Rocuronium versus Cisatracurium: onset of action, intubating conditions, efficacy, and safety.

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ABSTRACT

Background: *Neuromuscular blockers (NMB) are very important adjuvant to general anesthesia, Rocuronium bromide (aminosteroidal NMB) and cisatracurium besylate (benzyl isoquinoline NMB) are recently introduced non-depolarizing muscle relaxants. In a prospective randomized study we had compared both drug at a dose 2x (ED95) as regard the onset of action, intubating conditions, clinical duration, hemodynamic changes, and adverse effects.*

Method: *40 female patients ASA I&II, 20-50 year old underwent elective gynecological ambulatory surgery under general anesthesia (GA) were randomly assigned into 2 equal groups. ROC group, where 0.6mg/kg rocuronium was given and CIS group, where 0.1mg/kg cisatracurium was given. Neuromuscular monitoring was done by stimulating ulnar nerve and recording the action potential of the first dorsal interosseous muscle using Datex Relaxogram. Standardized GA was given to all patients as follows, fentanyl 1.5mcg/kg, propofol 2mg/kg, 2x (ED95)/kg of the examined NMB, intubation was tried by the same anesthetist who was blind to the given NMB after 60 sec of injection, intubation was done if the intubating condition was acceptable (excellent or good), and it was re-attempted every 30 sec if it was poor or inadequate. Anesthesia was maintained by 60% N2O in O2 and isoflurane to a total MAC 1.5, controlled ventilation was adjusted to normocarpia. Mean arterial blood pressure (MAP), heart rate, and intubating conditions were recorded. Interpretation of relaxogram for the onset of action, clinical duration, recovery index was done.*

Results: *Clinically acceptable intubating conditions were achieved after 60 sec more frequently after rocuronium (80%) than after cisatracurium(0%). Rocuronium had a significant shorter onset time than cisatracurium (70.6±18.2 versus 160.4±14.3sec), Rocuronium had a significant shorter duration of action than cisatracurium (30.3±5.2 versus 45.7±7.5min), and the spontaneous recovery index was significantly shorter with rocuronium than cisatracurium (9.2±1.8 versus 13.6±2.4min). There were no evidences of any significant clinical cardiovascular changes in both groups. There were no clinical signs of histamine release in both groups, but there was burning pain at the site of rocuronium injection in more than 50% of patients.*

Conclusion: *Rocuronium has a rapid onset of action with good intubating conditions, cisatracurium has an intermediate duration of action, both are potent and safe with excellent cardiovascular stability and without apparent histamine release.*

INTRODUCTION

Neuromuscular blockers (NMB) became an essential part of the anesthetist armamentarium. They aid endotracheal intubations, mechanical ventilation, decrease anesthetic requirement, prevent patient movement, facilitate surgery, and decrease oxygen consumption. Changes in the direction of drug development have occurred as a result of the ingenuity of pharmaceutical chemist to meet clinical needs. Rocuronium bromide (Esmeron) is a new aminosteroidal non depolarizing NMB introduced to the clinical use in [1994]. It is monoquaternary analogue of vecuronium, it is primarily eliminated via hepatic reuptake and biliary excretion, and up to 20% is excreted unchanged n urine[(1)] it has one metabolite 17-desacetyl rocuronium which has only 5-10% activity of the parent compound, it does not trigger histamine release, and the adult ED95 is 0.3 mg/kg[(2)]. Cisatracurium, besylate (Nimbex) is a new benzylisoquinoline NMB

introduced to clinical use in [1995], it is purified from one of the 10 stereo-isomers of atracurium, it is eliminated mainly by Hofmann degradation, it has one metabolite laudanosine which has no neuro-muscular blocking effect, it does not trigger histamine release, and the adult ED95 is 0.05 mg/kg[3]. In this study we compared the most recent NMB rocuronium and cisatracurium at a dose 2 x (ED95) as regard the onset of action, intubating conditions, efficacy, and safety during general anesthesia for adult gynecological ambulatory surgery.

PATIENTS AND METHODS

Forty adult female patients underwent elective gynecological ambulatory surgery under general anesthesia in Suez Canal University Hospital were enrolled in the study after approval by our local ethics committee and tacking informed written consent from the patients. The patients were ASA physical status 1&2, Mallampati class I&IIand their age ranged 20-50 years.

