Comparison of Modified and High Dose of Cisatracurium for Rapid Sequence Intubation

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ABSTRACT---

Introduction: Rapid Sequence induction is a safe method of endotracheal intubation in emergency settings. Succinylcholine rapid onset of effect and ultrashort duration of action permitted rapid endotracheal intubation. To avoid Succinylcholine adverse effects, Cisatracurium at high dose is candidate.

Aim: to compare rapid sequence intubation conditions using modified and high dose of cisatracurium.

Methods: In a randomized, double-blind clinical trial 300 patients were enrolled in the study and randomly assigned to receive modified dose (0.3 mg/kg) Cisatracurium or high dose (0.4 mg/kg) Cisatracurium for intubation. Primary outcome was larygoscopy and intubation conditions including vocal cords movement and position and secondary outcome was hemodynamics during and after intubation. All data and train of four (TOF) were recorded at 0 to 5 min after drug administration. Intubation was performed at 90 min after drug administration when TOF=0.

Results: 300 patients were divided into 2 groups of 0.3 mg/kg and 0.4 mg/kg. Age, sex and weight were not significantly different between two groups of study. The onset time of complete neuromuscular blockade (TOF=0) were not significantly different between modified dose (85±22 seconds) and high dose (86±26 seconds) of Cisatracurium. Vocal cords movements were observed in 3 patients in modified dose group and 2 patients in high dose group which was not significantly different (p=0.082). Blood pressure and heart rate were not significantly different between two groups of study at any time points (p>0.05).

Conclusion: 0.3 versus 0.4 mg/kg cisatracurium had the same effect in providing appropriate laryngoscopy condition for rapid sequence intubation after 90 seconds. it is safer to use modified 0.3 mg/kg instead of 0.4 mg/kg cisatracurium to achieve acceptable condition for rapid sequence intubation.

Keywords---- Cisatracurium, Rapid sequence intubation, hemodynamic

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1. INTRODUCTION

Rapid Sequence induction is a safe method of endotracheal intubation that is performed in emergency settings and full stomach patients because it provides muscle relaxation within 60 to 90 seconds. Succinylcholine, introduced by Thesleff[1] and Foldes and colleagues[2] in 1952, changed anesthetic practice drastically. Its rapid onset of effect and ultrashort duration of action permitted rapid endotracheal intubation. Administration of succinylcholine to an otherwise well individual for an elective surgical procedure increases plasma potassium levels by approximately 0.5 mEq/dL. This increase in potassium is due to the depolarizing action of the Succinylcholine. Several early reports suggested that patients in renal failure may be susceptible to a hyperkalemic response to succinylcholine[3,4]. Sinus bradycardia is particularly problematic in individuals with predominantly vagal tone, such as children who have not received atropine. Besides, Succinylcholine usually causes an increase in intraocular pressure (IOP). When succinylcholine is considered undesirable or contraindicated, the onset of action of nondepolarizing neuromuscular blocking drugs can be accelerated by larger doses of neuromuscular blockers[5].

To replace Succinylcholine intermediate drugs such as Cisatracurium are candidates, but it is a nondepolarizing muscle relaxant with a slow onset. ED95 os Cisatracurium is 0.05 mg/kg. Traditionally, Cisatracurium doses used to facilitate tracheal intubation are 2×ED95 (0.01 mg/kg), and the high dose for rapid intubating (8×ED95) is 0.4 mg/kg.

High-dose regimens, however, are associated with a considerably prolonged duration of action and potentially increased cardiovascular side effects[6].

High dose Cisatracurium at 0.4 mg/kg (8×ED95) is routinely used for rapid sequence induction when needed. However, it is important to select the proper dosage of Cisatracurium to ensure that the desired effect is achieved without overdose or side effects. It has not been investigated whether modified doses (6×ED95) of Cisatracurium could provide proper conditions for rapid tracheal intubation or not. The advantage of this modified dose could be to limit the duration of drug effect to match the anticipated length of surgery and to avoid unwanted cardiovascular side effects.

2. OBJECTIVES

To compare modified dose of cisatracurium at 0.3 mg/kg versus high dose at 0.4 mg/kg to provide similar onset time and tracheal intubation conditions.

3. METHODS

The study was reviewed and approved by the University Review Board and hospital ethics committee and been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki. Information about trial was given comprehensively both orally and in written form to the patients. All patients gave their written informed consents prior to their inclusion in the study according to University Hospital Ethics Board Committee.

