Original Article

Determination of dose and efficacy of atracurium for rapid sequence induction of anesthesia: A randomised prospective study

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Abstract

Background and Aims: Succinylcholine and high dose rocuronium are neuromuscular blocking agents commonly used for rapid sequence induction of anesthesia. Their usage is limited or contraindicated in some circumstances. The aim of this study is to determine the dosage and efficacy of atracurium without priming for rapid sequence induction of anesthesia.

Material and Methods: One hundred fifteen surgical patients under general anesthesia were randomised into three groups. All patients were given 2-3 mg/kg propofol and 1 μg/kg fentanyl intravenously for the induction of anesthesia followed by different doses of atracurium (0.6 mg/kg, 0.75 mg/kg or 1 mg/kg) without a priming dose. Tracheal intubation was performed within one minute after the administration of the study drugs. The intubating conditions, vocal cord movement and diaphragm movement were graded as the primary endpoints. Statistical analysis was done using one-way analysis of variance (ANOVA) and *Post Hoc* tests.

Results: Atracurium doses of 1 mg/kg, 0.75 mg/kg, and 0.6 mg/kg provided 51.4%, 43.6% and 26.3% success rates of intubation without coughing or bucking, respectively ($P = 0.03$). The intubating conditions were graded as excellent or good in 86.5% of the 1 mg/kg atracurium group patients and in 84.6% of the 0.75 mg/kg group patients ($P < 0.05$). An atracurium dose of 1 mg/kg facilitated significant differences in vocal cord and diaphragm paralysis compared with the dose of 0.6 mg/kg ($P = 0.03$).

Conclusion: The administration of a relatively high dose of atracurium without priming can be used as an alternative neuromuscular blocking agent for rapid sequence induction of anesthesia in some circumstances.

Keywords: Atracurium, muscle relaxant, rapid intubation, rapid sequence induction

Introduction

Rapid sequence induction (RSI) of anesthesia, commonly used in emergency settings, requires rapid tracheal intubation to minimize the risk of aspiration and hypoxia. Succinylcholine and high dose rocuronium have been established as standard neuromuscular blocking agents (NMBAs) because of their short and reliable onset of action. However, in some circumstances, succinylcholine is contraindicated for hyperkalemic patients as well as in patients with increased intracranial pressure (ICP) or intraocular pressure (IOP).[1,2] Rocuronium should be avoided in patients with renal impairment because of potentially prolonged excretion and residual neuromuscular

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blockade.[3,4] Atracurium is safe for use in renal failure patients and does not affect ICP or IOP.[2,5]

The onset of action of the recommended dose of atracurium for tracheal intubation is approximately 3 minutes.[5] The speed of onset of NMBAs is inversely correlated to their potency.[6] A previous study showed that the potency of atracurium was similar to rocuronium.[6] Therefore a higher dose of atracurium, approximately 3-4 times its ED95, would facilitate rapid tracheal intubation compared with a high dose of rocuronium. In a previous study, the timing principle method using a bolus of high dose atracurium prior to the induction agents satisfactorily demonstrated rapid tracheal intubation.[7] However, patients could experience discomfort, difficulty breathing and coughing, diplopia or awareness during the induction of anesthesia. The priming technique of administering 0.04-0.06 mg/kg atracurium 2-3 minutes prior to a single bolus dose facilitated rapid intubation in 1-2 minutes.[8,9] The timing principle or the priming technique is contraindicated in patients with increased risk of gastric aspiration or in uncooperative patients. Rapid sequence induction using high dose atracurium without the priming technique lacks supporting clinical data.

The advantages of atracurium include its renal-independent elimination, no cumulative effects with repeated dosing.[10,11] Thus, this randomised double-blind prospective study aims to determine the dosage and efficacy of high dose atracurium in combination with propofol and fentanyl for rapid sequence induction of anesthesia.

