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조선대학교 대학원

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지도교수 : 유 병 식

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Cisatracurium의 발현시간과 기관내삽관 상태에 대한 저농도 ketamine과 cisatracurium의 애벌 효과

안병량

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의학과

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배경: 케타민 주사와 근이완제의 애벌요법은 근이완제의 발현시간을 빠르게 하며 기관내삽관을 용이하게 한다. 본 연구는 저농도의 ketamine 주사요법과 cisatracurium 애벌요법을 시행하여 근이완제의 발현시간과 기관내삽관에 미치는 영향을 비교하였다.

대상 및 방법: 윤리위원회의 승인을 받은 후, 미국마취과학회 신체등급 I 또는 II에 속하는 120명의 전신마취가 예정된 환자를 무작위로 4개의 군으로 나누었다. 마취유도를 시행하기 전에 생리식염수를 정주한 C군 (n = 30), cisatracurium 0.01 mg/kg을 정주한 P군 (n = 30), ketamine 0.5 mg/kg을 정주한 K군 (n = 30) 그리고 cisatracurium 0.01 mg/kg과 ketamine 0.5 mg/kg을 같이 투여한 PK군 (n = 30) 으로 분류하였다. 3분 후 C와 K군은 cisatracurium 0.15 mg/kg를 투여하였고 P와 PK군은 0.14 mg/kg의 cisatracurium을 투여하였다. 근이완의 발현시간과 60초 후 기관내삽관의 상태를 평가하였다.

결과: 근이완 발현시간은 PK군에서 다른 군에 비해 현저한 감소를 보였으며 ($P < 0.05$), 평균값은 C, P, K, 그리고 PK군에서 각각 111.5 (80.0 - 134.0), 91.0 (64.0 - 121.0), 85.0 (60.0 - 110.0), 59.0 (45.0 - 74.0) 초였다. 기관내삽관의 상태는 P, K 그리고 PK군에서 C군에 비해 의미있는 개선을 보였으며 ($P < 0.008$) 특히 PK군에서 타군에 비해 현저한 기관내삽관 상태의 개선을 보였고 발현시간의 단축을 보였다 ($P < 0.008$).

결론: 저농도의 ketamine 주사요법과 cisatracurium 애벌요법의 병용은 cisatracurium 근이완의 발현시간을 단축시키고 기관내삽관 상태를 개선시키는데 효과적인 방법이다.

키워드: 기관내삽관, 발현시간, 애벌요법, cisatracurium, ketamine.

Introduction

In the past, succinylcholine was usually used for rapid intubation of general anesthesia. Although it is suitable for this purpose, its many potential complications have led to searching for an alternatives and new neuromuscular blocking agents (NMBAs) for rapid intubation. However, these NMBAs do not provide the satisfactory rapid tracheal intubating conditions in every situation because of their different pharmacologic properties. One of pharmacologic properties, the onset time of NMBAs is an important factor during a rapid sequence induction. Therefore, many efforts have been made to use the existing MNBAs by reducing onset time. In these efforts, priming of NMBAs, administration of a small dose of the drug before the larger intubating dose, was commonly used to hasten the onset time [1-4]. Other focus to reduce the onset time was on modifying hemodynamic factors such as cardiac output, circulation time and perfusion of muscles [2]. Its supporting hypothesis was that induction agents that increased cardiac output and perfusion of muscles can reach the NMBAs to the neuromuscular junction more rapidly, and it result in hastening of the onset time [5, 6].

Recent articles have been reported that ketamine was associated with better intubating conditions, resulting from the increase of the cardiac output [5, 7, 8]. However, there was controversy in the effect of ketamine on the onset time of rocuronium [5, 7, 8]. Cisatracurium and rocuronium are relatively recently introduced non-depolarizing muscle relaxants. Although they have similar hemodynamic effects, cisatracurium has a relatively long onset time that discourages rapid-sequence induction [9-12].

The author hypothesized that low dose ketamine would improve intubating conditions after cisatracurium while hastening the onset time, and priming of cisatracurium also improve them further more. The purpose of this study was to investigate the effects of both low dose ketamine and priming, given before the induction of anesthesia, on the onset time of cisatracurium and the intubating conditions.

Materials and Methods

The institutional Ethics Committee approved this prospective randomized placebo-controlled trial. Written informed consent was obtained from all patients. Author recruited the American Society of Anesthesiologists (ASA) physical status I or II patients, aged 18-65 years, scheduled for elective surgery. The study protocol adhered to the published guidelines on pharmacodynamic studies of NMBA. Patients with an allergy to cisatracurium, neuromuscular disease, expected difficult mask ventilation or intubation, receiving medications known to influence neuromuscular function (for instance, calcium channel blocker, aminoglycosides or phenytoine), electrolyte abnormalities, hepatic or renal insufficiency, a body mass index < 19 or > 28, and pregnant or breast feeding women were excluded from the study subjects.

