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ORIGINAL ARTICLE

Intubation time required for tracheal intubation with low-dose rocuronium in children with and without atropine

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Abstract
Purpose The purpose of this study was to determine the intubation time needed to facilitate tracheal intubation ($Time_{EI}$) with a low dose of rocuronium (0.3 mg/kg) during propofol induction, and to determine whether this time was reduced by the administration of atropine.
Methods Forty-six children, aged 3–10 years, were randomly assigned to receive either saline (control group) or atropine 10 μg/kg (atropine group). Anesthesia was induced with alfentanil 10 μg/kg, propofol 2.5 mg/kg, and rocuronium 0.3 mg/kg. Each $Time_{EI}$ at which tracheal intubation was attempted was predetermined according to the up-and-down method. The values of $Time_{EI}$ that provided excellent intubation conditions in 50 and 95 % of patients were defined as $Time_{EI}50$ and $Time_{EI}95$, respectively.
Results $Time_{EI}50 \pm SD$ was 160 ± 26.2 and 150 ± 13.7 s in the control and atropine groups, respectively. Using isotonic regression, $Time_{EI}95$ in the control and atropine groups was 199 s (95 % CI 198.8–200.7 s) and 171 s (95 % CI 171.3–172.1 s), respectively. $Time_{EI}95$ was significantly higher in the control group than in the atropine group ($P < 0.001$). HR was significantly higher in the atropine group than in the control group during the study period.
Conclusions This study demonstrated that the $Time_{EI}95$ of a low dose of rocuronium (0.3 mg/kg) required for excellent tracheal intubation was 199 s during i.v. anesthesia induction using propofol and alfentanil in children. Also, i.v. atropine (10 μg/kg) before anesthesia induction was able to reduce $Time_{EI}95$ by 28 s.

Keywords Atropine · Low-dose rocuronium · Intubation

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Introduction

Rocuronium bromide is frequently used to facilitate endotracheal intubation in children during general anesthesia. The usual intubating doses (0.6–1.0 mg/kg) of rocuronium are administered to achieve a rapid onset of effect [1]. However, these doses of rocuronium may cause a time delay in the spontaneous recovery of neuromuscular function after a short surgery [2]. Even though sugammadex is able to antagonize any degree of neuromuscular blockade efficiently and predictably [3], it may not be cost-effective for routine use [4]. Thus, a reduced dose of muscle relaxant is preferred during short surgical procedures. With lower doses of rocuronium, the duration of action should be shorter, but the onset of action may be delayed [5].

In previous studies, modification of hemodynamic factors has been shown to influence the onset of action of rocuronium in adults [6, 7]. The onset of rocuronium appears to be inversely proportional to cardiac output [8]. In children, heart rate is considered to be a major determinant of cardiac output, because they have a relatively fixed cardiac stroke volume [9]. In addition, atropine has been reported to induce an increase in cardiac output in anesthetized infants and children [10]. To the best of our

knowledge, there has been no study of the intubation time needed to facilitate tracheal intubation ($Time_{EI}$) with a low dose of rocuronium during i.v. anesthesia. Therefore, the purpose of this study was to determine the $Time_{EI}$ needed with a low dose of rocuronium (0.3 mg/kg) to achieve successful tracheal intubation conditions during i.v. anesthesia using propofol and alfentanil in children, and to determine whether the administration of i.v. atropine (10 μg/kg) during anesthesia induction reduces these times. We hypothesized that increasing the cardiac output by using atropine in children might reduce $Time_{EI}$.

Materials and methods

This study was approved by the Institutional Review Board (Ajou University Hospital, Suwon, Korea) and registered at ClinicalTrials.gov (ref: NCT01464489). Written informed parental consent was obtained from all patients. Forty-six children, who were American Society of Anesthesiologists (ASA) physical status I, aged 3–10 years, and scheduled for tonsillectomy or myringotomy, were included. Patients with a known allergy to the drugs used in this study, a history of reactive airway disease and asthma, a neuromuscular disorder, an anticipated-to-be-difficult airway, and children crying on arrival in the operating theater were excluded from this study.

