

# Comparison of two rocuronium bromide doses in adult and elderly patients who underwent laparoscopic surgery

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## ABSTRACT

### Background

The aim of our study was to evaluate the effects of two different doses of rocuronium bromide (0.5 mg/kg and 0.9 mg/kg) on the **length** of neuromuscular block, on the haemodynamic stability and on the side effects in patients of different ages.

### Methods

We recruited 80 patients who underwent laparoscopic surgery (cholecystectomy, appendicectomy, varicocelelectomy) belonging to ASA I–II classes and divided them into four groups:

- 20 adults (A0.5) who received rocuronium bromide 0.5 mg/kg
- 20 elderly patients (E0.5) who received rocuronium bromide 0.5 mg/kg
- 20 adults (A0.9) who received rocuronium bromide 0.9 mg/kg
- 20 elderly patients (E0.9) who received rocuronium bromide 0.9 mg/kg

Intubation conditions, continuous monitoring of HR, NIBP, SpO<sub>2</sub>, EtCO<sub>2</sub> were recorded. Onset time, REC 25%, TOF-ratio<sub>0.70</sub> were analysed by TOF-WATCH.

Nerve-evoked muscle tension and neuromuscular paralysis extension were expressed by strength of contraction of adductor pollicis, in response to a direct stimulation of the ulnar nerve (TOF).

### Results

The results showed that in elderly patients the effect of rocuronium bromide, at two different doses, was similar. Significant differences regarding the onset time was found among the groups showing that with the same dose of rocuronium bromide, the onset time was prolonged in elderly patients compared to adult patients. Moreover, increasing the dose, the onset time was reduced in both groups ( $p < 0.05$ ). Forty per cent of adult group A0.5 showed excellent intubation conditions versus 60% of A0.9 ( $p < 0.05$ ); elderly patients did not show any significant difference in the intubation procedure after different doses of rocuronium bromide.

### Conclusions

The results from the four groups showed that in elderly patients 0.5 mg/kg of rocuronium bromide resulted in a good recovery, while 0.9 mg/kg increased the recovery time. Moreover, in adults the high dose was more effective because it reduced the number of injections and post-operative recovery time.

## Introduction

Rocuronium, a derivative of vecuronium, is a non-depolarising myorelaxant. It has the fastest onset as compared to all non-depolarising neuromuscular blockers, with an intermediate duration of action and minimal haemodynamic effects and histamine release. There are several studies in the literature on rocuronium for fast and safe tracheal intubation (similar to succinylcholine).<sup>1</sup>

The action mechanism, metabolism and side effects for non-depolarising myorelaxants, like other drugs, occur not only for the properties of the molecule, but also for the characteristics

of the patient. Therefore, it is important to consider anatomic and physiologic characteristics of the subject treated with the drug and all the changes due to age, sex and disease in order to better determine the right dose.

Age is one of the most important factors. In fact, with ageing there is a reduction of two pharmacokinetic parameters: plasmatic clearance (C<sub>p</sub>) and apparent distribution volume (V<sub>d</sub>).

Many previous studies have shown that anatomic and physiologic conditions of the elderly significantly influenced the pharmacodynamic of administered molecules.<sup>2,3,4</sup> For this reason,

we decided to evaluate all the possible differences regarding tracheal intubation and duration of action of rocuronium and the effects of two different doses of rocuronium bromide (0.5 mg/kg and 0.9 mg/kg) in adults and elderly patients.

### Methods

The protocol for this study was approved by the Institutional Review Board at the Department of Anesthetics, Surgical and Emergency Science of the Second University of Naples and all participants provided written consent before taking part in the study. We studied 80 patients undergoing laparoscopic surgery (cholecystectomy, appendicectomy, varicocelelectomy), belonging to ASA I and II classes (see Table I). Patients were divided into two groups of 40 subjects according to age (adults: aged 20–50; elderly: aged  $\geq$  65). Each group was then divided into smaller groups of 20 patients treated with different doses of rocuronium bromide, 0.5 mg/kg and 0.9 mg/kg, according to the randomised sequence suggested by computer.

None of the patients presented congenital and/or acquired diseases of nose, tongue, teeth, temporo-mandibular joint and cervical spine, goitre or protruding chin and/or micrognathia. The distance chin-thyroid was  $>$  60 mm, the distance chin-hyoid  $>$  40 mm, the distance between teeth  $>$  30 mm; all were included in Mallampati classes 1–2.<sup>5</sup>

Patients were within 30% of their ideal weight as measured by body mass index (BMI). They had no known drug intolerances and they abstained from eating for eight hours and from drinking for two hours.