Material and Methods

The protocol for this study was approved by the Institutional Review Board and complied with the Declaration of Helsinki guidelines. This manuscript adheres to the applicable CONSORT guideline. Informed consent was obtained from 115 patients with ASA physical status I and II undergoing elective surgery under general anesthesia. The exclusion criteria were patients aged <20 or >65 years old, emergency cases, unstable hemodynamic status, neuromuscular disease, asthma, potentially difficult intubation, chronic use of anticonvulsants, and BMI >30 kg/m^2. The patients were randomised using block randomization with randomly selected block sizes into three groups. The anesthesiologist (W.T.) enrolled patients and prepared a 10-ml syringe of atracurium according to the sequential number. Each group received different doses of atracurium which were 0.6 mg/kg (2ED95), 0.75 mg/kg (3ED95) and 1 mg/kg (4ED95). In the operating room, the patients were not pre-medicated and received standard monitoring. After 3-minute pre-oxygenation with 100% high flow oxygen, all patients were given 2-3 mg/kg of propofol and 1 μg/kg of fentanyl intravenously for the induction of anaesthesia, immediately followed by different doses of atracurium. The patients remained apneic for one minute and face mask ventilation were allowed if desaturation occurred. Intubation was performed by trained anesthesiologists within one minute after the administration of the study drugs using a video laryngoscope. The two attending anesthesiologists who were blinded to the atracurium doses graded the intubating conditions as the primary endpoint. The intubating conditions were graded into 4 conditions: excellent (easy passage of the tube without coughing/bucking), good (passage of the tube with slight coughing/bucking), fair (passage of the tube with moderate coughing/bucking), and poor (not possible to intubate). The vocal cord and diaphragm movement during intubation also were rated into 4 conditions: excellent (totally paralyzed), good (partially paralyzed with slight movement), fair (partially paralyzed with moderate movement), and poor (unparalyzed diaphragm with vocal cords closed). The peripheral nerve stimulation was performed using a TOF-Watch®SX (Organon Ltd., Dublin, Ireland) placed along the ulnar nerve with the transducer against the thumb for assessing the degree of neuromuscular blockade. A Train-of-four (TOF) measurement, or the number of muscle twitches, represented the muscle function. The adductor pollicis muscle responding to TOF under the 50-mA current stimulation was monitored every 12 seconds from the onset of the induction of anesthesia until measurements reached zero. Then a post-tetanic count (PTC) equal to zero was used to confirm the maximum onset of action. After that, TOF stimulation was recorded every five minutes until two twitches were presented indicating the spontaneous recovery time. General anesthesia was maintained by inhaled anesthetic agents and no restriction on intraoperative pain medications usage until the end of operation. The blood pressure, heart rate and pulse oximeter were recorded every minute for 10 minutes, followed by monitoring every five minutes after the induction of anesthesia. The adverse effects of atracurium due to histamine release, such as cutaneous flushing, rash, bronchospasm and hypotension were closely observed. If patients developed sustained high airway pressure, wheezing, desaturation, or unacceptable hypotension, then the proper management was performed.

Statistical analysis

The sample size was calculated using the tests of proportions' formula according to the binary outcome. The power analysis was performed using the probability of excellent intubation with the standard dose of atracurium[7] with 15% minimum clinical difference and 90% power. A sample size

of 35 patients per group was required, resulting in the total of 115 patients, including a 10% drop out rate. Categorical data were compared using the Chi-square test or Fisher's exact test. Continuous data between groups were analyzed by one-way analysis of variance (ANOVA) and *Post Hoc* tests using SPSS version 22 (SPSS, Inc., Chicago, IL, USA). Vital signs were analyzed by a general linear model using Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). A P value of <0.05 was considered a statistically significant difference.

Results

One hundred fifteen surgical patients were prospectively randomised in this study between September 2017 to January 2018 [Figure 1]. One patient in the 1 mg/kg atracurium group was excluded because of difficulty with mouth opening, which prevented intubation within one minute. As such, data analysis was obtained from 38, 39 and 37 patients receiving atracurium doses of 0.6 mg/kg, 0.75 mg/kg and 1 mg/kg, respectively. Demographic data and patient characteristics are shown in Table 1. The primary outcome of the study is the intubating condition at one minute, as shown in Table 2. Atracurium dose of 1 mg/kg provided significantly higher success rate of intubation than 0.6 mg/kg. In addition, 1 mg/kg atracurium facilitated a significant difference in vocal cord and diaphragm paralysis compared with a dose of 0.6 mg/kg ($P = 0.03$). The vocal cord and diaphragm were clinically paralyzed in 94.9% and 89.7% of patients following administration of 1 mg/kg atracurium, in 94.6% and 89.2% of patients following 0.75 mg/kg atracurium, and 81.6% and 71.1% following 0.6 mg/kg atracurium doses.

The higher dose of atracurium provided a faster onset of action and a longer spontaneous recovery time [Table 3]. A dose of 1 mg/kg atracurium caused a significant decrease in the mean arterial pressure at 3 and 4 minutes after the induction of anesthesia compared with the lower doses [Figure 2]. However, when compared with the baseline mean arterial blood pressure, there was no significant change in these 3 groups. Heart rates following the highest dose significantly increased by approximately 6-10 bpm (8.4-10.6%) during 5-15 minutes after the induction of anesthesia compared with the other doses ($P < 0.05$) [Figure 3]. However, these significant changes did not persist.