Exclusion criteria included patients having major hepatic, renal, cardiovascular, pul-monary and neuromuscular diseases. Morbid obese, pregnant and patients under anticonvulsant, calcium channel blockers, B-blockers, steroids, frusemide, or amino glycoside therapy were also excluded.

All patients were preoperatively evaluated by history tacking, full clinical examination, ECG, and some laboratory investiga-tions for the presence of inclusion and exclusion criteria.

The patients were randomly assignned into 2 equal groups 20 patients each, in the first group Rocuronium 0.6 mg/kg was examined [group ROC], while in the second group Cisatracurium 0.1 mg/kg was examined [group CIS].

Anesthetic technique

After arrival of the patient to OR without premedication, an IV line was secured in the right forearm and the patient was monitored for ECG tracing, heart rate, non invasive arterial blood pressure, and pulse oximeter using (Datex cardiocap)also,end tidal CO2 was monitored using (side stream capnography).

Preparation of [Datex Relaxogram NMT 100] for monitoring of action potential of the first dorsal interosseous muscle as a result of percutaneous stimulation of the ulnar nerve at the wrist of the left forearm was done by cleaning the forearm and hand with alcohol, then the five surface electrodes of the device were fixed. Two were placed for the stimulation of ulnar nerve, two were placed for recording EMG response of that muscle, while the fifth was placed for grounding, and then the hand was carefully fixed with adhesive plaster. Following pre-oxygenation for 3 minutes, anesthesia was induced with fentanyl 1.5µg/kg iv followed by propofol 2 mg/kg iv, and the patient was allowed to breathe 60% nitrous oxide in oxygen with 2% isoflurane through face mask. Calibration of the relaxogram was performed using supramaximal stimulation delivered in train-of-four (TOF) every 20 seconds. And when twitch height was stable, it was considered as a control and then the intubating dose of MNB was injected. Rocuronium bromide 0.6 mg/kg IV was given for patient in the first group (ROC) and cisatracurium 0.1 mg/kg IV was given in the second group (CIS).Orotracheal intubation was performed by the same anesthetist who was blind to the given NMB after 60 seconds of its injection, then the intubating conditions were assessed using a four point scale [excellent, good, poor, or inadequate]. If the intubating condition was excellent or good, tracheal intubation was performed, and if it was poor or inadequate, intubation was postponed and was re-attempted every 30 second. Anesthesia was maintained with 60% N2O in O2 and isoflurane to total MAC of 1.5.

Mechanical ventilation was adjusted to maintain end tidal CO2 between 35-40 mmgh. Ringer acetate was infused at rate 7 ml/kg/h. Surface warming was applied to maintain esophageal temperature between 36-37^{0}C. No top-up doses of NMB were given. At the end of operation, themuscle relaxant effect was reversed by using neostigmine and atropine.

Clinical measurement:

A) Hemodynamic variables Mean arterial blood pressure (MAP) and heart rate (HR) were recorded at the following intervals:

- T0: before induction (baseline)
- T1: after induction and before injection of NMB.
- T2: after injection of NMB and before endotracheal intubation.
- T3: just after intubation.
- And then every 5 minutes for 30 min after intubation.

B) Intubation score [28]

This was done by 4 points scale:

- Excellent: relaxed jaw, abducted immobile vocal cords, and no diaphragmatic movement.
- Good: relaxed jaw, abducted immo-bile vocal cords, and some diaphrag-matic movement (bucking).
- Poor: relaxed jaw, moving vocal cords, coughing on intubation.
- Inadequate: jaw is not relaxed, add-ucted vocal cords, and impossible intubation.

C) Timing of intubation in seconds.

Interpretation of the relaxogram chart It was done at the end of operation to determine the following parameters:

- The onset time: time from NMB injection to 95% suppression of twitch height.(sec)
- The clinical duration: time from NMB injection to 25% recovery of twitch height.(min)
- The recovery index: time from 25% to 75% recovery of twitch height. (min)

D) Adverse events Any adverse events like histamine release in the form of skin reaction, bronchospasm, wheeze, increased airway pressure, O2 desaturation, or hypotension were recorded. Any postoperative pain at the site of injection of NMB was also recorded.

Statistics

Results are given as mean ±SD or number and percentage. The intragroup changes were tested by paired student t-test, the intergroup changes were tested by one way analysis of variance (ANOVA), and P value <0.05 was considered significant.