The groups studied were:

- Group A0.5: adults (age 20–50) treated with rocuronium bromide 0.5 mg/kg
- Group E0.5: elderly patients  $\geq$  65 treated with rocuronium bromide 0.5 mg/kg
- Group A0.9: adults (age 20–50) treated with rocuronium bromide 0.9 mg/kg
- Group E0.9: elderly patients  $\geq$  65 treated with rocuronium bromide 0.9 mg/kg

Exclusion criteria were:

- Neuromuscular disease
- Drug treatment interfering with neuromuscular function<sup>6</sup>
- Anaesthesia within 24 hours
- Impaired hepatic and/or renal function

Patients were treated with midazolam 2 mg, IV, one hour before anaesthesia. Then, ceftriaxone 2 g was administered IV five minutes before surgery as prophylaxis. This antibiotic does not interfere with neuromuscular function.<sup>6</sup> After three minutes of pre-oxygenation all the patients were anaesthetised with fentanyl 2  $\mu$ /kg IV followed by propofol 2 mg/kg IV. Immediately after anaesthetic induction, the patients received rocuronium bromide.<sup>7,8</sup> Intubation conditions were assessed using the criteria of Cooper et al. Each of the three items of this score, i.e. ease of laryngoscopy (evaluated together with jaw relaxation), aspect of vocal cords, and response of the diaphragm to tracheal intubation, offers a four-point scale (0–3). The appropriate values are selected and added up to a total numeric score of a maximum of 9. A total score of 8–9, 6–7, 3–5 and 0–2 is rated excellent, good, fair and poor intubation conditions respectively. Good and excellent intubation conditions were taken to be “clinically acceptable” by Cooper et al.<sup>9</sup> (Table II.)

If the first intubation failed the anaesthetist was instructed to continue the mask ventilation until the maximal twitch suppression necessary to try a second attempt.

Anaesthesia was maintained for all the patients with O<sub>2</sub> and NO<sub>2</sub> (35%+65%).

Continuous monitoring included:

- Heart rate (HR)
- Non-invasive blood pressure (NIBP)
- Arterial oxygen saturation (SpO<sub>2</sub>)
- End-tidal CO<sub>2</sub> (34–42 mmHg)

Data were recorded before and after anaesthesia, before myorelaxant and after rocuronium bromide administration during the following ten minutes with two minute intervals.

Neurotransmission monitoring was carried out with TOF-WATCH

**Table I:** Patient characteristics

Group	Age	Gender (M/F)	Weight (kg)	ASA ( I/II) A0.5
A0.5	34.4 $\pm$ 1.50	11/9	81.7 $\pm$ 6.49	8/12
E0.5	70.5 $\pm$ 1.58	0/10	71.8 $\pm$ 6.23	10/10
A0.9	35 $\pm$ 1.49	8/12	80.8 $\pm$ 5.39	9/11
E0.9	71.6 $\pm$ 1.02	10/10	72.2 $\pm$ 5.65	9/11

**Table II:** Score of intubation conditions (Cooper et al)

Score	Jaw relaxation (ease of laryngoscopy)	Vocal cords	Response to intubation
0	Poor (impossible)	Closed	Severe coughing or bucking
1	Minimal (difficult)	Closing	Mild coughing
2	Moderate (fair)	Moving	Slight diaphragmatic movement
3	Good (easy)	Open	None

Total score of 8–9 = excellent; 6–7 = good; 3–5 = fair; 0–2 = poor

starting with patient unconscious.<sup>10,11</sup> The reference nerve-evoked muscle tension (contraction) and the extension of neuromuscular paralysis were studied measuring the strength of adductor pollicis after indirect stimulation of the ulnar nerve by applying wrist electrodes. The electric stimulus was pulsed at maximal frequency every ten seconds, except during the final step at the end of rocuronium bromide administration when a train of four stimuli (TOF) (four stimuli 0.2 ms long, frequency 2 Hz in two seconds) repeated every 12 seconds was used. Adductor pollicis contraction was measured by joining the thumb to the Grass transducer (FT-10 adults) through a wood stabiliser and a silk thread.<sup>12,13</sup> The direction of thumb adduction was perpendicular to the transducer, of which rotating was parallel to the thumb. The contraction of the adductor pollicis was recorded on the Grass polygraph.