4. PATIENT SELECTION AND STUDY DESIGN

We performed a prospective, randomized, double-blind clinical trial in 300 patients candidate for emergency surgeries. 300 patients enrolled in the study and randomly assigned to one of groups of study. First group received 0.3 mg/kg Cisatracurium for rapid sequence induction and group 2 received 0.4 mg/kg Cisatracurium for induction. Randomization was performed based on odds codes to 0.3 mg/kg group and even numbers to 0.4 mg/kg group. Study was blinded to both sides, as patients were given a code and then code was registered as anonymous to the anesthesiologist inside operation room. Drugs were also coded unknown to the anesthesiologist administering drugs and anesthesiologist measuring hemodynamics and TOF.

Inclusion criteria were ASA physical status I or II, age between 18 to 60 years old, and no history of interacting drugs. Exclusion criteria were patients with history severe cardiac disease, metabolic or neuromuscular disorders, drug addiction, emergent surgeries, less than 30 min surgeries, predicted difficult airway patients.

5. DATA COLLECTION AND OUTCOMES

Primary outcome was larygoscopy and intubation conditions and **secondary outcome** was hemodynamics during and after intubation.

Onset time of the relaxants was determined by using TOF. Intubating conditions were scored on a defined interval scale by an anesthesiologist blinded to the relaxant administered. Heart rate and arterial blood pressure were measured noninvasively every minute from 5 min before to 5 min after the application of the muscle relaxant.

All measurable data including systolic blood pressure (SBP), Diastolic blood pressure (DBP), mean arterial pressure (MAP), Train of Four (TOF) ,and heart rate (HR) were measured at baseline, before induction (1 min), during intubation (90 seconds after induction), and 3 and 5 minutes after induction.

Laryngoscopy conditions including vocal cords movement (none, moving, closed), vocal cords position (abducted, intermediate, closed), bucking during laryngoscopy (none, diaphragmatic, sustained), laryngoscopy situation (easy, fair, difficult) which were measured by the same anesthesiologist during study at baseline, before induction (1 min), during intubation (90 seconds after induction), and 3 and 5 minutes after induction.

6. METHOD OF ANESTHESIA

Cisatracurium were prepared at two different doses of 0.3 and 0.4 mg/kg at the same volume in same size and shape syringes and were coded unknown to in hand anesthesiologist. Patients were preoxygenated for 5 min with 6 lit/min oxygen. Thereafter, Midazolam 0.02 mg/kg and Fentanyl 2 µg/kg was administered as premedication. Train of

four (TOF) was measured right 30 seconds after premedication from adductor policis muscle (XAVANT NMS300, Germany). Three minutes after premedication, induction was performed by sodium thiopental 5 mg/kg, 1.5 mg/kg Lidocain, and Cisatracurium at 0.3 and 0.4 mg/kg. After 90 seconds direct laryngoscopy and endotracheal intubation were performed using appropriate size of tube for each patient age and body mass index. At the same time, all hemodynamics, TOF, and laryngoscopy conditions were measured (90 seconds after administration of Cisatracurium and during laryngoscopy). After endotracheal intubation, tube was fixed by direct auscultation and then attached to ventilator under appropriate settings individualized to each patient.

7. STATISTICAL ANALYSIS

Statistical calculations were conducted using SPSS 18 (Chicago, IL, USA). The parametric variables were presented as mean±SD and were analyzed by student t- test or ANOVA and Pearson correlation test as appropriate. Statistical analysis was performed using Chi-Square or Mann-Whitney U-test and Spearman correlation coefficients for non-parametric samples. $P<0.05$ was considered as statistically significant. Sample size was estimated using sample size calculator software with 95% confidence interval and $p<0.05$.

8. RESULTS

300 patients were divided into 2 groups of 0.3 mg/kg and 0.4 mg/kg. Age, sex and weight were not significantly different between two groups of study (Table1). 171 patients (57%) were male and 129 were female (43%).

9. TRAIN OF FOUR (TOF)

TOF at both groups were 1 at baseline (Table2). TOF were not significantly different at 90 seconds post Cisatracurium administration (pos-induction time) while laryngoscopy and endotracheal intubation were performed ($p=0.16$) (Table2). Increasing the dosage of Cisatracurium from 0.3 mg/kg (85±22 seconds) to 0.4 mg/kg (86±26 seconds) did not significantly shortened the onset time of complete neuromuscular blockade (TOF=0) (mean ± SD). Intrestingly block duration (recovery of the first twitch of TOF [T1] to 25% of baseline) were not significantly different between 0.3 mg/kg Cisatracurium (47 ± 15 minutes) and 0.4 mg/kg Cisatracurium (46 ± 12 minutes) ($p=0.33$).

