

Comparison of intubating conditions with rocuronium and vecuronium at specific times judged by clinical criteria

Sathe Vishwas¹, Sivashankar K.R.¹, Sharma R.C.², Gangawane A.K.³

¹Department of Anaesthesiology, M.G.M Medical College, Sec-18, Kamothe, Navi Mumbai, MS, India, vishwassathe@hotmail.com

²Department of Physiology, M.G.M Medical College, Sec-18, Kamothe, Navi Mumbai, MS, India

³School of Biomedical Science, Department of Biotechnology, M.G.M Institute of Health Sciences, Sec-18, Kamothe, Navi Mumbai, MS, India

Abstract- To compare the two non depolarizing neuromuscular blocking agent Rocuronium bromide (0.6 mg/kg body weight) and Vecuronium bromide (0.1 mg/kg body weight) in elective surgery under general anaesthesia with respect to onset of action, intubating conditions and haemodynamic changes. It can be observed from the present study, the two groups were comparable for age, sex, weight and ASA status of the patients. Rocuronium at 0.6mg/kg bodyweight produced excellent and good intubating conditions at 95 ± 21.6 seconds and Vecuronium at 0.1mg/kg body weight produced excellent and good intubating condition at 168.0 ± 12.7 seconds after the intravenous administration. Both the drugs were comparable as regard to cardiovascular stability with the mean pulse rate was 80.10 ± 06.94 and 78.53 ± 08.510 per minute ($p = 0.4368$) in Rocuronium group and Vecuronium group respectively. The mean systolic pressure was 126.20 ± 08.06 mm of Hg and 129.73 ± 08.27 mm of Hg ($p=0.100$) and the mean diastolic pressure was 86.60 ± 07.70 mm of Hg and 85.80 ± 07.84 mm of Hg ($p= 0.691$) in Rocuronium group and Vecuronium group respectively. It can be observed from above result that Rocuronium provides earlier excellent and good intubating conditions than Vecuronium with similar cardiovascular stability at intubation and post intubation period. It is evident from the above study that Rocuronium had a more rapid onset of action and provided conditions suitable for more rapid tracheal intubation than Vecuronium during general anaesthesia with endotracheal intubation in surgical patients. The haemodynamic changes in surgical patients exhibited similar trend in their variation during intubation and post intubation period in both the Rocuronium and Vecuronium groups. Thus the advantage of Rocuronium, with its early onset of action, along with good to excellent intubating conditions and the cardiovascular stability, make this neuromuscular relaxant a desirable choice for rapid tracheal intubation in surgical procedures requiring general anaesthesia with endotracheal intubation for controlled ventilation.

Key words: - Vecuronium, Rocuronium, intubating and anaesthesia

Introduction

Neuromuscular blocking agents are firmly entrenched as an integral part of everyday anaesthesia practice. Anaesthesia providers practiced for nearly hundred years without these drugs, but it would be difficult to imagine the practice of modern day anaesthesia without these agents. The knowledge of muscle relaxants dates back to centuries where the natives of South America used poison tipped arrows to kill animals. The poison was an extract derived from the bark of the creeper *Chondodendron tomentosum*. The earliest documented reference of arrow poison is found in the work of Sir Walter Raleigh [1]. Benjamin Brodie, between 1811 and 1812 [1] experimented with curare. He demonstrated that curarised animals could be kept alive by artificial ventilation. Later in 1850, Claude Bernard [1] demonstrated that curare caused paralysis without affecting the spinal cord, the muscles or nerves directly. He also demonstrated the necessity to administer the drug via blood.

The formal introduction of muscle relaxants in clinical practice took place in 1942 when Harold Griffith [2] used a curare preparation to give muscle relaxation during surgery. However it was Bourne who pioneered the use of muscle relaxants for endotracheal intubation in the year 1947. Thesleff [3] and Foldes [4] revolutionized anaesthesia practice by introducing Succinylcholine in 1952, which provided intense blockade of short duration which permitted rapid endotracheal intubation. In 1967, Baird and Reid [5] first reported on the clinical administration of the synthetic aminosteroid pancuronium. This marked the advent of long acting muscle relaxants in clinical practice. Dr David Savage [6] of Organon Technika laboratories developed Vecuronium which

was later introduced into clinical practice by Durant et al. In the search for the ideal neuromuscular blocking agent, one compound was developed, Rocuronium Bromide. The clinical need for a non depolarizing agent with a rapid onset time and a brief duration of neuromuscular blockade effectively lead to development of Org. 9426 [7] Org. 9426 i.e. Rocuronium Bromide, 2-morpholino-16-allylpyrrolidine-3-desacetyl derivative of Vecuronium, is a new monoquaternary amino steroidal neuromuscular blocking agent. It is structurally similar to Vecuronium in its time course of neuromuscular blocking action [8].

Its major difference from Vecuronium is its more rapid onset of action which is probably a result of its lower potency [9]. Studies in animals show that Rocuronium is about one – fifth as potent as Vecuronium and has insignificant cardiovascular effects. The duration of action was similar to Vecuronium but its onset of block was about twice as rapid. In general the effect has been confirmed in humans. Org. 9426 in contrast to Vecuronium is stable in aqueous solution. The currently most frequently used agents Vecuronium and Atracurium have an onset of action that usually does not allow intubation earlier than 3 minutes after its injection [10]. The most important advantages of this new agent over Vecuronium are the more rapid rate of development of block and the good to excellent intubating condition within one minute after administration of Rocuronium [11], duration and recovery time were equal or slightly shorter than that of Vecuronium. It also has cardiovascular stability. Rocuronium has rapid onset of action, particularly at the vocal cords [12, 13] hence, this drug could be a valuable alternative to Succinylcholine when good intubating conditions are required rapidly [14]. It may be superior to other neuromuscular blockers available today as a result of speed with which it affords excellent intubation conditions. In adults, Rocuronium has an onset time which is close to that of Suxamethonium and shorter than that of Vecuronium, Atracurium and Mivacurium [15,16 &17]. Rocuronium has a rapid onset time, an intermediate duration of action and rapid recovery characteristics coupled with cardiovascular stability and virtually no histamine release [18] or any other side effects. Hence we aim to compare the intubating conditions with Vecuronium and Rocuronium at specific times based on clinical criteria.