Children were randomized using a computer-generated sequence of random numbers and allocated to one of two groups using a sequential sealed envelope technique. Patients were randomly assigned to receive either saline (control group, $n = 23$) or atropine (atropine group, $n = 23$) prior to anesthesia induction. The study syringe, containing either 5 ml of atropine 10 μg/kg diluted with normal saline (the atropine group) or the same volume of normal saline (the control group), was prepared by an independent researcher.

No premedication was administered prior to the induction of anesthesia. Before arrival at the operating room, a 24-gauge cannula was inserted into the dorsum of the hand, and its position was confirmed by a free flow of dextrose/saline infusion due to gravity. Upon arrival at the operating room, ASA standard monitoring began, including an electrocardiogram, pulse oximetry, and noninvasive arterial pressure. After pre-oxygenation, the study drug was administered according to the group. All patients received alfentanil (10 μg/kg) over 20 s to reduce pain or withdrawal associated with propofol injection. After 60 s, a bolus of propofol (2.5 mg/kg) was given over a period of 20 s. Following the loss of eyelash reflex, mask ventilation was initiated with 100 % oxygen, and rocuronium (0.3 mg/kg) was administered. Infusion of propofol (6 mg/kg/h) was started immediately after the injection of rocuronium to maintain anesthesia. For each patient, the intubation time was defined as the time from the end of rocuronium injection to the start of laryngoscopy.

Each $Time_{EI}$ at which tracheal intubation was attempted was predetermined according to the up-and-down method [11], starting at 120 s, in both groups. If intubation was successful (unsuccessful), the assigned intubation time was decreased (increased) by one interval for the next patients in that group. In this study, we adopted 69, 83, 99, 120, 144, 173, and 208 s, since these intubation times have equal intervals (0.08) on a logarithmic scale. The anesthesiologist who performed and assessed the intubation conditions was blinded to the study drug. Intubation conditions were assessed according to a scoring system described by Viby-Mogensen et al. [12] (Table 1). Successful intubation was defined as excellent intubation conditions when all variables were excellent. If any variable was rated as poor due to strong movement of the patients, inadequate jaw relaxation, closed vocal cords, or sustained coughing, additional rocuronium 0.3 mg/kg was administered. The values of $Time_{EI}$ that provided excellent intubation conditions in 50 and 95 % of patients were defined as $Time_{EI}50$ and $Time_{EI}95$, respectively.

Hemodynamic variables, including heart rate (HR) and mean arterial pressure (MAP), were measured and recorded at the following times: T0, pre-induction value (baseline value); T1, after alfentanil administration; T2, after the bolus dose of propofol; T3, just before laryngoscopy; T4, 1 min after intubation. Clinically significant hypotension and bradycardia were defined as >30 % decreases in the MAP and heart rate (HR) compared with the baseline value, respectively. Patients were treated with atropine or ephedrine where appropriate.

SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. The intubation time in 50 % of the patients ($Time_{EI}50$) for successful

Table 1 Assessment of intubating conditions

Variables	Intubating conditions		
	Acceptable		Unacceptable
	Excellent	Good	Poor
Ease of laryngoscopy (jaw relaxation)	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate	Closed
Vocal cord movement	None	Moving	Closing
Airway reaction (coughing)	None	Diaphragm	Sustained (>10 s)
Movement of the limbs	None	Slight	Vigorous

Intubating conditions: *Excellent* all criteria are excellent, *Good* all criteria are either excellent or good, *Poor* the presence of a single criterion listed under "poor"

tracheal intubation was determined by calculating the average of the midpoint time of all independent pairs of patients after six crossover points. For backup analysis, data were also analyzed using an isotonic regression to calculate the intubation time in 95 % of patients ($Time_{EI}95$) (using R 2.12.2). An adjusted response probability was easily calculated by the pool-adjacent-violators algorithm (PAVA), and the CI was estimated by a bootstrapping approach [13]. A two-sample Z-procedure was used to compare $Time_{EI}95$ between the two groups. Values are expressed as the mean ± SD or median [interquartile range] or number of patients (%). Kolmogorov–Smirnov tests were used to test the distributions of all measured and calculated data. An unpaired *t* test was used to compare patients' characteristics and induction profiles. Repeated-measures ANOVA was used to compare hemodynamic changes over time between the groups. To compare the MAP and HR between the groups at each time point, an independent *t* test was used. Significance was defined as $P < 0.05$.