RESULTS

Both groups were comparable as regard age, weight, Mallampati class, ASA status, and the duration of operation (table 1).

As regard hemodynamic variables, there was transient insignificant decrease in mean arterial blood pressure (MAP) after induction followed by return of the baseline after intubation without inter-group difference (table 2). Also, there was similar transient significant tachycardia after intubation in both groups required no treatment and of no clinical significance (table 3).

The intubating conditions at 60 sec were excellent in 10 patients (50%) and good in 6 patients (30%) in ROC group. Contrary, there were no excellent or good intubating conditions in CIS group. At 90 sec, the intubating conditions were excellent in 3 patients (15%) and good in 1 patient (5%) in ROC group. There were no excellent but only 1 good intubating condition (5%) in CIS group. At 120 sec, the intubating conditions were excellent in 1 patient (5%) and good in 1 patient (5%) in CIS group. At 150 sec, the intubating conditions were excellent in 7 patients (35%) and good in 8 patients (40%) in CIS

group. At 180 sec, there were 2 excellent intubating conditions (10%) in CIS group as shown in (table 4).

In ROC group, the intubation was performed for 16 patients after 60 sec and for 4 patients after 90 sec with mean intubation time 66+16.8sec.In CIS group, the intubation was performed for 1 patient after 90 sec, for 2 patients after 120 sec, for 15 patients after 150 sec and for 2 patients after 180 sec with mean intubation time 147+ 13.7 sec

The onset of action, the clinical duration, the spontaneous recovery index of NMB measured by relaxogram were shown in (table 5). The onset of action was 70.6±18.2 sec in ROC group, while it was 160.4±14.3 sec in CIS group. The clinical duration was 30.3±5.2 min in ROC group, while it was 45.7±7.5 min in CIS group. The recovery index was 9.2±1.8 min in ROC group, while it was 13.6±2.4 min in CIS group.

There was no intraoperative skin reaction, bronchospasm, O2 desaturation, or hypotension in both groups. There was postoperative burning pain at the site of NMB injection in 11 patients in ROC group.

DISCUSSION

Neuromuscular blockers (NMB) are very important adjuvant to general anesthesia. Rocuronium is the most recent available aminosteroidal NMB, [rapacuronium was withdrawn from the US market at 2001 because of its hazardous bronchospasm[4]]. Cisatracurium is the most recent iso-quinolone NMB which is 3-4 times more potent than atracurium, has thesame advantage of Hofmann degradation and it does not seem torelease histamine [5]. This study was performed to compare rocu-ronium and cisatracuriumat a dose 2 x (ED95) as regard onsetof action, clinical duration, recovery index intubating conditions, hemodynamic changes, and adverse effects Rocuronium had a significant shorter onset time than cisatracurium (70.6±18.2sec versus 160.4±14.3sec) and this rapid onset of rocuronium correlate with previous study done by Levy et al [6]. Also Lowry et al [7] recorded an onset time of approximately one minute after rocuronium 0.6 mg/kg in 3 groups of patients, who received sevoflurane, isoflurane and pro-pofol, this is parallel with previous study done by Puhringer et al [8] who reported an onset time of approximately 1 min. In contrast Zhou et al [9] demonstrated less rapid onset after 0.6 mg/kg rocuronium (141±65sec). The delayed onset of action of cisatracurium was also documented by Kim et al [10] who reported 3.9 min at adductor pollicis and 3.0 min at larynx.

Rocuronium had a significant shorter duration of action than cisatracurium (30.3 ±5.2 min versus 45.7±7.5 min) and this finding is consistent with Lepage et al [11] who concluded that cisatracurium is a very potent NMB with an intermediate duration of action characterized by excellent cardiovascular stability, with no apparent histamine release. The short duration of action of rocuronium was also documented by Bock et al [12] and Zhou et al [9] who reported prolongation of the duration of action by sevoflurane. The spontaneous recovery index was insignificantly shorter in rocuronium than cisatracurium (9.2±1.8 min versus 13.6±2.4 min). In another study, the recovery index after a single dose of rocuronium was prolonged during sevoflurane as compared with isoflurane or propofol[7]. Wulf et al[13] stated that the recovery index after cisatracurium was prolonged during desflurane and sevoflurane compared with isoflurane or propofol.