Booij et al [19] published the first abstract on Rocuronium at the Ninth World Congress of Anesthesiologists at Washington in 1988. Since then many abstracts and publications on Rocuronium have followed. In the year 1991, Francis Donati [12] studied Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis and concluded that total relaxation of vocal cords require large doses of Vecuronium but that maximal effect is reached more rapidly than adductor pollicis. In the same year of 1991, J Mark et al [20] investigated the pharmacodynamics and pharmacokinetics of a new non-depolarizing neuromuscular blocking agent; Org 9426, and concluded that intubating conditions at one minute following the administration of dose of Org 9426 were excellent. The pharmacokinetic behaviour of it was identical to that of Vecuronium but volume of distribution appeared to be smaller.

M.G. Booth et al, [21] in the year 1992 conducted a study comprising comparison of the pharmacodynamics of Rocuronium and Vecuronium during Halothane anaesthesia and found that the onset of neuromuscular blockade following Rocuronium was more rapid than Vecuronium. All other pharmacodynamic parameters were similar. In year 1992, Mayer et al [22] studied the onset and recovery of Rocuronium and Vecuronium under Enflurane anaesthesia and found that Rocuronium had a significantly shorter onset time compared with Vecuronium, while clinical duration time was similar for both. Clude Meistelman in the year 1992 [12] studied the effects of Rocuronium on adductor muscles of the larynx and adductor pollicis in 14 adult patients and revealed that with Rocuronium, the onset and recovery are faster at the laryngeal muscles, but blockade is less intense than at the adductor pollicis. Cooper et al in the year 1992 [14] have assessed intubating conditions after administration of Org 9426 (0.6mg) at 60 or 90 seconds and compared the data with those obtained after Suxamethonium (1mg/kg) and concluded that the intubating conditions after Org 9426 were found to be clinically acceptable (excellent or good) in 95 % of patients at 60 seconds and in all patients at 90 seconds and in all patients at both times after Suxamethonium.

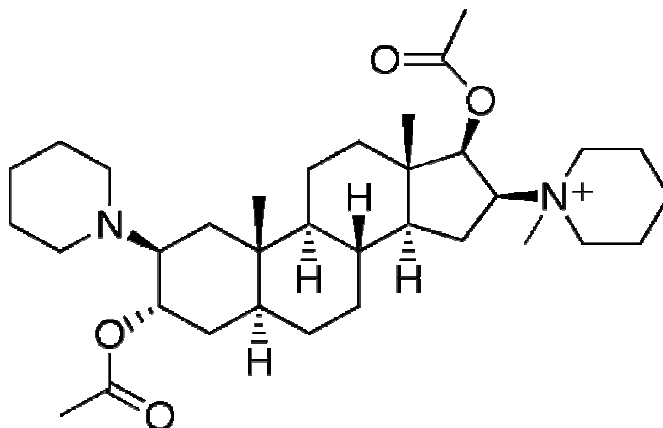
In the year 1992 Beven et al [23] studied pharmacodynamic behaviour of Rocuronium in the elderly and concluded that it is an intermediate acting neuromuscular blocking drug with a similar potency in elderly and young patients, but the onset and recovery of neuromuscular blockade are slower in the elderly. Cooper R A in the year 1993 [24] studied neuromuscular effects of

rocuronium during Fentanyl and Halothane anaesthesia and concluded that time to complete block decreased from about one minute with a dose of 0.6mg/kg; to approximately 45 seconds with a dose of 0.9 mg/kg. Mc Coy EP in the year 1993 [24] studied haemodynamic effects of Rocuronium during Fentanyl anaesthesia in comparison with Vecuronium and concluded that in patients receiving either of this drug, all changes in these parameters remain within clinically acceptable limits. Wierda et al in the year 1995 [25] studied the time course of action and intubating conditions following Vecuronium, Rocuronium and Mivacurium, and concluded that Rocuronium might be of advantage whenever the interval between the administration of the muscle relaxant and tracheal intubation must be short, whereas Mivacurium may be of benefit if fast spontaneous recovery is required. In 1996, Sparr H J et al [26] assessed the influence of induction technique on intubating conditions after Rocuronium in adults. They concluded that opioids (in doses equivalent to Alfentanyl 0.02mg/kg) contribute an integral part of an induction regime containing Rocuronium 0.6mg/kg, regardless of whether or not Thiopentone or Propofol is used. Sparr et al in their study to compare intubating conditions after Rocuronium and Succinylcholine with Thiopentone as an induction agent in elective cases and healthy patients found Rocuronium a suitable alternative to Succinylcholine.

Scheiber G et al [11] performed a randomized controlled trial in young children in 1996. They pointed out that clinically acceptable intubating conditions are produced more rapidly with Rocuronium than with Atracurium and Vecuronium. In 1997, Wierda et al [27] studied the cardiovascular effects of an intubating dose of Rocuronium 0.6mg/kg in anaesthetized patient paralysed with Vecuronium, thereby eliminating any haemodynamics effects related to paralysis itself. They concluded that an intubating dose of Rocuronium resulted in a limited increase in heart rate without change in mean arterial pressure, probably because of its weak vagolytic activity. Smith and Saad (1998) [28] conducted a study which compared intubating conditions after Rocuronium or Vecuronium when the timing of intubation is judged by clinical criteria; which confirmed the faster onset and significantly better intubating conditions with Rocuronium with no significant reduction in the haemodynamic response to intubation.

In the year 2000, T M Hemmerling et al [29] compared the onset of neuromuscular block with Succinylcholine (1 mg/kg) and two doses of Rocuronium (0.6 mg/kg and 0.9 mg/kg) at the adductor pollicis muscle using electromyography (EMG) and acceleromyography (AMG), and at the adductor laryngeal muscles with a new electromyographic method using a disposable surface electrode attached to the cuff of a tracheal tube. They found that, at the adductor pollicis muscle, 90% block and the onset time were significantly shorter in the Succinylcholine group ($p < 0.01$) than in both Rocuronium groups. Also 90% block and the onset time of Succinylcholine at the larynx were significantly shorter than that for both doses of Rocuronium. Benolt Plaud et al [30] in the year 2001 studied neuromuscular effects of Rocuronium at adductor pollicis muscle, the orbicularis oculi, and the corrugator supercilli in the dose of 0.5 mg/kg. In another group of patients, they studied neuromuscular effects of Rocuronium at adductor pollicis muscle, corrugator supercilli and the laryngeal adductor muscles in the dose of 0.6 mg/kg. They found that the neuromuscular responses to Rocuronium recorded at the eyelid (orbicularis oculi) and the thumb (adductor pollicis) are very similar. Also, the superciliary arch (corrugator supercilli) and the laryngeal adductor muscles demonstrate virtually the same neuromuscular profile. Norezalee Ahmed et al [31] in the year 2005 compared the efficacy of intravenous Fentanyl and intravenous Lignocaine as a pretreatment for the prevention of withdrawal response to pain after Rocuronium injection. They found that significant reduction in incidence of withdrawal response in both Fentanyl and Lignocaine groups when compared with the placebo group, with the Fentanyl group being more effective.