All patients were premedicated with midazolam 0.05mg/kg, intramuscularly, 30 min before anesthesia. Standard monitoring included an ECG, noninvasive blood pressure, end-tidal partial pressure of carbon dioxide, and peripheral pulse oximetry. Study medications were produced and randomized (using a random number table) by the non-investigable nurse as indistinguishable, numbered syringes.

All patients were allocated to one of four groups of 30 patients each. They were injected one of normal saline (group C), cisatracurium 0.01 mg/kg (group P), ketamine 0.5 mg/kg (group K) and combination of cisatracurium 0.01 mg/kg and ketamine 0.5 mg/kg (group PK) diluted into a 5 ml solution. Anesthesia was induced with the targeted effect-site concentration of propofol 4 μg/ml, followed 3 min later by cisatracurium 0.15 mg/kg in group C and K, and 0.14 mg/kg cisatracurium in priming groups. For the maintenance of anesthesia, a propofol effect-site concentration of 3 ± 2 μg/ml with 50% oxygen air mixture was used. Time sequence of laryngoscopy and intubation should be clearly recorded. For example, when intubation is planned to be carried out at 1 min, laryngoscopy should be started at 50 sec and intubation carried out at 60 sec, being completed within 20 sec. To

avoid vocal cord injury, tracheal intubation was not attempted if the vocal cords were fully closed, in which case, intubation was reattempted 30 sec later. The intubating conditions were evaluated by the criteria established by Fuchs-Buder et al. (Table 1)[13].

Neuromuscular function was assessed by electromyography of the adductor pollicis on the opposite side to blood pressure cuff and intravenous line with a single twitch using the neuromuscular transmission module and was displayed on an anesthetic monitoring system (Anesthetic Monitoring System S/5™, Datex-Ohmeda Inc., Helsinki, Finland). Surface electrodes were placed on cleaned skin over the ulnar nerve on the volar side of the wrist. The arm was kept in the same position during the whole study procedure. The stimulus current needed to achieve the maximal response of the adductor pollicis muscle was automatically searched in each patient. It began with 10 mA single twitch stimuli of 0.2 ms duration applied every 1 sec in steps of 5 mA. And then, the stimulating current was automatically increased by 15% to produce a supramaximal current. If the supramaximal current was not found or the response was too weak, the current was set at 70 mA. Each patient's supramaximal stimulation was applied with 0.2 ms duration square waves (1 sec interval, 2 Hz). After having obtained stable baseline measurements and induction of anesthesia, a bolus dose of cisatracurium 0.14 or 0.15 mg/kg was administered intravenously. Measurements were recorded by single twitch method or computed as follows: (1) the time in sec from the start of injection of cisatracurium until the first change of single twitch response (lag time; LT); (2) the time in sec from the start of injection of cisatracurium until 95% depression of the single twitch (Onset time, OT).

Sample size was calculated that 30 patients per group were required with a 0.05 level of significance and 80% power to detect at least a 50% difference between the control group and any of the other three groups with respect to good and excellent intubating conditions.

SPSS (Windows ver. 19.0, SPSS Inc., Chicago, IL) was used for statistical analysis. All the values that were measured were summarized by descriptive

statistics (number of patients, mean ± standard deviation or medians and ranges) or frequency distributions (number of patients and percentages), as appropriate. For height, weight, and supramaximal current, one-way ANOVA test was used and if a significant difference was found, a Bonferroni Post-Hoc test was used. For gender, χ^2 tests were used for analysis. For all data except of gender, height, weight and supramaximal current, Kruskal-Wallis test was used and if a significant difference was found, Mann-Whitney test for Post-Hoc test was used. P values < 0.05 for gender, height, weight and supramaximal current, and P values < 0.008 for others using a non-parametric test were considered statistically significant.

Results

A total of 120 patients received the assigned study treatment and no patients were withdrawn due to refusal, missed data and adverse effects during the study. No significant differences in age, gender, height, weight and supramaximal current were found among all the groups (Table 2).

There was most significant hasten in Group PK than others on the lag time and onset time ($P < 0.008$). There was also significantly more hastened in Group P and K compared with Group C ($P < 0.008$), but there was no differences between group P and K(Fig. 1).