10. LARYNGOSCOPY CONDITIONS

Laryngoscopy conditions were compared beween two groups (Table3). Extremity movements were not observed at any of patients in both groups at 90 seconds post induction during laryngoscopy and intubation. Diaphragmatic bucking were observed at only 2 patients in 0.3 mg/kg Cisatracurium and 1 patients in 0.4 mg/kg Cisatracurium group which was not significantly different ($p=0.49$). Vocal cords movements were observed in 2 patients in 0.3 mg/kg Cisatracurium group and 2 patients in 0.4 mg/kg Cisatracurium group which was not significantly different ($p=0.99$). Vocal cords position were intermediate in 2 patients in 0.3 mg/kg Cisatracurium group and 1 patient in 0.4 mg/kg Cisatracurium group which was not significantly different ($p=0.54$). Mouth opening during larygoscopy was easy in 148 patients in 0.3 mg/kg Cisatracurium group and 148 patients in 0.4 mg/kg Cisatracurium group which was not significantly different ($p=0.99$) (Table3).

11. HEMODYNAMIC

Systolic blood pressure were not significantly different between two groups of study at any time points ($p>0.05$) (Figure1). Diastolic blood pressure were also not significantly different at any time points between two groups of study ($p>0.05$). Heart rate increase were also not significantly different at any time points between two groups of study ($p>0.05$) (figure1).

12. DISCUSSION

Here in this study we attempted to compare the effect of two different doses (0.3 versus 0.4 mg/kg) Cisatracurium in providing appropriate condition for rapid sequence intubation. Cisatracurium has been considered a drug with a relatively slow onset but that has the significant benefit of having faster onset time when used at higher doses. Currently the desired dose of Cisatracurium in rapid sequence intubation is 0.4 mg/kg (8×ED95). We showed that the modified dose of Cisatracurium could provide the same intubation conditions in rapid sequence induction.

Cisatracurium at both 0.3 and 0.4 mg/kg provided appropriate muscle relaxation in diaphragm (bucking), adductor policicis (TOF=0), and laryngeal muscles (direct laryngoscopy).The speed of onset of neuromuscular blockade

in airway muscles is one of the requirements for rapidly securing the airway and it is affected by several factors, including the rate of delivery of drug to the neuromuscular junction, receptor affinity, plasma clearance[7]. Besides, different Muscles vary tremendously in their response to non-depolarizing muscle relaxant. For example, Vecoronium could produce muscle relaxation in less than 2 minutes but it does not provide relaxation in laryngeal muscles and diaphragm which makes it a poor choice for rapid sequence intubation. Instead rocuronium neuromuscular blockade develops faster, lasts a shorter time, and recovers more quickly in laryngeal muscles[8]. Kim et al found that the laryngeal adductors were more resistant to the action of cisatracurium than the adductor pollicis muscle, but onset and recovery were faster at the larynx[9]. Our results showed that the onset of neuromuscular blockade is rapid in the muscles that are relevant to obtaining optimal intubating conditions (laryngeal adductors, diaphragm, and masseter) by using a high dose cisatracurium. These observations may seem contradictory because there is also convincing evidence that the median effective concentration (EC_{50}) for almost all drugs studied is between 50% and 100% higher at the diaphragm or larynx than it is at the adductor pollicis[10,11]. Considerably onset time and intubating condition would be faster than previously reported when cisatracurium at high dose is given[12]. The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blockers[13]. A high ED_{95} (i.e., low potency) is predictive of rapid onset of effect and vice versa[14].

2 ED95 doses of cisatracurium (0.1 mg/kg) do not create satisfactory intubating conditions such as those seen with equipotent doses of atracurium. The slow onset time at the laryngeal muscles after low dose cisatracurium (2ED95) can be explained by the higher potency as compared with atracurium[15]. The same dose (2ED95) atracurium is more effective neuromuscular blocking agent than cisatracurium, while higher doses of cisatracurium 4ED95 and 6ED95 provide more effective, more rapid neuromuscular blocking with longer duration of action and stable hemodynamic status[16]. Nondepolarizing neuromuscular blockers of low potency (e.g., rocuronium) have more molecules to diffuse from the central compartment into the effect compartment compare to high potency (cisatracurium) [17]. Weaker binding of the low-potency drugs to receptors prevents buffered diffusion, a process that occurs with more potent drugs. Buffered diffusion causes repetitive binding and unbinding to receptors, which keeps potent drugs in the neighborhood of the effector sites and potentially lengthens the duration of effect.