PHARMACOLOGY OF VECURONIUM (ORG NC 45)



Vecuronium is a nondepolarizing neuromuscular blocker of intermediate duration belonging to the steroidal group of compounds. It is a 2-desmethyl analogue of pancuronium synthesized in the mid 1970s by Savage, Durant, Bowman and Marshall and recognized to have much less vagolytic effect and a shorter duration of action than pancuronium in the cat. These properties were subsequently confirmed in humans [35, 36].

Structure and chemistry Vecuronium is pancuronium minus a quaternary methyl group (a mono quaternary relaxant) of the pancuronium molecule at the 2-piperidine position. Demethylation reduces the acetylcholine like characteristics of the molecule and increases the lipophilicity, which encourages hepatic uptake.

A number of physicochemical factors are associated with the selective action of pancuronium, the inter-atomic distance calculated in the crystal structure approximates those present in the biological receptor. There is an inherent rigidity of the androstane nucleus fixed by the presence of two acetylcholine fragments. A high degree of asymmetry contributes to the selectivity of action.

Pharmacokinetics [32, 33] Vecuronium fits the three compartment pharmacokinetic model. In doses of 25-50 µg/kg, the t of dilutional phase ($t_{1/2}$) is 2.2 minutes. The distribution t ($t_{1/2}$) is 13 minutes. Elimination t ($t_{1/2}$) is 75 minutes (this is 150 minutes in case of pancuronium but t and t' are similar with both pancuronium and Vecuronium. This explains the similar onset of action but different durations of action for both drugs. The steady state Volume of distribution (V_{dss}) is 0.25 to 0.28 lit/kg. (similar to pancuronium). Clearance rate is 2.5 ml/kg/min (almost three times greater than pancuronium). Plasma protein binding occurs to the extent of 30%. After a single bolus dose, recovery from Vecuronium depends more on distribution than on elimination. Recovery after long-term infusion (> 6 hours) is slower because the peripheral storage sites are saturated and the decrease in plasma concentration now depends on metabolism and elimination.

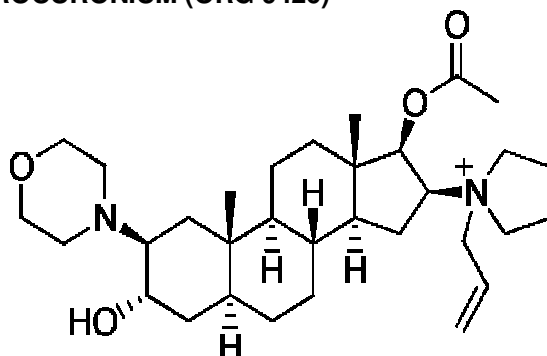
Metabolism and elimination [33, 34] 30-40% of Vecuronium is metabolised mainly in the liver by deacetylation at the 3- and 17- positions. The major metabolite (30%) is 3-desacetylvecuronium that is excreted by kidneys. It is a potent (~80% of Vecuronium) neuromuscular blocking drug, which has a lower clearance rate and longer duration of action than Vecuronium. Continuous infusions in Intensive Care Unit patients with renal failure can produce prolonged neuromuscular blockade due to accumulation of this metabolite. Liver is the main site for both metabolism and excretion. Most of the drug and its metabolites are excreted in the bile. Upto 25% of the drug can be excreted unchanged by the kidneys (Pancuronium depends more on renal excretion, upto 50% of the drug is excreted unchanged in urine). The duration of action of Vecuronium is prolonged in liver disease, renal disease and in children less than one year of age.

Pharmacodynamics : The onset of action and the time to development of maximal block are dose dependent with larger doses, in the presence of volatile agents, time to onset is two minutes. With a bolus of 0.1 mg/kg, the onset of action is 2.7 minutes and complete neuromuscular block continues for upto 10 minutes, when there is approximately 50% recovery of

twitch height. The overall duration of action extends to 30 minutes. Once recovery begins, at about 15 minutes after complete paralysis, the time from 25% recovery to 75% recovery is less than 10 minutes. When an infusion of 1-1.5 g/kg/min is used, the steady state plasma concentration giving at least a 90% block is about 0.2 µg/ml. On discontinuing the infusion, plasma concentrations fall rapidly in 6 to 12 minutes. At a concentration of 0.14 µg/ml only 50% twitch depression remains. At a concentration of 0.1 µg/ml, block is less than 25% and occurs at 30 mm. Full recovery is present after a bolus injection is less than 60 mm.

Pharmacological actions

PHARMACOLOGY OF ROCURONIUM (ORG 9426)



Rocuronium is a non depolarizing neuromuscular blocking agent with mainly a post-junctional effects and a high degree of selectivity for the receptors at the neuromuscular junction. Muscle paralysis is produced by competitive antagonism of the nicotinic cholinergic receptors of the skeletal muscle. Its potency is about 15-20 % of that of Vecuronium. Rocuronium does not produce block of autonomic ganglia. It has a faster rate of onset of action, an intermediate duration of action, rapid recovery and shows minimal cumulation. Being an aminosteroid compound, it has a low tendency to produce histamine release

Chemistry :- Rocuronium is the 2-morpholino-3-desacetyl-16-N-allyl-pyrrolidinium derivative of Vecuronium, differing from Vecuronium at three positions of the steroid nucleus. The chemical formula is $C_{32}H_{53}BrN_2O_4$ -1-allyl-1-(3 α -17 β -dihydroxy-2 β -morpholino-5 α -androstan-16 β -yl)pyrrolidinium bromide 17-acetate.