In intubating conditions, 'excellent' was most significantly higher in Group PK (70%) than others (3.3, 36.7 and 26.7% in Group C, P and K, respectively) ($P < 0.008$) and significantly higher in Group P and K compared with Group C ($P < 0.008$). However, there were no differences between group P and K (Fig. 2).

Table 1. Assessment of intubating conditions(according to Fuchs-Buder et al. [13])

Evaluation of intubating conditions *.

Variable assessed	Clinically acceptable		Not clinically acceptable
	Excellent	Good	Poor
1. Laryngoscopy #	Easy	Fair	Difficult
2. Vocal cord position	Abducted	Intermediate /moving	Closed
3. Reaction to insertion of the tracheal tube and cuff inflation (Diaphragmatic movement/coughing)	None	Slight+	Vigorous /sustained ‡

*Intubation conditions

Excellent: all qualities are excellent

Good: all qualities are either excellent or good

Poor: the presence of a single quality listed under `poor`

#Laryngoscopy

Easy: jaw relaxed, no resistance to blade insertion

Fair: jaw not fully relaxed slight resistance to blade insertion

Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy.

+One to two weak contractions or movement for less than 5 sec.

‡More than two contractions and/or movement for longer than 5 sec.

Table 2. Demographic data and supramaximal current.

	Group C (n = 30)	Group K (n = 30)	Group P (n = 30)	Group PK (n = 30)
Gender (M/F)	20/10	17/13	15/15	13/17
Age (year)	44.9 ±12.5	42.6 ± 14.6	41.3 ± 13.5	45.9 ± 8.3
Height (cm)	165.9 ± 10.0	167.6 ± 8.2	165.0 ± 10.1	161.5 ± 9.2
Weight (kg)	66.7 ± 10.4	65.7 ± 11.1	63.9 ± 13.9	63.4 ± 13.4
Supramaximal current (mA)	35.8 ± 8.1	35.0 ± 9.4	36.3 ± 11.2	30.9 ± 7.6

Values are expressed as mean ± SD, numbers of patient. There are no significant differences between groups. Groups divided according to injection of normal saline (group C), cisatracurium 0.01 mg/kg (group P), ketamine 0.5 mg/kg (group K) and combination of cisatracurium 0.01 mg/kg and ketamine 0.5 mg/kg (group PK) diluted into a 5 ml solution.

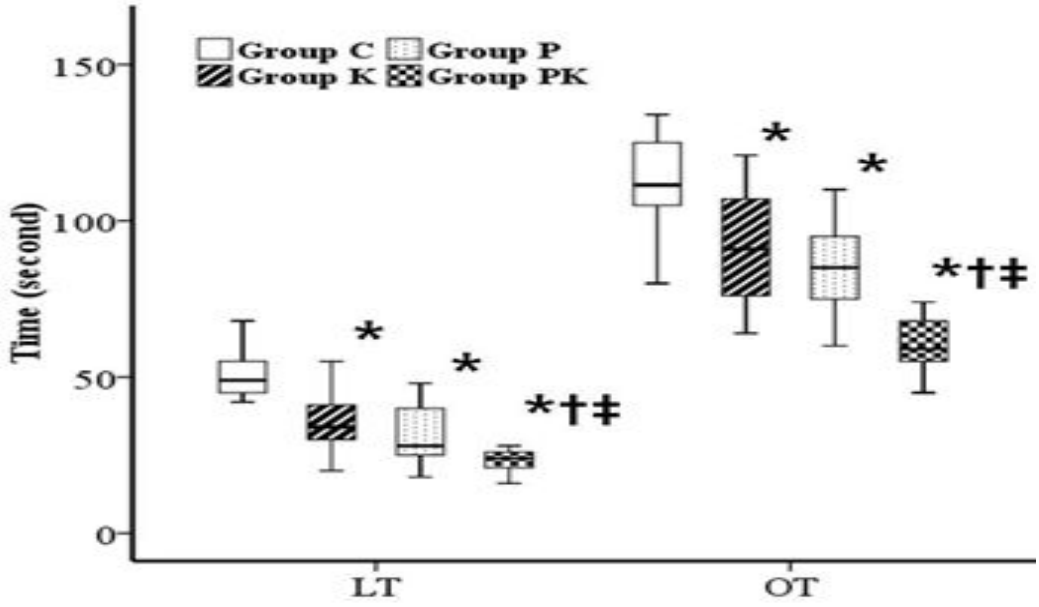

Fig. 1. Lag time (LT) and onset time (OT). There was most significant hasten in Group PK than others on the lag time and onset time. There was also significantly more hastened in Group P and K compared with Group C, but there were no differences between group P and K. LT is the time in sec from the start of injection of cisatracurium until the first change of single twitch response. OT is the time until 95% depression of the single twitch. Groups divided according to injection of normal saline (group C), cisatracurium 0.01 mg/kg (group P), ketamine 0.5 mg/kg (group K) and combination of cisatracurium 0.01 mg/kg and ketamine 0.5 mg/kg (group PK) diluted into a 5 ml solution.