Results

A total of 44 patients completed the study. One patient in each group was excluded from analysis due to severe withdrawal movement associated with injection of propofol and rocuronium during induction and the inability to meet the time schedule of this study. No significant differences in patient characteristics and induction episodes were observed between the two groups (Table 2). Excellent intubation conditions, where the intubation was considered successful, were present in 10/22 (45 %) children in the control group and in 11/22 (50 %) children in the atropine group. Intubating conditions were poor in 3/22 and 2/22 patients in the control and atropine groups, respectively. In both groups, the most common event leading to poor intubating conditions was sustained coughing and vigorous movement.

Table 2 Patient characteristics and induction episodes

	Control ($n = 22$)	Atropine ($n = 22$)
Sex (M/F)	13/9	10/12
Age (years)	7 [6–9]	7 [5.5–8]
Weight (kg)	28.5 ± 8.5	25.6 ± 9.0
Induction episodes (*n*)		
Cough	1 (5.2 %)	2 (9.5 %)
Pain from propofol injection	9 (40.9 %)	8 (36.4 %)
Rocuronium withdrawal	8 (36.4 %)	7 (31.8 %)

Values indicate the mean ± SD or median [interquartile range] or the number of patients. No significant differences between the groups were noted

Figure 1 shows the sequences of $Time_{EI}$ for successful and unsuccessful tracheal intubation in the two groups. Using Dixon's up and down methods, $Time_{EI}50$ was 160 ± 26.2 and 150 ± 13.7 s in the control and atropine groups, respectively. Using isotonic regression estimated from the PAVA response rate, $Time_{EI}50$ in the control and atropine groups was 175 s (95 % CI 173.0–177.8 s) and 146 s (95 % CI 143.8–148.1 s), respectively. $Time_{EI}95$ in the control and atropine groups was 199 s (95 % CI 198.8–200.7 s) and 171 s (95 % CI 171.3–172.1 s), respectively. $Time_{EI}50$ and $Time_{EI}95$ for the control group were significantly higher than those for the atropine group ($P < 0.001$).

Figure 2 shows MAP and HR during anesthesia induction. MAP did not differ significantly between the two groups at any time point. Compared with the pre-induction baseline values (T0), MAP was significantly decreased before laryngoscopy (T3) and significantly increased after

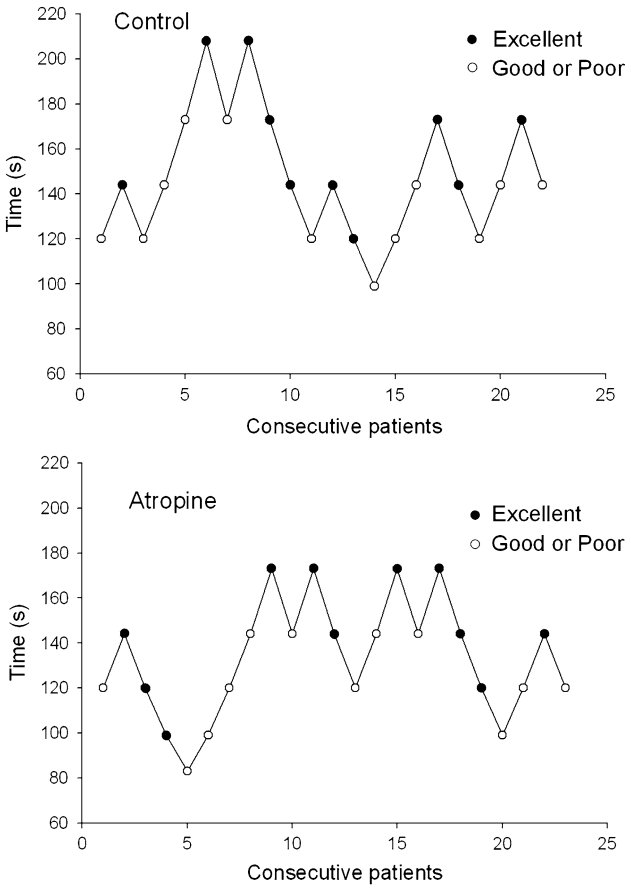

Fig. 1 Consecutive induction time and response to intubation of each patient in the control group (*top*) and atropine group (*bottom*). The intubation time at which tracheal intubation conditions were excellent in 50 % of children ($Time_{EI}50$) was 160 ± 26.2 and 150 ± 13.7 s in the control and atropine groups, respectively