The molecular weight is 609.7. An interesting molecular characteristic of Rocuronium is the absence of the Acetylcholine like fragment that is found in the steroid nucleus of Vecuronium in the A- ring. The replacement of the methyl group attached to the quaternary nitrogen of Vecuronium by an allyl group and the absence of the Acetylcholine like fragments in the A-ring may be partly responsible for the decrease in potency seen with Rocuronium. It is available as a stable solution because of the replacement of the acetate group attached to the A- ring by hydroxy group.

HISTAMINE RELEASING PROPENSITY

Rocuronium being an aminosteroid based muscle relaxant is therefore, unlikely to release histamine [35]. Pharmacokinetics variables of a bolus administration of Rocuronium bromide 0.6mg/kg obtained from studies in patients under Propofol or Halothane or Isoflurane anaesthesia respectively. Adapted from Wierda et al [36].

Influence of anaesthesia technique:- The pharmacokinetics of Rocuronium bromide have been compared during various anaesthetic techniques. Van den Boek et al [37] concluded that the anaesthetic technique did not influence the pharmacokinetics of Rocuronium bromide. Consequently, the Isoflurane related potentiation of Rocuronium bromide induced neuromuscular block must be primarily based on an increased sensitivity of the muscle for the relaxant.

PHARMACODYNAMICS OF ROCURONIUM

Dose Effect Relationship: As the dose of Rocuronium increases, the percentage of neuromuscular blockade increases. Foldes et al [38] determined ED₅₀, ED₉₀ and ED₉₅ values of 0.17, 0.28, 0.305mg/kg respectively under balanced anaesthesia.

Onset and intubation: Rocuronium bromide has rapid onset of action. Rocuronium is seven to eight times less potent than Vecuronium but has the same molecular weight (609.7); therefore greater number of drug molecules may reach junctional receptors within a few circulation times enabling faster development of neuromuscular blockade. At a standard intubating dose of 0.6mg/kg, Rocuronium provides good to excellent intubating conditions at 60- 90 seconds [14]. However, at higher doses i.e. 3 x ED95 doses (0.9 mg/kg) safe rapid sequence intubation can be carried out within 45 seconds [39]. With lower doses (0.3 – 0.45 mg/kg) acceptable intubating conditions are present after 90 seconds [40]. ‘Priming’ or ‘precurarizing’ dose of Rocuronium is not necessary to obtain good to excellent intubating conditions 1 min after administration of an intubating dose. A priming dose of Rocuronium is ineffective in reducing the onset time [37]

Low potency → Weaker binding to receptor, → prevents buffered diffusion → easier diffusion of less potent drug from receptor → limits the duration of blocking effects.

I.V doses of Rocuronium with corresponding clinical duration of action. [41]

ED95	Doses (0.3-0.4mg/kg)	Clinical Duration (min)
Intubation	0.6-1	45-75
Relaxation (N ₂ O-O ₂)	0.3-0.4	30-40
Relaxation (vapor)	0.2-0.3	30-40
Maintenance	0.1-0.15	15-25
Infusion	8-12 micro/kg/min	-

A continuous infusion of Rocuronium can be used for long surgical procedures and intensive care units. This should be adjusted to maintain twitch height response at 10% of control twitch height.

SPECIAL GROUPS

Paediatrics: The onset time of Rocuronium in children and infants is faster than in adults. It has an intermediate duration of action at the standard intubating dose. The clinical duration is slightly shorter in children and slightly larger in infants than in adults [11]. Elderly: The clinical duration can be slightly prolonged in geriatric patient (> 65 yrs) compared to younger patient, possibly caused by age related changes in the distribution and elimination of Rocuronium [23]. Hepatic dysfunction: Patient having hepatic disease have an increased volume of distribution but no alteration in the plasma clearance elimination [42]. Therefore, the elimination half life is prolonged leading to longer duration of action, particularly after prolonged administration of Rocuronium in the patient with liver failure. The onset of action is not affected. Khalil et al [43], however, observed a slower onset of action in cirrhotic patient. This could be explained by an increase in the central volume of distribution in these edematous patients. Therefore, it should be used with caution in patients with clinically significant hepatic and /or biliary disease.

Renal dysfunction: Pharmacodynamics and kinetics parameters seem to be altered only to a limited extent in patient with renal disease [44, 45]. However, it should be used with caution in this patient group.

Cardiac surgery: Its apparent lack of clinically significant cardiovascular effects makes Rocuronium suitable for cardiac surgery. The mild vagolytic property may in fact offer an advantage during high dose fentanyl anaesthesia [24].

Surgery under hypothermic condition: Hypothermia prolongs the time course of action of Rocuronium [46].

Ophthalmic surgery: Rocuronium has no significant effects on intraocular pressure, and is therefore useful in penetrating eye injury [47].

Obesity: It exhibits prolonged duration and a prolonged spontaneous recovery in obese patient [48].

Pregnancy and Caesarean Section: Rocuronium is safe for mother and fetus. Animal studies have shown that Rocuronium does not cause embryotoxicity nor teratogenicity. It provides adequate intubating conditions in patients for caesarean section in 60 – 90 seconds [49].

MORPHOLOGY [52] The neuromuscular junction is specialized both on the nerve side and on the muscle side to transmit and receive chemical messages. Each motor neuron runs without interruption from the ventral horn of the spinal cord to the neuromuscular junction as a large myelinated axon. As it approaches the muscle it branches repeatedly to contact many muscle cells and to gather them in a functional group known as motor unit. Hence all the muscle cells on stimulation contract simultaneously seen as fasciculation.

QUANTAL THEORY [52, 53] End plate potential produced by nerve stimulation is due to release of 200 to 300 quanta simultaneously from several hundred vesicles. Acetylcholine is released in uniformly fixed packages or quanta. Each vesicle at the nerve terminal holds one quantum of transmitter

MATERIALS AND METHODS

The study was conducted in a tertiary care hospital and was approved by the Hospital Ethics Committee and conducted as a prospective randomized clinical trial on 60 adult patients. Sample size is selected based on the calculation according to EPI Info 6 version of guidelines issued by Centre for Disease Control (CDC) Atlanta, Georgia, United States with population size of 1000 and with high expectation of 10 % and low expectation of 0.05 %.

INCLUSION CRITERIA :- ASA physical status Class I and II, male or female patients, scheduled for elective surgery under general anaesthesia, Age 17 to 70 years, Patients in whom the results for pre-operative laboratory , assays are within the normal range, Patients giving written or witnessed informed consent.