After anaesthesia and before myorelaxant administration, a supramaximal neuromuscular stimulus induced a contraction considered as standard (control). This was reached by progressive increase of amperage of the nerve stimulator until a peak of maximal contraction considered as measure of control.

The analysis of the standard control was necessary to establish the following rocuronium bromide dose after the first administration. When adductor pollicis reached 25% contraction (REC 25%) compared to a single twitch standard, one-third of myorelaxant initial dose was administered. Before the end of surgery, rocuronium bromide administration was interrupted and contraction tension was left to progressive spontaneous resolution.

Therefore, we measured:

- Intubation gradation
- Time of maximal depression of the muscle contraction after single stimulus (onset time)
- Recovery time of muscle contraction equal to 25% of the standard control (subsequent doses)
- Time of TOF-ratio<sub>0.70</sub> (recovery time available to start the reversal of neuromuscular blockade)<sup>14</sup>
- No neostigmine was given, but the anaesthetist waited until TOF-ratio was  $\geq 0.85$  and the patient had regained consciousness before extubating the trachea.<sup>15</sup>

#### Statistical analysis

Statistical analysis was performed with G<sup>®</sup> Power software, which gave an effect size of 0.64, a sample size of 40 patients and a study power equivalent to 0.80. Comparisons between the two groups studied were made by ANOVA and, if needed, corrections with Bonferroni's test were performed to identify the significant differences. We used a repeated measures analysis of variance for continuous outcomes (ANOVA) and  $\chi^2$ -test for categorical outcomes. Intubation procedures were analysed by the exact Fisher's test. The threshold for statistical significance was  $p < 0.05$ . Tests were performed with programme SPSS, version 13.0 for Windows.

#### Results

Demographical characteristics of the patients

are reported in Table I. All the patients presented a complete neuromuscular block due to rocuronium bromide administration. A significant difference regarding the onset time was found among the groups (Table III), showing that with the same dose of rocuronium bromide the onset time was prolonged in elderly patients compared to adult patients. Moreover, increasing the dose, the onset time was reduced in both groups ( $p < 0.05$ ). Forty per cent of adult group A0.5 showed excellent intubation conditions versus 60% of A0.9 ( $p < 0.05$ ); elderly patients did not show any significant difference in the intubation procedure after different doses of rocuronium bromide; the percentage of excellent intubation was 60% and 70% ( $p > 0.05$ ) after treatment with rocuronium bromide. For groups E0.5 and E0.9, excellent and good intubation conditions were taken to be clinically acceptable and there were no differences in either groups (Table IV).

Data of REC 25% showed that in adult patients (groups A0.5 and A0.9) the different doses increased the time of subsequent rocuronium bromide administration with an effective improvement at 0.9 mg/kg. No significant difference could be detected in elderly patients (groups E0.5 and E0.9) (Table III). The analysis of recovery time (TOF-ratio<sub>0.70</sub>) showed that A0.5 vs E0.5 did not present particular differences, whereas the two doses had different results in the elderly: the low dose reduced recovery time, determining a fast and complete restart of spontaneous ventilation. The results (Table V) showed that both doses of rocuronium bromide were not haemodynamically significant in all the groups ( $p > 0.05$ ) (Figures 1 and 2).

**Table III:** Onset time and length of action of rocuronium

Group	Onset time (min)	REC 25% (min)	TOF-ratio 0.70 (min)
A0.5	3.3 $\pm$ 3.2	36.3 $\pm$ 2.1	53.0 $\pm$ 4.6
E0.5	4.1 $\pm$ 2.2	46.8 $\pm$ 3.5	58.1 $\pm$ 4.0
A0.9	2.9 $\pm$ 3.3	41.4 $\pm$ 2.2	59.1 $\pm$ 2.8
E0.9	3.8 $\pm$ 2.3	47.7 $\pm$ 1.9	64.7 $\pm$ 1.2
Statistic			
A0.5 vs E0.5	S	S	N.S.
A0.5 vs A0.9	S	S	S
E0.5 vs E0.9	S	N.S.	S
A0.9 vs E0.9	S	S	S