Interestingly our results showed that hemodynamics was maintained acceptable in which BP and HR did not changed significantly from baseline at any time point. Although minor increase was observed after intubation but it was not significant. Besides both doses of cisatracurium induces the same trend of hemodynamic changes during rapid sequence induction. In fact, 0.3 mg/kg cisatracurium were even lower than 0.4 mg/kg, but still could hold a perfect situation for laryngoscopy at 90 seconds. other studies also showed that there were no changes in heart rate, blood pressure, or plasma histamine concentrations during the first 5 min after administration of cisatracurium at doses up to 8×ED95 (0.4 mg/kg) [18,19,20].

In conclusion, 0.3 (6×ED95) and 0.4 (8×ED95) mg/kg cisatracurium had the same effect in providing appropriate condition for rapid sequence intubation after 90 seconds. Therefore, it is safer to use modified 0.3 mg/kg instead of 0.4 mg/kg cisatracurium to achieve acceptable condition for rapid sequence intubation.

Table 1. Demoghraphic characteristics of patients in two groups of study received 0.3 mg/kg versus 0.4 mg/kg Cisatracurium.

	0.3 Cisatracurium	0.4 Cisatracurium	p-value
Age	47±4.5	49±5.6	0.29
Weight	73.5±12.7	74.3±11.5	0.37
Sex (female/male)	64/86	62/88	0.12

Table 2. Train of four (TOF) of patients before and after induction in two groups of study received 0.3 mg/kg versus 0.4 mg/kg Cisatracurium.

	0.3 Cisatracurium	0.4 Cisatracurium	p-value
TOF before induction	1	1	NA
TOF after 90 sec	0.05±0.02	0.04±0.01	0.16
TOF after 3 min	0	0	NA
TOF after 5 min	0	0	NA

TOF: train of four

Table 3. Intubation conditions in two groups of study received 0.3 mg/kg versus 0.4 mg/kg Cisatracurium.

	0.3 Cisatracurium	0.4 Cisatracurium	p-value
Bucking			
None	148	149	
Diaphragm	2	1	0.49
sustained	0	0	
Vocal cords movements			
None	148	148	
Moving	2	2	0.99
closed	0	0	
Vocal cords position			
Abducted	148	149	
Intermediate	2	1	0.54
closed	0	0	
Mouth opening			
easy	148	148	
fair	2	2	0.99
difficult	0	0	

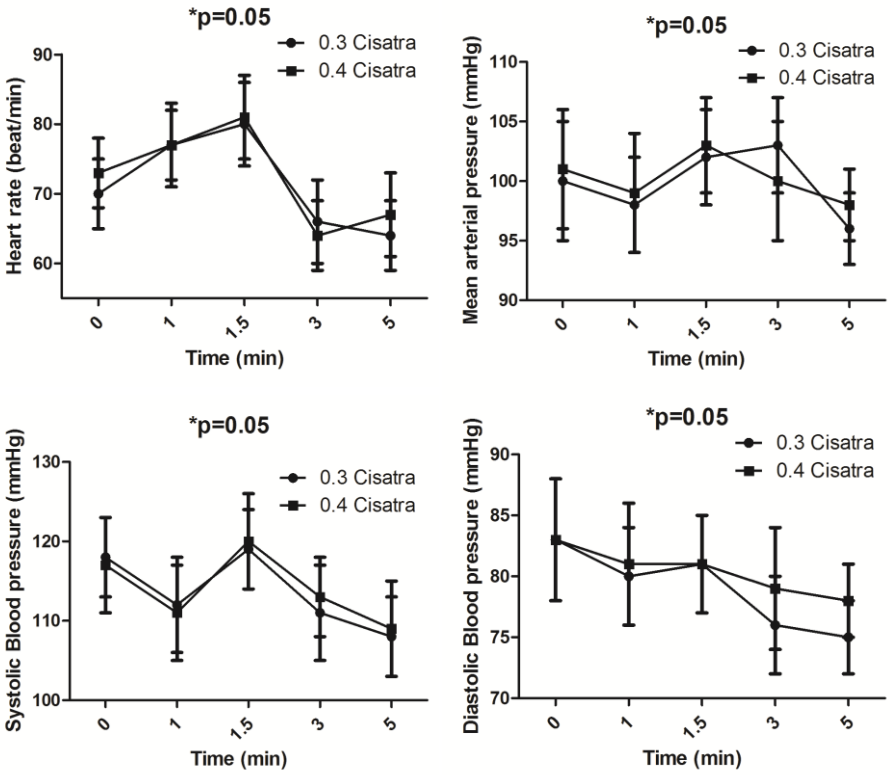

Figure 1. Heart rate, mean arterial blood pressure (MAP), systolic and diastolic blood pressure in two groups of study at baseline, before induction (1 min), during intubation (90 seconds after induction), and 3 and 5 minutes after induction.

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