EXCLUSION CRITERIA: - Patients not meeting the inclusion criteria, Patients with known or suspected renal, hepatic, metabolic, or neuromuscular disorder. Patients with known history of difficult intubation or anticipated difficult intubation (Mallampati class III or IV), Patients are known or suspected to have an allergy to narcotics neuromuscular blocking agents or other medications used during general anaesthesia, Patients are receiving or scheduled to receive drugs during the study period known to interfere with the action of neuromuscular blocking agents, with the exception of the anaesthetic drug indicated in the underlying protocol. Pregnant or breast - feeding patients. Patient refusal

TECHNIQUE:

A detailed pre - anaesthetic evaluation including history of previous medical illness, previous surgeries, general examination and appropriate baseline investigations was carried out. An informed written consent was obtained. Nil by mouth status for 6 hours preceding surgery was confirmed. Patients were re-examined on table, baseline values of pulse, blood pressure were recorded with the help of Non Invasive Blood Pressure (NIBP) monitoring system and pulse oximeter. Examination of the cardiovascular and respiratory system was done. Intravenous access was obtained with 18 G venous cannula.

These 60 patients were randomly divided into following 2 groups:

Group I : 30 patients, each receiving neuromuscular blockade with Vecuronium in dosage of 0.1) mg/kg, prepared as 6 ml solution containing Vecuronium 10 mg (1.67 mg/ml)

Group II : 30 patients, each receiving neuromuscular blockade with Vecuronium in dosage of

0.1mg/kg, prepared as 6 ml solution containing Vecuronium 10 mg (1.67 mg/ml)

Bias removal : Both the relaxant drugs were prepared as clear, colourless 6 ml solutions containing either Vecuronium 10mg (1.67 mg/ml) or Rocuronium 60 mg (10mg/ml). Airway management and tracheal intubation to be carried out by anaesthetist who is unaware of the group allocation. DOUBLE BLIND procedure is where not only the patient, but also the investigator is unaware which group of patient or patients are given drug or drugs and which group is on placebo. Both placebo and drug are labeled accordingly by the principle investigator.

Premedication: Inj. Glycopyrolate 0.04 mg/kg body weight, Inj. Midazolam 0.03 mg/kg body weight and Inj. Pentazocine 0.3 mg/kg given 15 minutes prior to induction.

Induction: All patients were pre -oxygenated with 100 % oxygen by face mask for 3 minutes. Patients both the groups received 2.5 % Thiopentone sodium in a dose of 5-7 mg / kg body weight intravenously as induction agent, titrated to loss of eyelash reflex and patient was control ventilated with oxygen & nitrous oxide (40 : 60%) with bag and mask. Muscle relaxant was administered as per the randomly allocated group (i.e. group I Rocuronium 0.6mg/kg body weight and group II Vecuronium 0.1mg/kg/ body weight.). Sixty seconds after administration of the muscle relaxant, using appropriate blade, direct laryngoscopy was performed every 15 seconds in sniffing position by the same experienced anesthesiologist who performed tracheal intubation thereafter. Once vocal cords abducted and jaw completely relaxed patient was intubated with appropriate size cuffed portex endotracheal tube. The time of intubation was noted from the time of administration of muscle relaxant and intubating conditions was scored according to the scoring system described by Goldberg et al.

The hemodynamic parameters, namely heart rate, systolic and diastolic blood pressure were recorded initially in the pre-operative period and noted as the baseline value, subsequent records were maintained at time of sedation, induction (included administration of muscle relaxant), laryngoscopy, intubation and at pre-determined 1 minute intervals over the next 5 minutes, followed by a 5 minute interval over the next 5 minutes and 10 minute intervals thereafter till the next 20 minutes. The total duration monitored over the post intubation period was 30 minutes.

Maintenance of anaesthesia: Anaesthesia was maintained with O₂:N₂O as 40:60 ratio with intermittent positive pressure ventilation. Clinical duration of action of intubating dose of both Rocuronium / Vecuronium were noted as the time from administration of intubating dose to the patients spontaneous attempt at respiration or reservoir bag resistance or movement of the patient. Additional top-ups of muscle relaxant were given as required. At the end of surgery, reversal with adequate doses of neostigmine and glycopyrolate was done and patient was extubated. The patient was assessed post operatively after shifting to recovery room and for one or two days after surgery.

RESULTS

STATISTICAL ANALYSIS

Data analysis was done using appropriate unpaired t-test, Chi-square test and non parametric test. A p value < 0.05 was considered statistically significant.

OBSERVATION AND RESULT

The present study was randomized, prospective, clinical trial carried out in sixty adult patients undergoing elective surgeries under general anaesthesia with endotracheal intubation. Patients were randomly divided into two groups of 30 patients each.

Group I- (Rocuronium bromide group):- Patients received Injection Rocuronium 0.6 mg/kg body weight intravenously.

Group II- (Vecuronium bromide group):- Patients received Injection Vecuronium 0.1 mg/kg body weight intravenously.

The data obtained was subjected to statistical analysis using Students unpaired 't' test to find out significant difference between the groups and Chi square test was used for qualitative data. For statistical comparisons, difference was considered significant when P value found less than 0.05. The patients were demographically similar in both groups (Table 1). The above table shows that

age of the patients was ranging from 16 – 70 years with mean age of 46.43 years in Rocuronium group and 46.63 years among Vecuronium group which was same and difference was not statistically significant (Table1).