*: $P < 0.008$ vs. Group C.

+: $P < 0.008$ vs. Group P.

‡: $P < 0.008$ vs. Group K (Mann-Whitney test).

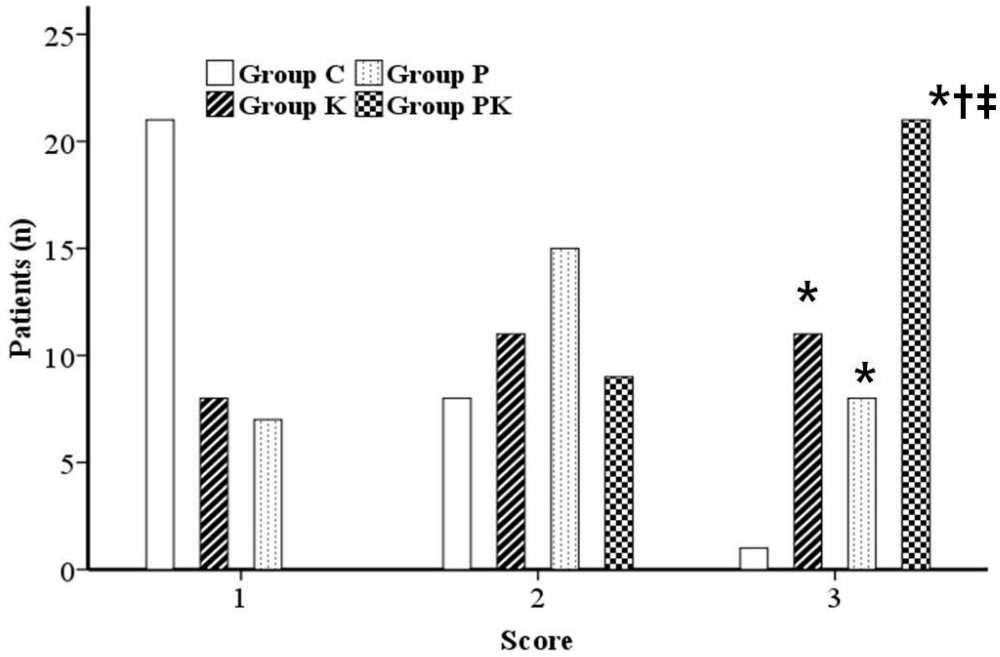

Fig. 2 Intubating conditions at 60 sec after cisatracurium administration. 'Excellent' was most significantly higher in Group PK without poor intubating conditions than others, and also significantly higher in Group P and K compared with Group C. However, there were no differences between group P and K. 1= Poor, 2 = good, 3 = Excellent. Groups divided according to injection of normal saline (group C), cisatracurium 0.01 mg/kg (group P), ketamine 0.5 mg/kg (group K) and combination of cisatracurium 0.01 mg/kg and ketamine 0.5 mg/kg (group PK) diluted into a 5 ml solution.

*: P < 0.008 vs. Group C.

†: P < 0.008 vs. Group P.

‡: P < 0.008 vs. Group K (Mann-Whitney test).

Discussion

In this study, low dose ketamine, priming of cisatracurium or the combination of both agents was showed to improve the intubating conditions and hasten the onset time of cisatracurium, especially the combination of low dose ketamine (0.5 mg/kg) and priming (0.01 mg/kg cisatracurium) provided the intubating conditions and the shorter onset time as enough as for rapid tracheal intubation. There were no signs of muscular weakness, evidences of respiratory difficulty and adverse effects related to ketamine administration.

