

Comparison of the Course and Effect of Neuromuscular Block Following the Intubating Dose of Rocuronium for the Tracheal Intubation in Males and Females

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ABSTRACT

Introduction :General anaesthesia is a reversible state of loss of consciousness, complete muscle paralysis, amnesia, analgesia, sedation and blockade of stress response. For adequate quality of muscle relaxation neuromuscular blocker should have desirable duration of action as per the duration of surgery. Traditionally, body weight, body surface area and or body mass index are the usual variables used to calculate the dose of the drug, females may be the more susceptible to the effects of the drug, while males requiring larger doses of another one to achieve the same effect. Aim was to compare the onset of time for 95% depression in T1, clinical duration until 25% recovery, recovery index from 25% to 75% recovery after giving single bolus dose of rocuronium(0.6mg/kg) in males and females.

Material and methods: Following ethics committee approval and written informed consent, with duration of one year,102 patients (49males and 53 females) and stational data analysis has done in appropriate stational software by unpaired t test and p value <0.05 taken as level of significance.

Results: In demographic parameters it is found that males are heavier, longer, larger than females in study group and there is no relationship between age and gender and BMI is also identical for both of group. In pharmacodynamic parameter onset time for females is shorter (140.35 v/s 181.16sec) than males ,clinical duration for females is longer (47.2min vs 30.37min, respectively)and recovery index is (15.47 v/s 15.96 min) identical for both groups.

Conclusion: The study confirms significantly gender differences in the rocuronium effect. Females having increased absorption time, fat distribution, organ flow, decreased volume of distribution and slow clearance which will increase the free fraction of drug in females. Thus, females have shorter onset of time, long clinical duration for rocuronium as compared with males.

Keywords: Rocuronium, Intubation, Males, Females

INTRODUCTION

Rocuronium is modern nondepolarizing monoquaternary aminosteroid intermediate acting neuromuscular blocking agent. For adequate quality of muscle relaxation, neuromuscular blocker should have desirable duration of action as per the duration of surgery. If the recovery from the effect of neuromuscular blocking agents(NMBA) is incomplete, it can give rise to serious life threatening complications. Rocuronium steroidal group of neuromuscular blocker ,was designed to provide dose dependant rapid onset of action. It is cardiostable, has short onset and predictable

duration of action.

Traditionally the body weight, body surface area and body mass index are the usual variables used to calculate the dose of the drug. females may be the more susceptible to the effects of the drug, while males requiring larger doses of another one to achieve the same effect. There are some of factors which mainly affect the drug metabolism in males and females.

With this study we examined response of neuromuscular agents in males and females, so we will be able to determine gender specific dose.

Aim and objectives

- 1) To compare the onset time for 95% depression in T1 after giving rocuronium in males and females (sec).
- 2) To compare the clinical duration to 25% recovery after giving rocuronium in males and females(min).
- 3) To compare the recovery index from 25% to 75% recovery after giving rocuronium in males and females (min).

MATERIAL AND METHODS

After taking approval from hospital ethics committee along with written and informed consent, patients in the age group of 18-60 years, belonged to ASA 1 and 2 and undergoing elective surgery lasting for 2 to 3 hours schedule for the study. Study was conducted on 200 patients,100 patients in each group of sex.

Patients with poor Glasgow coma scale , taking alcohol and other known substances, abuse disorder, pregnant or breast feeding females, patients receiving medication known to interfere with neuromuscular blocking agents (anticonvulsants, aminoglycosides or polypeptides), Patients with anticipated difficult intubation (mallampati score 3or more) and patients with disease affecting neuromuscular transmission(myopathy) were excluded.

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Preoperative

After all routine investigation (CBC, LFT, KFT, chest Xray, ECG) patients were kept nil by mouth for surgery. The electrodes were placed over the ulnar nerve on the volar side of wrist so that distal electrode is positioned where the proximal crease line crosses the radial side of flexor carpi ulnaris muscle. The proximal electrode can be placed either 2- 3 cm proximal to the distal electrode.

Intraoperative

Preoxygenation performed with 100% oxygen for 3 min via face mask and patient is asked to breathe normally during that period. Premedications with injection glycopyrrolate 0.004mg/kg, injection fentanyl 0.2microgram/kg, injection midazolam 0.02mg/kg followed by inducing agent injection propofol 2mg/kg were given slowly. Patient allowed to breathe through facemask, when the patient stopped breathing, checked whether patient can be ventilated. After giving induction dose but before giving NMBA, 0.1Hz single twitch stimulation was applied via neuromuscular monitor and supramaximal response was noted for that individual patient. Intubating dose of NMBA rocuronium 0.6mg/kg was injected. Intermittent positive pressure with 50% O₂ and 50% N₂O was applied for two mins and 100% O₂ for last one minute through facemask. Following NMBA neuromuscular monitor is switched to TOF stimulation assessed at 12 sec intervals by stimulation of ulnar nerve with four rectangular impulses at 2Hz, duration 0.2ms with supramaximal current. Following maximal depression of T1 (onset of time), direct laryngoscopy was done followed by tracheal intubation. After confirmation of correct placement of endotracheal tube, breathing circuit was attached delivering oxygen, air and inhalational anaesthetic agent. The adjustable pressure limiting valve was fully closed and anaesthetic gases were delivered via ventilator to lungs. Clinical duration of NMBA was assessed by recovery of T1 to 25% of control with the help of neuromuscular monitor. After end of surgery anaesthesia was reversed with injection neostigmine 0.05mg and injection glycopyrrolate 0.008mg/kg. After full reversal of neuromuscular block, return of reflexes, spontaneous ventilation, ability to follow verbal commands were assessed. A spontaneous recovery until 75% of T1 was allowed and noted. Time interval from T1 =25% to T1 =75% noted as recovery index. Patient shifted to post anaesthesia care unit.