The mean weight of the Patient was comparable in both the groups (Table1). In the study 66.7% of patients in Rocuronium group and 73.3% of patients in Vecuronium group of the total patients were male (Table1). While 76.7% of patient in Rocuronium group and 83.3% of patient in Vecuronium group belong to ASA physical status I and 23.3% of patient in Rocuronium group and 16.7% of patient in Vecuronium group belong to ASA physical status II (Table 1).The mean onset time was considered as the time interval (in minutes) between the end of administration of muscle relaxant and completion of intubation and was 95 ± 21.63 seconds in Rocuronium group and 168.0 ± 12.7 seconds Vecuronium group which was statistically significant $p < 0.001$ (Table 2). In the above study after administration of the muscle relaxant, intubating conditions with Rocuronium were excellent in 19 (63.3%) and good in 9(30%) patients while in the Vecuronium group, intubating condition were excellent in 18(60%) and good in 11(36.7%) patients which were comparable. None of the patient in either group had impossible intubation. The mean pulse rate was 80.10 ± 6.94 minute and 78.53 ± 8.51 minute ($p=0.4368$) in the Rocuronium and Vecuronium group respectively which is statistically not significant. In Rocuronium and Vecuronium group the mean systolic pressure was (126.20 ± 8.06 and 129.73 ± 8.27) mm of Hg ($p=0.0995$) and diastolic pressure was (82.60 ± 7.70 and 80.80 ± 7.84) mm of Hg ($p=0.3733$) respectively which were comparable. No significant difference was noted between the two groups in the changes of heart rate or systolic and diastolic blood pressures at the designated time intervals during the surgery. Pulse rate after muscle relaxant has shown slight increase. While there was significant rise in pulse rate at the time of laryngoscopy and intubation as compared to baseline and slow return to baseline pulse rate after intubation in both the groups (Table 5). During the study the systolic blood pressure after muscle relaxant has shown slight increase while there was significant rise in systolic blood pressure at the time of laryngoscopy and intubation as compared to baseline and slow return to baseline systolic blood pressure after intubation in both the groups (Table 6). Similarly diastolic pressure during the study was found to increase after muscle relaxant and significant increase in diastolic blood pressure seen at laryngoscopy and intubation and followed by a slow decline in postintubation period till end of surgery (Table 7)

DISCUSSION

It is generally agreed that the time interval between the suppression of the protective reflexes by the induction of anaesthesia and the development of satisfactory intubating conditions is a dangerous phase of anaesthesia. Regurgitation and tracheobronchial aspiration of stomach contents occur most frequently during this period. It is desirable therefore, that, this time interval should be as short as possible. A non - depolarizing neuromuscular blocker with a rapid onset of action and preferably of a shorter duration of action for rapid sequence tracheal intubation, especially to prevent aspiration pneumonia, is desirable. The search for the so called ideal muscle relaxant in the last years was focused on a non depolarizing compound that could replace Succinylcholine for rapid intubation. Succinylcholine is currently the only available neuromuscular blocking drug with an onset of action that makes it useful for rapid sequence tracheal intubation. However, it has several side effects, some of which are inconvenient, while others may be harmful. In addition, its use may be contraindicated in some condition. In our study demographic data was comparable (Table 1). The mean age of the patient was 46.43 years in Rocuronium group and 46.63 years among Vecuronium group which was same and difference was not statistically significant. Mean weight of patient was 59.67 kg in Rocuronium group and 61.07 kg in Vecuronium group. There were 66.7% of male in Rocuronium group and 73.3% of male in Vecuronium group of the total patients in both the groups. Similarly 76.7 % and 23.3% of patient were of ASA physical status I and II respectively in Rocuronium group– while 83.3% and 16.7 % of the patient belong to ASA physical status I and II respectively in Vecuronium group. Mishra M N et al [39] in his study considered 90 patients in age group of 16-60 years with ASA physical status I and II of either sex for a comparative study of Rocuronium, Vecuronium and Succinylcholine for rapid sequence induction of anaesthesia which was comparable. Aparna Shukla [54] et al in her study included patients in age group 20-60 years with ASA physical status

I and II for comparative evaluation of haemodynamic effects and intubating conditions after the administration of org 9426 (Rocuronium) and Succinylcholine which was also comparable. In our study after the administration of muscle relaxant onset time was considered as the time interval (in minutes) between the end of administration of muscle relaxant and completion of intubation, which was 95 ± 21.6 seconds versus 168.0 ± 12.7 seconds ($P < 0.001$) in Rocuronium and Vecuronium group respectively for most of the patients under the study. Weirda et al [25] found intubating conditions at 60 seconds using standard intubating dose i.e. of 0.6 mg/kg body wt. (2 X ED 95) of Rocuronium under intravenous anesthesia were excellent. The study conducted by Cooper et al [14] found onset time decrease from about 60 seconds with a dose of 0.6mg/kg of Rocuronium to approximately 45 seconds with a dose of 0.9 mg/kg of Rocuronium. Toni Magorian et al [15] conducted similar studies and found onset time for patient receiving 0.9 mg/kg, 1.2 mg/kg Rocuronium and Succinylcholine 1.0 mg/kg was (75 ± 28 sec), (55 ± 49 sec) and (50 ± 17 sec) respectively. Gerd Scheiber et al [11] had done similar study and found excellent to good intubating conditions developed significantly faster in the Rocuronium group, as compared to Vecuronium and Atracurium group in a study of 20 patients. Boek et al [55] found better intubating conditions with Rocuronium than Vecuronium at 90 seconds. During our study clinical judgement predicted satisfactory tracheal intubation conditions after Rocuronium and Vecuronium administration allowing intubation to be complete within acceptable period of time. Nitschman et al [56] in his study compared Rocuronium, Vecuronium and Pancuronium. The haemodynamic changes in patients undergoing coronary artery bypass surgery demonstrated that pancuronium caused significant tachycardia and sympathetic response to intubation whereas Vecuronium and Rocuronium decreased the heart rate during surgery.

CONCLUSION

The present study was performed as a randomized, prospective, double blind, clinical trial in 60 adult patients in age group of 16-70 years with ASA physical status I or II patients, to compare the two non depolarizing neuromuscular blocking agent Rocuronium bromide (0.6 mg/kg body weight) and Vecuronium bromide (0.1 mg/kg body weight) in elective surgery under general anaesthesia with respect to onset of action, intubating conditions and haemodynamic changes. It can be observed from the present study, the two groups were comparable for age, sex, weight and ASA status of the patients. Rocuronium at 0.6mg/kg bodyweight produced excellent and good intubating conditions at 95 ± 21.6 seconds and Vecuronium at 0.1mg/kg body weight produced excellent and good intubating condition at 168.0 ± 12.7 seconds after the intravenous administration. Both the drugs were comparable as regard to cardiovascular stability with the mean pulse rate was 80.10 ± 06.94 and 78.53 ± 08.510 per minute ($p = 0.4368$) in Rocuronium group and Vecuronium group respectively. The mean systolic pressure was 126.20 ± 08.06 mm of Hg and 129.73 ± 08.27 mm of Hg ($p = 0.100$) and the mean diastolic pressure was 86.60 ± 07.70 mm of Hg and 85.80 ± 07.84 mm of Hg ($p = 0.691$) in Rocuronium group and Vecuronium group respectively. It can be observed from above result that Rocuronium provides earlier excellent and good intubating conditions than Vecuronium with similar cardiovascular stability at intubation and post intubation period. It is evident from the above study that Rocuronium had a more rapid onset of action and provided conditions suitable for more rapid tracheal intubation than Vecuronium during general anaesthesia with endotracheal intubation in surgical patients. The haemodynamic changes in surgical patients exhibited similar trend in their variation during intubation and post intubation period in both the Rocuronium and Vecuronium groups. Thus the advantage of Rocuronium, with its early onset of action, along with good to excellent intubating conditions and the cardiovascular stability, make this neuromuscular relaxant a desirable choice for rapid tracheal intubation in surgical procedures requiring general anaesthesia with endotracheal intubation for controlled ventilation.