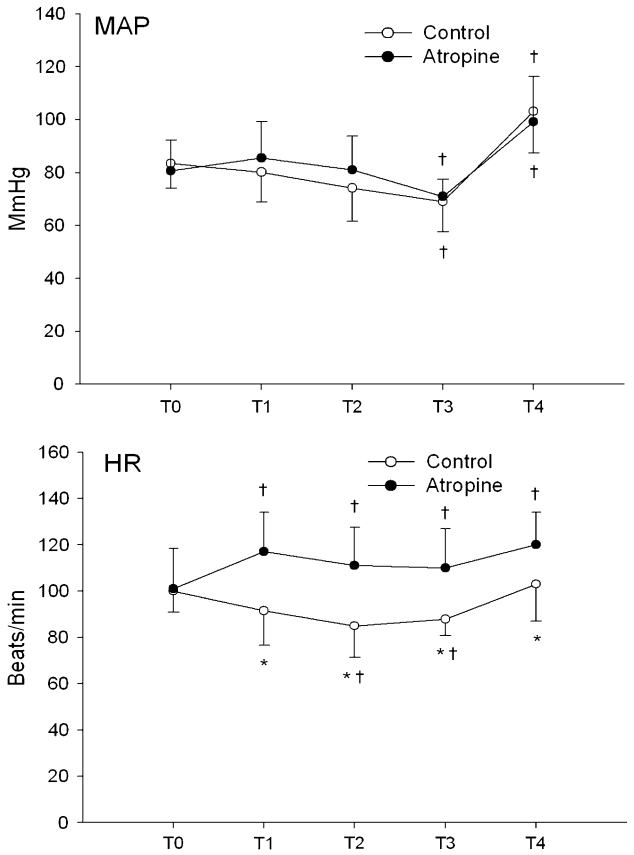

Fig. 2 Changes in mean arterial pressure (MAP) and heart rate (HR) during anesthesia induction. Each *error bar* indicates a standard deviation (SD). *T0* baseline value, *T1* after alfentanil administration, *T2* after the bolus dose of propofol, *T3* just before laryngoscopy, *T4* 1 min after intubation. $^{*}P < 0.05$ compared with the atropine group, $^{\dagger}P < 0.05$ compared with the baseline value (T0) within the group

tracheal intubation (T4) in both groups. HR was significantly higher in the atropine group than in the control group at all time points, except at T0 (all, $P < 0.001$). Compared with T0, HR was significantly decreased at T2 and T3 in the control group, and significantly increased after anesthesia induction (T1–4) in the atropine group. None of the patients experienced episodes of tachy- or bradyarrhythmia or hypotension requiring treatment during the study. None of the patients suffered from desaturation, truncal rigidity, or laryngospasm throughout the study.

Discussion

This study of pediatric patients has resulted, first, in the determination of the $Time_{EI}50$ for a low dose of rocuronium (0.3 mg/kg) that is required for successful tracheal intubation during i.v. anesthesia induction using propofol and alfentanil, and, second, in clinical evidence showing that atropine (10 μg/kg) can reduce the $Time_{EI}95$ of rocuronium. Notably, the 95 % CIs of the $Time_{EI}95$ values of the control and atropine groups did not overlap.

A previous study by Eikermann et al. [14] reported that during light sevoflurane anesthesia, high doses of rocuronium (0.5–1.0 mg/kg) did not result in further improvement of intubation conditions in children. They suggested that, with these high doses, the time for complete neuromuscular recovery is too long to be suitable for short pediatric procedures [14]. In this study, we selected the dose of rocuronium based upon a report by Oztekin et al. [15], who found the optimal rocuronium dose (0.3 mg/kg) for acceptable intubating conditions during propofol-remifentanil-based anesthesia induction in children when they evaluated the intubation conditions 90 s after rocuronium injection. In addition, a previous study of adults reported that a high proportion of optimal intubation conditions could be achieved at 2 min after the administration of a rocuronium dose of 0.3 mg/kg during anesthesia induction with propofol and alfentanil [16].