**Table IV:** Difficulty during intubation (number of patients)

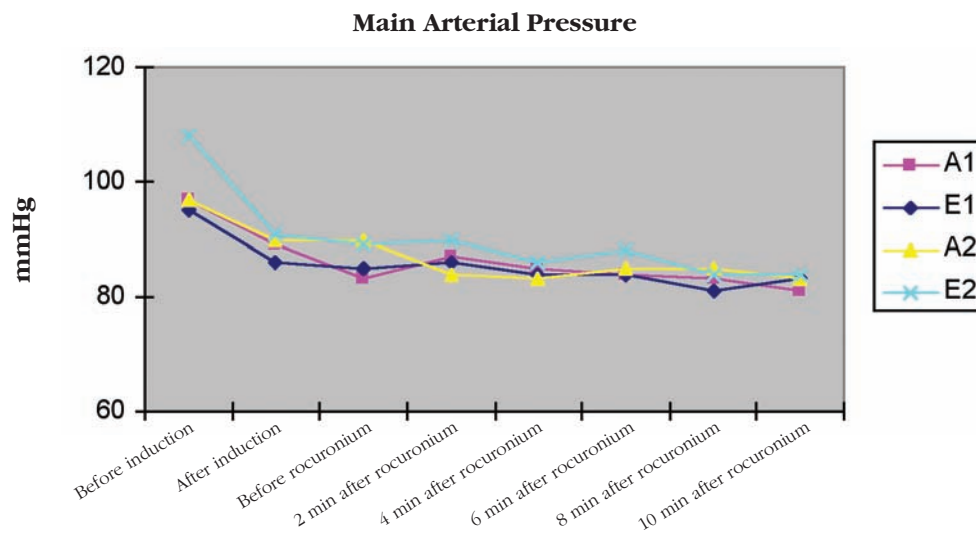
Total score	A0.5	E0.5	A0.9	E0.9
Excellent	8	12	12	14
Good	8	6	4	4
Fair	4	2	4	2
Poor	0	0	0	0

\* Data are showed as mean  $\pm$  SD; S =  $p < 0.05$ ; N.S. =  $p > 0.05$

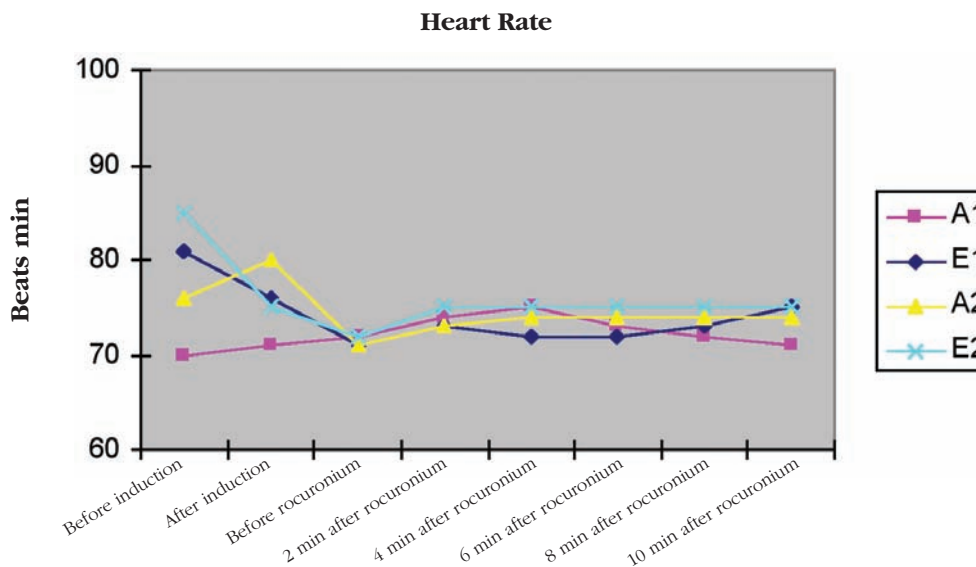
**Table V:** Blood pressure mean (MAP) and heart rate mean (HR) before and after intubation and before and after rocuronium administration