STATISTICAL ANALYSIS

After data collection, data entry will be done in excel and data analysis will be done with appropriate statistical software, Quantitative data will be presented with the help of mean, standard deviation, Median and Interquartile range. Comparison among the group will be done with the help of unpaired t test or Mannwhitney test as per results of normality test. Qualitative data will be presented with the help of frequency and percentage table. Comparison among study group will be done with the help of Chi-square test. P value < 0.05 will be taken as level of significance.

RESULT

Demographic parameters

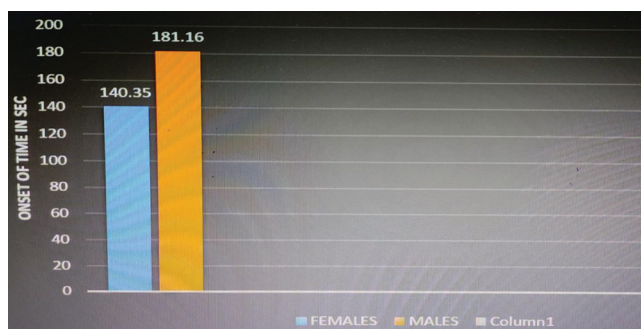
Table 1 showing that mean body surface area, mean height, mean weight of males are significantly more than females in dynamic parameters. Mean age and mean body mass index is same for both groups.

Pharmokinetic parameter

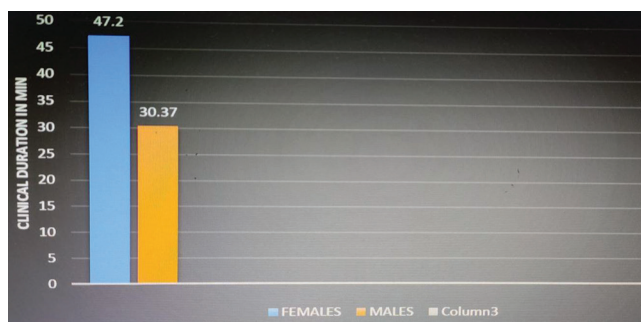
Table 2 and graph 1 is showing that onset of time for action of neuromuscular agent rocuronium is significantly less in females (140.35 sec with std deviation 51.06) than males (181.16 sec with std deviation 37.07) with p value < .05.

Table 3 and graph 2 is showing that clinical duration of action of rocuronium in females is significantly more (47.20 min std deviation 14.67) as compared with males (30.37 min std deviation 10.57) with p value < .05.

Table 4 and graph 3 is showing that there is no difference in recovery index in females (15.96 min with std deviation 1.56) and males (15.47 min with std deviation 1.72) with p value > .05.



Graph-1: Onset of time



Graph-2: Clinical duration (to T25%)



Graph-3: Recovery index

Parametres	Males	Females	p value
Mean body surface area	1.62 kg/m ²	1.49 kg/m ²	<0.001
Mean body mass index	22.10	22.51	>0.05
Mean age	44.52 years	41.61 years.	>0.005
Mean weight	58.95 kg	53 kg	<0.001
Mean height	163.45 cm	153.12 cm	<.0001

Table-1:

	Groups	Number	Mean	Std. Deviaton	P value
Onset of time (sec)	Male	49	181.1666	37.07	<.05
	Female	53	140.3541	51.06	

Table-2: Comparison of onset of time for action of rocuronium in two groups

	Groups	Number	Mean	Std deviation	P value
Clinical duration (Min)	Male	49	30.37	10.57	<.05
	Female	53	47.208	14.67	

Table-3: Comparison of clinical duration for rocuronium between two groups.

	Groups	Number	Mean	Std deviation	P value
Recovery index(min)	Male	49	15.47	1.72	>.05
	Female	53	15.96	1.56	

Table-4: Comparison of recovery index for rocuronium between two groups.

DISCUSSION

The NMBA has become an important part of general anaesthesia for wide variety of surgeries as well as a component of balanced anaesthesia. The ideal NMBA should have short onset time, adequate depth of relaxation, cardiostability, minimum interaction with other anaesthetic agents and drugs, total excretion without further metabolic products, predictable duration of action, complete and adequate reversibility of blockade by reversing agents and should not be affected by fluctuation in pH and temperature. Rocuronium bromide is a nondepolarizing NMBA with high degree of selectivity for the receptors at the neuromuscular junction. Rocuronium has faster rate of onset, intermediate duration of action, rapid recovery and minimal cumulative property.