There were no serious adverse effects (bronchospasm, severe hypotension) from the highest dose of atracurium as well as no desaturation was reported. Cutaneous flushing of the face and upper trunk was the most common adverse effect and resolved spontaneously within 10 minutes. The incidences of cutaneous flushing were similar among the three study groups which were 28.9%, 17.9% and 21.6% following atracurium doses of 0.6 mg/kg, 0.75 mg/kg, and 1 mg/kg, respectively.

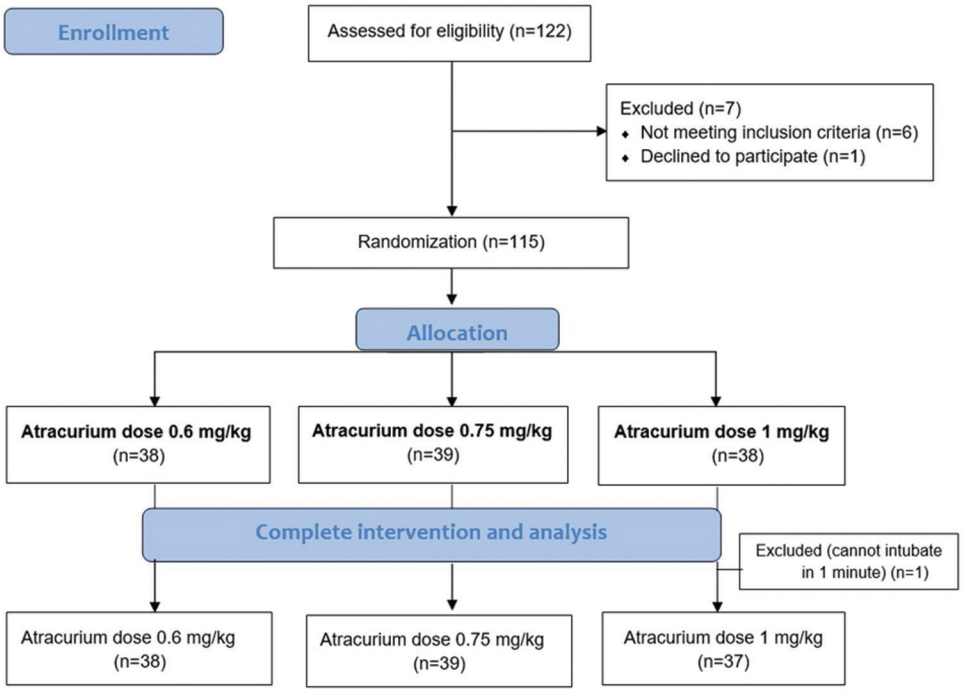

Figure 1: A CONSORT flow diagram of the study

Table 1: Baseline patient characteristics

	Atracurium dose 0.6 mg/kg (*n*=38)	Atracurium dose 0.75 mg/kg (*n*=39)	Atracurium dose 1 mg/kg (*n*=37)
Age (year)	44.1±13.5	48.9±10.2	47.8±11.3
Gender			
Female	31 (81.6)	26 (66.7)	31 (83.8)
Weight (kg)	60.6±13.0	62.0±11.7	56.2±9.1
Height (cm)	160.4±7.0	161.3±8.5	159.8±7.3
BMI (kg/m^2)	23.5±4.0	23.6±3.1	22.0±2.8
ASA physical status			
I	18 (47.4)	24 (61.5)	29 (78.4)
II	20 (52.6)	15 (38.5)	8 (21.6)
Operations			
Breast surgery	11 (28.9)	15 (38.5)	16 (43.2)
Thyroid surgery	5 (13.2)	5 (12.8)	5 (13.5)
Laparoscopic surgery	14 (36.8)	8 (20.5)	14 (37.8)
Exploratory laparotomy	2 (5.3)	6 (15.4)	1 (2.7)
Colostomy	2 (5.3)	1 (2.6)	0 (0)
Others	4 (10.5)	4 (10.3)	1 (2.7)

Value presented as mean±SD. and frequency (%).