Group	A0.5		E0.5		A0.9		E0.9	
	MAP	HR	MAP	HR	MAP	HR	MAP	HR
Before induction	97 ± 6	70 ± 3	95 ± 2	81 ± 4	97 ± 1	76 ± 1	108 ± 3	85 ± 3
After induction	89 ± 4	71 ± 3	86 ± 1	76 ± 2	90 ± 1	80 ± 1	91 ± 2	75 ± 2
Before rocuronium	83 ± 1	72 ± 1	85 ± 4	71 ± 2	90 ± 3	71 ± 1	89 ± 3	72 ± 2
2 min after rocuronium	87 ± 1	74 ± 1	86 ± 3	73 ± 2	84 ± 2	73 ± 2	90 ± 2	75 ± 2
4 min after rocuronium	85 ± 1	75 ± 2	84 ± 2	72 ± 2	83 ± 3	74 ± 2	86 ± 3	75 ± 3
6 min after rocuronium	84 ± 2	73 ± 1	84 ± 4	72 ± 2	85 ± 3	74 ± 4	88 ± 2	75 ± 3
8 min after rocuronium	83 ± 1	72 ± 2	81 ± 1	73 ± 2	85 ± 5	74 ± 4	84 ± 2	75 ± 3
10 min after rocuronium	81 ± 1	71 ± 1	83 ± 1	75 ± 1	83 ± 4	74 ± 3	84 ± 2	75 ± 3

**Figure 1:** Blood pressure mean before and after rocuronium administration



**Figure 2:** Heart rate mean before and after rocuronium administration



## Discussion

Rocuronium bromide is a 2-morfolinum-3desacetyl-16 allil-pirrolydine of vecuronium. It belongs to the steroidal myorelaxant class, with an intermediate duration of action and rapid onset time.<sup>16</sup> The efficacy is seven times lower than vecuronium: ED<sub>95</sub> is 350 µg/kg. With a dose equal to three times the ED<sub>95</sub> (about 1 mg/kg) the intubation could be performed within 60 seconds. A similar time was observed with succinylcholine (Sch).<sup>16,17,18,19</sup> Therefore, with a suggested dose of 0.5 mg/kg tracheal intubation is possible within 60–90 seconds. After the administration of this dose during general anaesthesia the duration of the effect is 30–40 minutes. Muscle activity recovery is prolonged with the higher dose. After two hours of continuous intravenous infusion (10 µg/kg/min), a complete recovery can be observed after 45 minutes after interrupting the drug. The pharmacokinetics is similar to vecuronium, with the same metabolism (hepatic). The kidneys metabolise only a very low percentage (< 30%). A prolonged drug action at 0.5 mg/kg was observed in patients with hepatic and/or biliary diseases and/or with renal failure. Rocuronium bromide of 0.9 mg/kg causes an intubation condition similar to 1.5 mg/kg of succinylcholine after 60 seconds; a different result appears with 0.7 mg/kg.

With ageing there is a reduction of two pharmacokinetic parameters: plasmatic clearance (Cp) and apparent distribution volume (Vd). Plasmatic clearance decreases following the reduction of splanchnic blood flow, of blood volume and liver and kidney function. The pharmacokinetics of different molecules change depending on hepatic metabolism and the amount excreted in urine. In contrast, the reduction of the apparent distribution volume occurs when water content and muscle mass decrease as in elderly people.<sup>20,21</sup>

In our study we compared four groups of patients who differ with regard to age and dose of rocuronium in order to obtain intubation and myoresolution. We found a statistically significant difference in the onset time between adults and elderly patients, groups E0.5 and E0.9 (Table III). The onset time for group E0.9 was not much higher than that of group E0.5 (average of 4.1 minutes versus 3.9 minutes respectively). This was the evidence of the efficacy of a low dose of rocuronium in elderly patients.

Data regarding REC 25% showed that in adults (groups A0.5 and A0.9) the different dose increased the time between subsequent administrations of rocuronium bromide, especially at 0.9 mg/kg; in the elderly (groups E0.5 and E0.9) no such difference was found (Table III). For this reason, we preferred 0.5 mg/kg in elderly patients for safety reasons. The analysis of recovery time at the beginning of decurarisation (TOF-ratio<sub>0.70</sub>) showed that with 0.5 mg/kg rocuronium bromide there was no significant difference between adults and elderly patients in terms of complete restart of spontaneous ventilation.

Intubation after rocuronium bromide was excellent for 40% of adult patients treated with 0.5 mg/kg versus 60% of patients who received the higher dose ( $p < 0.05$ ). In contrast, in elderly patients there was no significant difference during intubation after the two doses of rocuronium. In groups E0.5 and E0.9 the percentage of excellent intubation was 60% and 70% respectively ( $p > 0.05$ ) (Table IV).