In our study out of 102 study population, mean age of 49 males is 44.52 years and 53 female is 41.61 years. P value derived is >0.05 (0.2) not significant, there is no relationship in gender and age. Mean weight of 49 males is 58.95 kg which is greater than mean weight of 53 female 53.0kg with p value derived is <.001 significant thus, males are heavier than females. Mean height for 49 males is 163.45 cm and for 53 females is 153.12cm and p value is <.0001 significant thus males are taller than females. Mean body surface area for 49 males is 1.62 m² and for 53 females is 1.49m²and p value is <.001 significant thus, males are larger than females. Mean body mass index for 49male is 22.10 kg/m² and for 53 females is 22.51 kg/m²with p value is >.05 (27) not significant thus, males and females have identical body mass index. Mean onset time of NMBA in 49 male patients were 181.16 sec and females 140.35 secs with p value<.05 significant, thus onset time is shorter for females.

Clinical duration of NMBA for 49 males is 30.37 min and for 53 females is 47.2 min with p value <.05 significant, thus clinical duration is longer for females as compared to males. Recovery index of NMBA for 49 males is 15.47±1.72 min and for 53females is 15.96±1.56 min with p value >.05 (.14) not significant),thus recovery index for males and females is identical. Our result show that females were significantly more sensitive to rocuronium than males.

Until now gender aspect in pharmacokinetic (PK) and pharmacodynamic (PD) of anaesthetic drug has been the focus of research. However, ongoing research in order to further optimize treatment in anaesthesia shows gender should be taken into account while administering anaesthetic agents including NMBA¹. There is increasing evidence for gender difference in PK and PD of anaesthetic drugs and NMBA². Females having increased absorption time, fat distribution, organ flow, decreased volume of distribution and slow clearance which will increase the free fraction of drug in females. Thus, females are more susceptible than male. Females have 20-30% greater sensitivity to the effects of aminosteroid muscle relaxants³. When rapid onset or short duration of action is important, gender modified dosing may be considered.

It is found in one of the study that women are frequently overdosed due to smaller volume of distribution, larger free fraction of drug and slower clearance of drug from body. Women are more sensitive than males due to alteration in receptor number, receptor binding and altered signal transduction pathway after receptor binding. The main enzyme for drug metabolism is of P450(CYP) group. Increased level of estrogen and progesterone in females alter hepatic enzyme activity which can increase drug accumulation and decrease

elimination of some drugs. Metabolic changes which also depends upon on the hormone that change during menstrual cycle. Sex related differences arise due to variation in the regulation of the expression and activity of CYP isoenzyme, may be due to endogenous hormonal influences⁴.

Studying rocuronium induced block after 0.45mg/kg, Mencke and colleagues³ demonstrated slower onset by 26% and shorter clinical duration by 35% in males. One of the study showed that the dose response curve of rocuronium in males was shifted to the right, indicating a decrease in the sensitivity to the rocuronium induced neuromuscular block in comparison with females⁵. After the intravenous administration of total dose of 0.4mg/kg rocuronium, neuromuscular block was significantly longer in females than males (clinical duration 18.5 vs 12.5 min). To analyse the typical course of neuromuscular block following relaxant injection, we used the most usual dose of rocuronium 2 X ED95 that is larger than the doses used in above mentioned studies. The lower difference in onset of times in our study may be due to larger dose of rocuronium administered, resulting in more uniformity and lesser scatter in onset of time.

An easiness of intravenous injection of muscle relaxant, resulting in neuromuscular block, contrasts with clinically serious consequences following its application and considerable interindividual variability of the effect, particularly at the end of the anaesthesia, this may lead to a problem. In one patient, the effect of a single bolus dose of NMBA may have fully subsided, while in another one, there is significant degree of block still present⁶⁻¹⁰. This expected variability of action may be further accentuated by gender differences. The degree of weakness for the relaxant groups was unaltered to age but was strongly influenced by the patient's sex¹¹. The degree of weakness for the relaxant groups was unaltered to age but was strongly influenced by the patient's sex. One hour postoperatively, female patients showed a marked decrease in handgrip strength after both vecuronium and rocuronium (32% and 34%, respectively) compared to males (14% for vecuronium and 19% for rocuronium)¹². These results suggest that females are more likely to have residual weakness after anaesthesia with muscle relaxants and therefore may be more predisposed to postoperative pulmonary complications and postoperative respiratory muscle weakness, which may be catastrophic if not detected early and involves high mortality. This constitutes convincing evidence that patients undergoing surgery benefit from perioperative neuromuscular monitoring to detect any residual neuromuscular blockade. In anaesthesia practice, it involves high litigation medicolegal issues. So, the timing of observation under ICU care becomes at most important in the patients receiving NMBA.¹³⁻¹⁵

CONCLUSION

The study confirms significantly gender differences for rocuronium effect. The onset of time was shorter and clinical duration was longer in females as compared to males. For obtaining the same duration of response in both groups, we

need to reduce the dose in females or with same dose we need to observe the females for longer duration of time in postoperative recovery period as they will be more prone for inadequate reversal and respiratory depression.

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