reactions, suggesting a high safety of its application. A study reported no significant differences in heart rate, mean arterial pressure, cardiac output, and simultaneous ECG monitoring of S-T segment and left heart function in patients with 4-fold ED95 high dose compared with conventional dose, indicating that high dose of rocuronium use is safe [27].

In conclusion, 4-fold high-dose rocuronium bromide can shorten the onset time of muscle relaxation, provide better intubation conditions and longer duration time, and shorten the operative time, without increasing adverse reactions. There are also some shortcomings in this study. Firstly, the effect of different doses of rocuronium bromide on the hemodynamics of patients was not explored. Secondly, the limited sample size was included, which may lead to some biases in the results.

Acknowledgements

This work was supported by Science and Technology Project of Jiangxi Health Commission (No.: 202140867).

Disclosure of conflict of interest

None.

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