The onset time for rocuronium (0.3 mg/kg) has been reported to be 87.3 s (range 30–150 s) in healthy children under halothane anesthesia [17]. However, we found that the $Time_{EI}$ for successful tracheal intubation in 50 % of children was more than 2 min in both groups under i.v. anesthesia induction with rocuronium (0.3 mg/kg). One possible explanation for the different results may be that Driessen et al. [17] used halothane anesthesia, which dramatically increases the neuromuscular blockade and shortens the onset time of any muscle relaxant compared to intravenous anesthesia. Bartolek et al. [18] found that the onset time of rocuronium 0.45 mg/kg was 3.1 min in children when a volatile agent was not used. Another explanation may be the difference in the definition of successful tracheal intubation. In earlier studies, "excellent" and "good" intubating conditions were regarded as clinically "acceptable," whereas in the current study, successful intubation was defined as "excellent" intubating conditions [14, 19]. Indeed, Mencke et al. [20] reported that excellent conditions are less frequently associated with postoperative hoarseness and vocal cord sequelae. If this had been considered, the $Time_{EI}$ for low-dose rocuronium would have been shorter.

The onset of neuromuscular blocking agent action is reportedly influenced by the potency of the agent itself, the injected dosage, and circulation factors, which may influence its course to the neuromuscular junction [21]. An earlier study comparing the change in cardiac output before and after the administration of atropine demonstrated that i.v. atropine (10 μg/kg) could induce a significant increase in cardiac output during constant rate infusion of propofol in adult patients [22]. In this study, although cardiac output was not measured during anesthesia induction, HR was higher in the atropine group than in the control group

during the study period. Therefore, in this study, atropine may increase cardiac output, with resultant favorable effects on rocuronium as well as i.v. anesthetics.

In contrast to previous studies in children [15, 19], this study adopted a slightly different point of view, characterized by "time" rather than "dose." In pediatric anesthesia, reducing the time required for the mask ventilation is very important during anesthesia induction. The results of this study showed that determination of $Time_{EI}$ is possible using a small intubation dose of rocuronium (0.3 mg/kg) during propofol anesthesia in children. However, $Time_{EI}95$ for the groups was relatively long. Although atropine before anesthesia induction reduced $Time_{EI}95$ from 199 to 171 s in this study, this reduction in $Time_{EI}95$ was limited. Thus, if the 0.3 mg/kg dose of rocuronium is selected for endotracheal intubation, other combinations of larger doses of propofol and/or opioids or inhaled induction using high concentrations of sevoflurane, rather than i.v. atropine, might be clinically helpful to facilitate intubation conditions. Among opioids, alfentanil has a rapid onset of 1 min, which does not delay the induction time, and has a duration of 20–30 min, which can be ideal for short surgeries. Although remifentanil also has a fast onset and an even shorter duration of action, we chose alfentanil because it is less expensive and can be used as a bolus dose instead of an infusion.

There are several limitations to this study. One of them is the lack of cardiac output measurement. The hemodynamic effects of atropine may differ depending on the induction agents used as well as the chosen dose of atropine. Thus, further studies to elucidate the ideal dose of atropine along with quantitative measurements of the onset of neuromuscular block might be needed in children. Another limitation of this study is that we could not assess neuromuscular function due to frequent withdrawal movement associated with the injection of propofol or rocuronium. Although we administered alfentanil 10 μg/kg before propofol injection in order to reduce withdrawal movement, the incidence of withdrawal movement was 40 % in this study. Because neuromuscular function was not monitored in this study, we could not demonstrate the effect of atropine on the onset of rocuronium action. However, complete paralysis of the adductor pollicis muscle, the most frequent site at which neuromuscular blockade is measured, has been reported to be a poor indicator of intubation time [12].

In conclusion, the $Time_{EI}95$ of a low dose of rocuronium (0.3 mg/kg) that is required for excellent tracheal intubation was 199 s during i.v. anesthesia induction using propofol and alfentanil in children. Although i.v. atropine (10 μg/kg) before anesthesia induction reduced $Time_{EI}95$ by 28 s, further evaluation is required to elucidate whether atropine could facilitate the onset of rocuronium in children.