Intubating condition can be influenced by physiologic factors, such as the onset time of NMBAs itself, cardiac output and perfusion of muscles. Cardiac output, one of these factors, can be maintained by administration of agents such as ephedrine, etomidate and ketamine. Hans et al.[5] reported that high dose (2.5 mg/kg) of ketamine for induction of anesthesia provided the excellent and good intubating conditions in 100% of patients one min after 0.6 mg/kg rocuronium injection. They suggested that the better condition in ketamine pretreatment resulted from either better laryngeal relaxation or a deeper level of anesthesia, and higher cardiac output could shorten the onset time of NMBAs despite there was not significant different. Baraka et al.[7] also demonstrated that 1.5 mg/kg ketamine could provide the excellent or good intubating condition in all patients, but could not significantly shorten the onset time of NMBAs. In a similar study, they demonstrated that the combination of the priming and low dose ephedrine provided better intubating conditions compared with the other groups at 60 sec after 0.15 mg/kg cisatracurium [14]. However, many previous reports reveal that the priming of cisatracurium shortened the onset time of cisatracurium [15, 16]. Deepika et al. [16] showed that the priming with 0.01 mg/kg, followed by the 0.14 mg/kg cisatracurium provided good to excellent intubating conditions in all patients and can offer an onset time comparable to or faster than the recommended dose of 0.2 mg/kg. Topcuoglu et al. [8] demonstrated that a low-dose (0.5 mg/kg) ketamine, the priming of rocuronium or combination of

these improved intubating conditions and hastened the onset time of rocuronium, but according to the result of stepwise regression test, the hastened onset time and improved intubating condition were correlated with a low dose ketamine rather than priming of rocuronium. In this study, low dose ketamine was used along with cisatracurium priming during induction with propofol, and the results were somewhat different to the mentioned previous study. Intubating conditions were better and the onset time was shorter in the ketamine alone, the priming alone and the combination of ketamine and priming than control group. Especially, the combination of low dose ketamine and priming of cisatracurium provided the best intubating conditions and most significantly shortened onset time.

There are some possible explanations of good intubating condition and the different results on the onset time. First, ketamine can compensate the propofol's hemodynamic changes such as hypotension and bradycardia, result in maintaining blood pressures and heart rates. We detected that blood pressure was slightly higher in ketamine groups than priming and control group, even if we did not described in result. Topcuoglu et al. [8] demonstrated the similar results and suggested that ketamine's effect on the blood pressure and heart rate causes rapid delivery of NMBAs to the synaptic cleft, consequently results in providing the good intubating conditions. Second, ketamine's analgesic and hypnotic effects can provide the deep anesthesia and obtund airway reflexes. Author did not reduce the infusion dose of propofol in all groups, and a synergic effect between propofol and ketamine may cause the deep anesthesia favoring intubating conditions [17]. Third, author speculate that differences in the pharmacodynamic properties of NMBAs reflect differences in the effect of ketamine on the onset time. Most authors studied the effect of ketamine on the onset time of NMBAs that have faster onset time compared with cisatracurium, and reported that ketamine did not significantly effective in shortening the onset time [5, 7]. Only one report demonstrated that the low dose ketamine is effective to reduce the onset time of rocuronium [8]. None of them explained the cause of

these different results on the onset time. According to the previous reports, author suggest that the shorter the baseline onset time of the NMBA, such as rocuronium, the less effect of low dose ketamine would have on its reduction.

In the time of assessment of intubating conditions, most previous studies were performed at 60 to 90 sec to compare with the onset time of succinylcholine [5, 6, 8, 14]. In this study, author performed the tracheal intubation at 60 sec because author want to see if study agents contributed to improve the intubation conditions and hasten the onset time of cisatracurium as enough as a alternative of succinylcholine.

As an alternative to succinylcholine, high doses of NMBAs have been used for rapid sequence intubation. 0.15 mg/kg of cisatracurium (3 × ED_{95}) provided intubating conditions within 90 sec and its mean onset time was 3.4 min, which was not sufficient as an alternative to succinylcholine [18]. In this combination of low dose ketamine and priming, the mean onset time was 60.4 sec, which was significantly hastened compared with 0.15 mg/kg of cisatracurium alone. However, priming may result in adverse effects such as muscle weakness, dysphasia, and respiratory failure. Thus, author have to pay attention to decide the priming dose. No adverse effects were reported in recent studies that used a priming dose of cisatracurium 0.01 mg/kg [9, 16, 19]. Schmidt et al. [19] demonstrated that high dose of priming of cisatracurium was effective to shorten the onset time of cisatracurium, but did not recommended clinical routine use due to possible side-effects. In this study, author used the same priming dose and priming interval as in Schmidt's study (cisatracurium 0.01mg/kg, 3 min) and this findings were similar from Schmidt et al.'s.

In conclusion, the author demonstrates that the low dose (0.5 mg/kg) ketamine alone as well as the priming cisatracurium (0.01 mg/kg) provide the satisfactory intubating condition and hasten the onset time of cisatracurium, furthermore the combination of them provide the most significantly improved intubating condition and shorten the onset time.

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