The low dose (0.5 mg/kg) in elderly patients was not significantly different from the high dose. These findings justified the lower dose in patients over 65 years old for a complete restart of

spontaneous ventilation and for better post-operative outcome. In contrast, we preferred 0.9 mg/kg for longer surgical procedures in adult patients without evident liver or kidney failure to reduce the number of administrations. A short time lapse (36 minutes) between subsequent administrations could interfere with an appropriate myoresolution during surgery, causing an increasing post-operative recovery time.

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## References

- Klein J, Loffelholz K. Cholinergic mechanism: From molecular biology to clinical significance. Amsterdam, Elsevier; 1996.
- Flood P. The importance of myorelaxants in anesthesia. *Curr Opin Pharmacol* 2005 Jun;5(3):322–7.
- Zlotos DP. Recent advances in neuromuscular blocking agents. *Mini Rev Med Chem* 2005 Jun;5(6):595–606.
- Baykara N, Solak M, Tokar K. Predicting recovery from deep neuromuscular block by rocuronium in the elderly. *J Clinical Anesth* 2003 Aug;15(5):328–33.
- Romano E. *Anestesia generale e speciale*; UTET Editori, Torino 1997:173–174.
- Amici M, Eusebi F, Miledi R. Effects of the antibiotic gentamicin on nicotinic acetylcholine receptors. *Neuropharmacology* 2005 Oct 18, 102(42):15219–23.
- Maidatsi PG, Zalaridou AT, Gorgias NK, Amaniti EN, Karakoulas KA, Giala MM. Rocuronium duration of action under sevoflurane, desflurane or propofol anaesthesia. *Eur J Anaesthesiol* 2004 Oct;21(10):781–6.
- Rotundo RL. Expression and localization of acetylcholinesterase at the neuromuscular junction. *J Neurocytol* 2003 Jun–Sept;32(5–8):743–6.
- Sparr HJ, Luger TJ, Heidegger T, Putensen-Himmer G. Comparison of intubating conditions after Rocuronium and Suxamethonium following “rapid-sequence induction” with thiopentone in elective cases. *Acta Anesth Scand* 1996;40:425–30.
- Sessler CN. Train of four to monitor neuromuscular blockade? *Chest* 2004 Oct;126(4):1018–22.
- Bevan DR. Monitoring and reversal of neuromuscular block. *Am J Health Syst Pharm* 1999 Jun 1;56(11 Suppl 1):S 10–3.
- Nepveu ME, Donati F, Fortier LP. Train of four stimulation for adductor pollicis neuromuscular monitoring can be applied at the wrist or over the hand. *Anesth Analg* 2005 Jan;100(1):149–54.
- De Haes A, Eleveld DJ, Wierda JM. The relationship between rate of administration of an intubating dose of rocuronium and time to 50% and 90% block at the adductor pollicis muscle. *J Clin Monit Comput* 2000;16(3):219–22.
- Ali HH, Bavarese JJ. Monitoring of neuromuscular function. *Anesthesiology* 1976;45:216–49.
- Brand JB, Cullen DJ, Wilson NE, Ali HH. Spontaneous recovery from nondepolarizing neuromuscular blockade: Correlation between clinical and evoked responses. *Anesth Analg* 1977 56:55.
- Kopman AF, Zhaku B, Lai KS. The “intubating dose” of succinylcholine: The effect of decreasing doses on recovery time. *Anesthesiology* 2003 Nov;99(5):1050–4.
- Kron SS. Optimal intubating dose of succinylcholine. *Anesthesiology* 2004 Jun;100(6):1628–9.
- Lien CA, Belmont MR, Heerd PM. Succinylcholine: Pharmacodynamics and potential adverse effects. *Anesthesiology* 2005 Apr;102(4):861–2.
- Chung YT, Yeh LT. Effectiveness and safety of rocuronium-hypnotic sequence for rapid-sequence induction. *Acta Anaesthesiol Sin* 2001 Mar;39(1):3–9.
- Arain SR, Kern S, Ficke DJ, Ebert TJ. Variability of duration of action of neuromuscular-blocking drugs in elderly patients. *Acta Anesth Scand* 2005 Mar 49(3):312–5.
- Koo Bn, Bai SJ, Shin YS, Lee WC. The relationship of the anthropometric variables to the infusion rate of rocuronium in the elderly. *Yonsey Med J* 2005 Oct 31;46(5):643–7.