References

1. Stoddart PA, Mather SJ. Onset of neuromuscular blockade and intubating conditions one minute after the administration of rocuronium in children. Paediatr Anaesth. 1998;8:37–40.
2. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology. 2003;98:1042–8.
3. Meretoja OA. Neuromuscular block and current treatment strategies for its reversal in children. Paediatr Anaesth. 2010;20:591–604.
4. Fuchs-Buder T, Meistelman C, Schreiber JU. Is sugammadex economically viable for routine use. Curr Opin Anaesthesiol. 2012;25:217–20.
5. Nava-Ocampo AA, Velázquez-Armenta Y, Moyao-García D, Salmerón J. Meta-analysis of the differences in the time to onset of action between rocuronium and vecuronium. Clin Exp Pharmacol Physiol. 2006;33:125–30.
6. Tan CH, Onisong MK, Chiu WK. The influence of induction technique on intubating conditions 1 min after rocuronium administration: a comparison of a propofol-ephedrine combination and propofol. Anaesthesia. 2002;57:223–6.
7. Szmuk P, Ezri T, Chelly JE, Katz J. The onset time of rocuronium is slowed by esmolol and accelerated by ephedrine. Anesth Analg. 2000;90:1217–9.
8. Ezri T, Szmuk P, Warters RD, Gebhard RE, Pivalizza EG, Katz J. Changes in onset time of rocuronium in patients pretreated with ephedrine and esmolol—the role of cardiac output. Acta Anaesthesiol Scand. 2003;47:1067–72.
9. Stafford MA. Cardiovascular physiology. In: Motoyama EK, Davis PJ, editors. Smith's anesthesia for infants and children. 6th ed. St. Louis: C V Mosby Co.; 1996. p. 76–8.
10. McAuliffe G, Bissonnette B, Cavallé-Garrido T, Boutin C. Heart rate and cardiac output after atropine in anaesthetised infants and children. Can J Anaesth. 1997;44:154–9.
11. Dixon WJ. Staircase bioassay: the up-and-down method. Neurosci Biobehav Rev. 1991;15:47–50.
12. Viby-Mogensen J, Engbaek J, Eriksson LI, Gramstad L, Jensen E, Jensen FS, Koscielniak-Nielsen Z, Skovgaard LT, Ostergaard D. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand. 1996;40:59–74.
13. Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology. 2007;107:144–52.
14. Eikermann M, Renzing-Köhler K, Peters J. Probability of acceptable intubation conditions with low dose rocuronium during light sevoflurane anaesthesia in children. Acta Anaesthesiol Scand. 2001;45:1036–41.
15. Oztekin S, Hepaguşlar H, Kilercik H, Kar AA, Boyaci F, Elar Z. Low doses of rocuronium during remifentanil-propofol-based anesthesia in children: comparison of intubating conditions. Paediatr Anaesth. 2004;14:36–41.
16. Barclay K, Eggers K, Asai T. Low-dose rocuronium improves conditions for tracheal intubation after induction of anaesthesia with propofol and alfentanil. Br J Anaesth. 1997;78:92–4.
17. Driessen JJ, Robertson EN, Van Egmond J, Booij LH. Time-course of action of rocuronium 0.3 mg kg^{-1} in children with and without endstage renal failure. Paediatr Anaesth. 2002;12:507–10.
18. Bartolek D, Jakobović J, Bartolek F, Finci D, Munjiza A. Reduced-dose rocuronium for day-case tonsillectomy in children where volatile anaesthetics are not used: operating room time saving. Paediatr Anaesth. 2010;20:47–55.

19. Eikermann M, Hunkemöller I, Peine L, Armbruster W, Stegen B, Hüsing J, Peters J. Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children. Br J Anaesth. 2002;89:277–81.
20. Mencke T, Echternach M, Kleinschmidt S, Lux P, Barth V, Plinkert PK, Fuchs-Buder T. Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. Anesthesiology. 2003;98:1049–56.
21. Donati F. Onset of action of relaxants. Can J Anaesth. 1988; 35:S52–8.
22. Takizawa E, Takizawa D, Al-Jahdari WS, Miyazaki M, Nakamura K, Yamamoto K, Horiuchi R, Hiraoka H. Influence of atropine on the dose requirements of propofol in humans. Drug Metab Pharmacokinet. 2006;21:384–8.