Table 2: Intubating conditions

Intubating conditions	Atracurium 0.6 mg/kg (*n*=38)	Atracurium 0.75 mg/kg (*n*=39)	Atracurium 1 mg/kg (*n*=37)
Poor Not possible to intubate	2 (5.3)	0 (0)	2 (5.4)
Fair Passage of tube with moderate coughing/bucking	13* (34.2)	6 (15.4)	3* (8.1)
Good Passage of tube with slight coughing/bucking	13 (34.2)	16 (41)	13 (35.1)
Excellent Easy passage of tube without coughing/bucking	10† (26.3)	17 (43.6)	19† (51.4)

*Value presented as frequency (%). *1 mg/kg vs 0.6 mg/kg: P=0.01. †1 mg/kg vs 0.6 mg/kg: P=0.03*

Table 3: The maximum effect and the duration of action of atracurium according to the peripheral nerve stimulator

	Atracurium 0.6 mg/kg (*n*=38)	Atracurium 0.75 mg/kg (*n*=39)	Atracurium 1 mg/kg (*n*=37)
Time until PTC=0 (sec)	232.3±113.1*†	191.1±58.1*†	144.2±57.7*
Time until TOF counts=2 (min)	63.5±11.8*†	70.7±13.9*†	80.9±14.3*

*Value presented as mean±SD. PTC=Post-tetanic count, TOF: Train-of-four. *1 mg/kg vs 0.75 mg/kg and 0.6 mg/kg: P<0.01. †0.75 mg/kg vs 0.6 mg/kg: P<0.05*

Discussion

The incidence of clinically acceptable intubating conditions with 1 mg/kg, 0.75 mg/kg and 0.6 mg/kg atracurium were 86.5%, 84.6%, and 60.5%, respectively. Concerning the atracurium-evoked histamine release, only cutaneous flushing was reported which spontaneously resolved and did not clinically affect the patients' hemodynamic status.

Regarding rapid tracheal intubation, succinylcholine provides similar intubation conditions to 1.2 mg/kg rocuronium.[12] A previous study showed that rocuronium clearance was reduced by 39% in renal failure patients and the duration of the residual blockade was increased up to 84% compared with patients with normal kidney function.[13] Although sugammadex is effective in reversing neuromuscular blockade by rocuronium, the recovery time is more prolonged in patients with chronic renal failure.[4,14] Therefore, atracurium is an alternative NMBA because of its elimination via ester hydrolysis and Hofmann degradation. The potency of rocuronium and atracurium are 1.0 and 1.2, respectively,[6] suggesting that an atracurium dose of 1 mg/kg (4ED95) may be comparable with a rocuronium dose of 1.2 mg/kg (4ED95).

Atracurium at a dose of 0.8 mg/kg with or without a priming dose had shorter onset time and allowed rapid intubation within 90 seconds.[15] Another previous study using the