The intubating conditions at 60 sec after rocuronium were clinically acceptable in about 80% of patients in our study and this is similar to the results of Chetty et al[14]. In consistent with our results Zhou et al[9] reported 84% clinically accepted intubating conditions after 60 sec. In contrast, Pino et al[15]

Table 1: Demographic characteristics in both groups (Mean ± SD)

	ROC	CIS
Age (year)	33±9	35±7
Weight (kg)	77.5±6	75.8±9
ASA class I,II	8/12	7/13
Mallampati class 1:2	9/11	8/12
Duration of surgery (min)	55±12	60±11

Table 2: Changes in mean arterial blood pressure (MAP) in both groups

Time	ROC mmHg	CIS mmHg
T0	93.6±10.6	98.3±12.6
T1	90.2±11.3	96.4±14.4
T2	89.1±12.5	94.2±13.3
T3	98.5±19.9	103.6±15.8
5 min	95.4±10.5	100.5±11.9
10 min	93.3±13.4	98.4±10.7
15 min	90.7±12.8	94.8±12.5
20 min	94.2±11.7	98.5±11.2
25 min	93.6±10.9	99.3±13.1
30 min	95.8±11.3	97.7±10.4

Table 3: Changes in heart rate (HR) in both groups

Time	*ROC* Beat/min	*CIS* Beat/min	P value
T0	77.4±9.3	82.4±10.3	
T1	75.3±10.2	83.2±11.4	
T2	76.3±9.1	84.6±9.2	
T3	89.5±8.8 *	96.8±8.9 *	P<0.05
5 min	85.9±9.5	92.2±10.5	
10 min	81.2±12.2	88.1±12.1	
15 min	77.4±10.4	82.6±9.4	
20 min	78.1±11.6	81.3±10.5	
25 min	80.6±12.4	83.4±11.3	
30 min	79.2±11.6	82.9±12.7	

*P < 0.05

Table (4): The intubating conditions at different time intervals (sec) in both groups

Intubating conditions	60 sec		90 sec		120 sec		150sec		180 sec	
	ROC	CIS	ROC	CIS	ROC	CIS	ROC	CIS	ROC	CIS
Excellent	10	--	3	--	--	1	--	7	--	2
Good	6	--	1	1	--	1	--	8	--	--
Poor	3	4	--	4	--	12	--	2	--	--
Inadequate	1	16	--	15	--	5	--	--	--	--
Intubation	16 *		--	4	1	--	2	--	15	--

P<0.005

Table (5): The relaxogram interpretation in both groups

Time	ROC	CIS	
Onset of action (sec)	70.6±18.2	160.4±14.3	P<0.001
Clinical duration (mir	30.3±5.2	45.7±7.5	P<0.001
Recovery index (min	9.2±1.8	13.6±2.4	P<0.023

found that only 40% of intubation to be acceptable at 90 sec. The intubating conditions after cisatra-curium in our study were only acceptable after 150 sec and this is similar to the results of Doenicke et al[16]. In contrast, Kim et al[10] reported acceptable intubating condition after 3 min. Because of the rapid onset of rocuronium and the acceptable intubating conditions after 60 sec, rocu-ronium was used for rapid sequence intubation[17, 18, 19].

There were no evidences of any significant clinical cardiovascular changes in both groups. The heart rates were significantly elevated in both groups (P <0.05) after intubation only and this is consistent with Schultz et al[20] who reported a lack of cardiovascular respo-nses throughout a wide clinical dose range of rocuronium, also Levy et al [6] observed no dose-related changes in heart rate and blood pressure after rocuronium. Reich et al[21] demonstrated similar safe cardio-vascular changes after cisatracurium in patients with coronary heart disease.

There were no signs of histamine release in both groups in our study but McD Neal et al[22] reported broncho-spasm in 1 of 350 patients after rocuro-nium, also Doenicke et al [16] suggested that cisatracurium has modest chemic-ally mediate histamine release but it did not seem to be of clinical significance in their study.

There was burning pain at the site of injection of NMB in more than 50% of patients after rocuronium. This is also documented by Ruetsch et al [23] who reported withdrawal movements associ-ated with the injection of rocuronium. Although the mechanism by which rocuronium causes pain is unclear; the relatively low PH (4) may be a possible cause as Klement et al [24] reported, while Borgeat et al [25] postulated the release of mediator such as kininogen as a cause. There were a lot of studies comparing different strategies to reduce the pain associated with IV adminis-tration of rocuronium [26, 27].

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