REFERENCES

- [1] Ronald D. Miller *Miller's Anesthesia 7th Edition, Volume 1; Churchill Livingstone; History of Anesthetic Practice: 24-26.*
- [2] Griffith H., Johnson G. (1942) *Anesthesiology* 3: 418-420.
- [3] Thesleff S., Von Dardel O., Holmberg F. (1952) *Br J Anaesth*; 24: 238 – 244.
- [4] Foldes F. F., McNall P.G., Borrego-Hinojosa J.M. (1952) *N Engl J Med*; 247: 596-600.

- [5] Baird W. L., Reid A. M. (1967) *Br J Anaesth*; 39: 775-780.
- [6] Savage D. S., Sleigh T., Carlyle I. (1980) *Br J Anaesth*; 52(Suppl 1): 3S-9S.
- [7] Wierda J. M., de Wit A.P., Kuizenga K., Agoston S. (1990) *Br J Anaesth*; 64: 521-523.
- [8] Wierda J. M., Proost J. H. (1995) *Eur J Anaesthesiol Suppl*; 11: 45-54.
- [9] Naguib M., Samarkandi A. H., Bakhamees H. S. et al. (1995) *Br J Anaesth*; 75: 37-42.
- [10] Bartkowski R. R., Witkowski T. A., Azad S. et al. (1993) *Anesth Analg*; 77: 574-578.
- [11] Scheiber G., Ribeiro F. C., Marichal A. et al. (1996) *Anesth Analg*; 83: 320-324.
- [12] Meistelman C., Plaud B., Donati F. (1992) *Can J Anaesth*; 39: 665-669.
- [13] Wright P. M., Caldwell J. E., Miller R. D. (1994) *Anesthesiology*; 81: 1110-1115.
- [14] Cooper R., Mirakhur R. K., Clarke R. S., Boules Z. (1992) *Br J Anaesth*; 69: 269-273.
- [15] Magorian T., Flannery K. B., Miller R. D. (1993) *Anesthesiology*; 79: 913-918.
- [16] Bartkowski R. R., Witkowski T. A., Azad S. et al. (1993) *Anesth Analg*; 77: 574-578.
- [17] Naguib M. (1994) *Anesthesiology*; 81: 388-395.
- [18] Naguib M., Samarkandi A. H., Bakhamees H. S. et al. (1995) *Br J Anaesth*; 75: 588-592
- [19] Marshall R. J., Muir A. W., Booij L., Crul J., Marshall I. G. (1988) *9th World Congress of Anaesthesiologists*; Vol II: AO534.
- [20] Mark J., Wierda K. H., Ursula W Kleef, Ludwina M Lambalk, Wybe D Kloppenburg and Sandor Agoston. (1991) *Can J Anaesth*: 38 (4) : 430 – 435
- [21] Booth M. G., Marsh B., Bryden E. M. M., Robertson E. N., Baird W. L. M. (1992) *Anaesthesia*; 47: 832-4.
- [22] Mayer M. et al (1992) *Br J Anaesth*; 69: 511-512.
- [23] Bevan D. R. et al. (1993) *Can J Anaesth*: 40 (2): 127- 132.
- [24] McCoy E. P., Maddineni V. R., Elliop P., Mirakhur R. K., Carson I. W., Cooper R. A. (1993) *Can J Anaesth*; 40 (8): 703 – 708
- [25] Weirda J. M. K. H., Hommes F. D. M., Nap H. J. A., Van den Boek L. (1995) *Anaesthesia*; 50: 393-396.
- [26] Sparr H. J. et al (1996) *Br J Anaesth*, 77: 339-342.
- [27] Wierda J. M. et al: (1997) *Br J Anaesth*; 78 (5): 586-587.
- [28] Smith and R. S. G. Saad. (1998) *Br J Anaesth*; 80: 235-237.
- [29] Hemmerling T. M. et al: (2000) *Br J Anaesth*; 85: 251-5.
- [30] Benolt Plaud et al. (2001) *Anaesthesiology*, 95: 96 – 101
- [31] Norezalee Ahmed et al. (2005) *Anaesth Analg*; 100: 987 – 90
- [32] Fahey M. R., Morris R. B., Miller R. D. et al. (1981) *Anesthesiology*; 55-56.
- [33] Collins V. J. *Principles of Anaesthesiology, General and Regional anesthesia, 3rd edition: Relaxant Pharmacology and use. Volume 2*; 938-1022.
- [34] Agoston S., Salt P., Newton D. et al (1980) *A pilot study, Br J Anaesth*: 52-53.
- [35] Levy J. H. et al (1994) *Anaesthesia Analgesia*; 78: 318-321.
- [36] Wierda J. M. K. H. et al (1994) *Eur J Anaesthesia*; 11(9): 66-74.
- [37] Van den Broek L. et al (1994) *J Clin Anaesth*; 6: 288-296.
- [38] Folders F. F. et al (1991) *Anaesthesiology*; 75: 191- 196.
- [39] Mishra M. N., Agarwal M., Pandey R. P. (2005) *Indian Journal Anaesthesia*: 49 (6): 469-473.
- [40] Pollard B. J. et al (1995) *Eur J Anaesthesia*; 12 (11): 81 – 83.
- [41] Miller R. D. (1994) *Anaesthesia 4th Vol-1 Churchill Livingstone, N.Y.. John J. S. et al: Pharmacology of muscle relaxants and their antagonists page 417.*
- [42] Magorian T. et al (1995) *Anaesthesia Analgesia*; 80: 754-759.
- [43] Khalil M. et al (1994) *Anaesthesiology*; 80: 1241-1247.
- [44] Szenohradzky J. et al (1992) *Anaesthesiology*; 77: 899- 904.
- [45] Khuel-Brady K. S. et al (1993) *Anaesthesia*; 48: 873-875.
- [46] Beaufort A. M. et al (1995) *Eur J Anaesthesia*; 12 (11): 95-106.
- [47] Robertson E. N. et al (1994) *Eur. J. Anaesthesia*; 11 (9) 116- 121.
- [48] Pearson K. S. et al: *Anaesthesia Analgesia*; 76: S 327.
- [49] Abouleish E. et al. (1994) *Br J Anaesthesia*; 73: 336-341.
- [50] Cooper R. et al (1993) *Br J Anaesth*; 71: 222-226.
- [51] Oris B., Crul J. F., Vandermeersch E., Van Aken H., Van Egmond J., Sabbe M. B. (1993) *Anaesth Analg*; 77: 570 – 573.