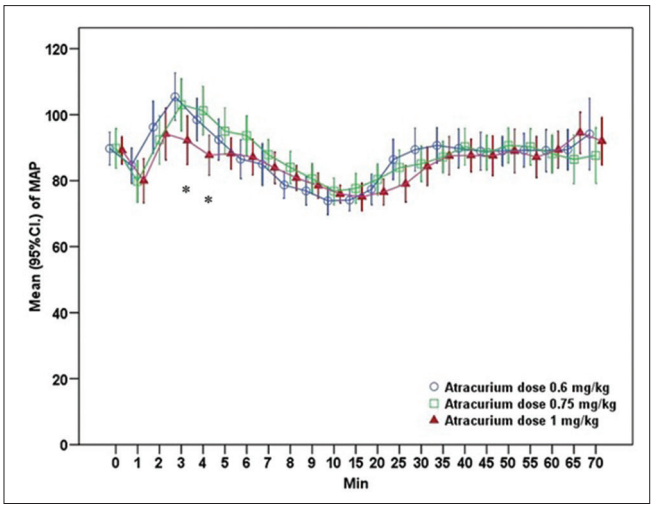

Figure 2: Mean arterial pressure (mmHg) of different doses of atracurium

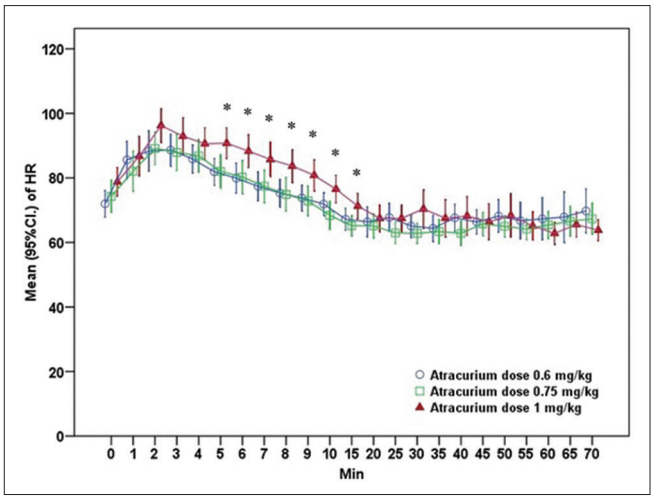

Figure 3: Heart rate (beats per minute) of difference doses of atracurium

timing principle by the bolus of a high dose of atracurium prior to induction resulted in satisfactorily rapid tracheal intubation.[7] However, there were reports of weakness and cough inhibition during induction. Alternatively, the priming technique using 0.1 mg/kg rocuronium one minute prior to administration of 0.42 mg/kg atracurium provided good to excellent intubating conditions in 91% of patients.[16] The clinical limitations of the timing principle and the priming technique are the increased risk of gastric aspiration. Rocuronium-atracurium mixtures have been reported to possess synergistic or additive activity, resulting in faster onset and longer duration of action.[17] Overall, the success of rapid tracheal intubation with those techniques were poor and may not be clinically applicable. In our study, co-administration of propofol and fentanyl immediately prior to the NMBAs could suppress laryngeal reflex, thus facilitating satisfactory intubating conditions in 86.5% of patients one minute after administration. However, the effect of the induction agents was minor as the control group (0.6 mg/kg) showed only 26.3% of patient with excellent intubating condition. In addition, the vocal cord and diaphragm were clinically paralyzed in 94.9% and 89.7% of patients, respectively, following 1 mg/kg atracurium. These results support the use of a high dose of atracurium for rapid tracheal intubation.

A previous study in burn population showed that 1 mg/kg atracurium provided excellent and good intubating condition in 60% and 40% of patients, respectively.[9] However, intubation was performed in 2 minutes in which rapid sequence induction of anesthesia was not applied. The higher dose of atracurium provided significantly faster onset of action and prolonged spontaneous recovery time. In this study, the spontaneous recovery time was monitored by the presence of TOF = 2 as the timing for less intense neuromuscular blockade.[18] The actual duration of action of high dose atracurium could not be identified because of the ongoing surgery. For 1 mg/kg atracurium, the spontaneous recovery time was 80.86 ± 14.26 minutes in this study, compared with the duration of action which was 57 minutes in a previous study.[19] Our study demonstrated that the use of a high dose of atracurium for rapid tracheal intubation was suited for surgical procedures lasting more than 60 minutes. A previous study showed that onset time and recovery time of atracurium were affected by age and gender.[20,21] Women have shorter onset times and longer recovery times than men. We unintentionally recruited more women and this might affect the outcome.

There has been concern regarding decreased blood pressure from histamine release after a bolus of high dose atracurium. The highest dose (1 mg/kg) showed a statistically significant decrease in mean arterial pressure within 3-4 minutes and significantly increased within 5-15 minutes after induction compared with the other lower doses. Tachycardia probably resulted from the compensation of decreased systemic vascular resistance because of histamine release. A previous study found the same hemodynamic pattern regarding mild hypotension and tachycardia after administration of high dose atracurium.[7,9,22] In our study, the mild hypotension observed was not clinically significant and appeared to counteract sympathetic stimulation during laryngoscopy. In addition, the mean arterial pressure (MAP) among the three groups did not change compared with baseline values. The most common adverse effect regarding histamine release was cutaneous flushing. A previous study reported that cutaneous flushing was dose-dependent, with higher incidence rates of 40-60%.[7,9] Atracurium increased plasma histamine levels by 234% and 148% at 1 minute and 3 minutes, respectively, and returned to baseline levels within 5 minutes without any treatment.[22] In our study, the occurrence of cutaneous flushing was low, and resolved spontaneously.

The limitation of this study was the recruitment of patients with ASA physical status I or II, therefore, changes in hemodynamic status due to high dose atracurium may be underestimated. Other limitations include the exclusion of patients with anticipated difficult intubation or with BMI >30 kg/m^2. Future studies evaluating this technique in emergency scenarios as well as a comparison with high dose rocuronium in terms of intubating conditions and spontaneous recovery time are required.

In conclusion, a significant dose-dependent success rate of intubation was observed. At 1 mg/kg, atracurium facilitated a significant difference in vocal cord and diaphragm paralysis. The onset of maximal effect was dose-dependent. Cutaneous flushing was the most common adverse effect, but this effect resolved without intervention.

Ethical committee approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB number 294/59). This study was registered prior to patient enrolment at clinicaltrials.in.th (Thai Clinical Trials Registry number TCTR20170912003, Principle investigator: Pornpan Chalermkitpanit, Date of registration: 12/9/2017).

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Conflicts of interest

There are no conflicts of interest.

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