- [52] William F Ganong. *Review of Medical Physiology, 22nd edition, Tata McGraw Hill, Neuromuscular Transmission, Pages 116-117.*
- [53] Guyton and Hall. *Textbook of Medical Physiology, 10th edition, Saunders Elsevier, The Neuromuscular Junction, Pages 80-83.*
- [54] Aparna Shukla, Dubey K P, Sharma M. S. N. (2004) *Indian J Anaesth*; 48 (6): 476-479.
- [55] Van den Boek L. et al. (1993) *J Clin Anaesth*; 6: 288-296.
- [56] Nitschmann P. et al. (1994) *Eur J Anaesth*; 11: 113-115.

Table 1 - Demographical Data Between Two Group
 @ By Student't' Test Not Significant

Parameters	Rocuronium	Vecuronium	p value
No. of patients	30	30	
@Age (yrs) Mean SD Range	46.43 13.82 16 – 65 yrs	46.63 11.67 22 – 70 yrs	0.9519
@Weight (kgs) Mean SD Range	59.67 8.93 40 – 75 kgs	61.07 7.94 48 – 78 kgs	0.5236
#Sex (%) Male Female	20 (66.7) 10 (33.3)	22 (73.3) 08 (26.7)	0.5731
#ASA Grade (%) I II	23 (76.7) 07 (23.3)	25 (83.3) 05 (16.7)	0.5186

By Chi – Square Test

Table 2- comparison of mean time of onset between two groups

Groups	Mean Time ($\bar{X} \pm SD$)	p value
Rocuronium	*95.50 ± 21.63	0.0000
Vecuronium	168.00 ± 12.70	

By Student 't' test

* Significant

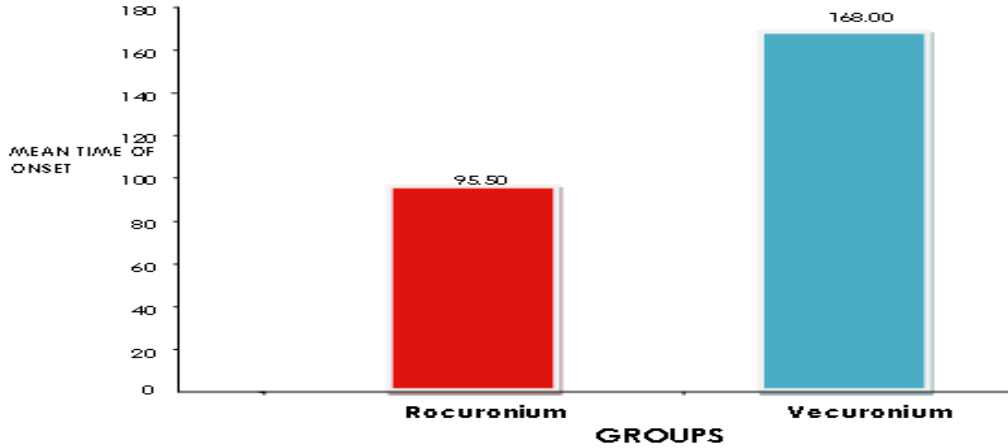


Fig. 3- comparison of mean time of onset between the groups

Table 3- profile of intubating conditions between two groups

Condition	Rocuronium (n = 30)		Vecuronium (n = 30)	
	No.	%	No.	%
Excellent	19	63.3	18	60.0
Good	09	30.0	11	36.7
Fair	02	06.7	01	03.3

By Chi – Square Test p = 0.4541

Not Significant

Table 4- comparison of mean haemodynamic parameters between two groups

By Student't' Test

Not Significant

Parameters	Mean Haemodynamic Parameters ($\bar{X} \pm SD$)		
	Rocuronium	Vecuronium	p value (Betn Grps)
Pulse Rate	80.10 ± 6.94	78.53 ± 8.51	0.4368
Systolic Blood Pressure	126.20 ± 8.06	129.73 ± 8.27	0.0995
Diastolic Blood Pressure	82.60 ± 7.70	80.80 ± 7.84	0.3733

Table 5- comparison of changes in mean pulse rate between two groups

Duration in mins	Mean Pulse rate($\bar{X} \pm SD$)		
	Rocuronium	Vecuronium	P value (Betn Grps)
Baseline	80.10 ± 06.94	79.53 ± 08.51	0.7772
Sedation	81.10 ± 06.76	80.00 ± 07.33	0.5481
Induction	84.60 ± 06.79	83.47 ± 11.91	0.6533
Laryngoscopy	*101.53 ± 11.82	*100.27 ± 10.96	0.6702
Intubation	*95.10 ± 14.69	*94.50 ± 08.86	0.8487
1 minute	80.80 ± 10.55	79.27 ± 05.58	0.4854
2 minutes	*77.03 ± 04.51	*75.50 ± 06.60	0.2988
3 minutes	*76.80 ± 06.12	*74.33 ± 05.45	0.1042
4 minutes	*76.87 ± 06.88	*74.10 ± 06.98	0.1271
5 minutes	*76.97 ± 04.30	*75.00 ± 05.30	0.1193
10 minutes	*76.87 ± 04.51	*75.57 ± 04.34	0.2600
20 minutes	*77.63 ± 05.71	*74.80 ± 05.74	0.0605
30 minutes	*76.92 ± 05.78	*74.57 ± 05.31	0.1064

By Student 't' test *p < 0.05 Significant Between Groups p > 0.05 Not Significant

Table 6- comparisons of changes in mean systolic blood pressure between two groups

Duration in minutes	Mean Systolic blood pressure ($\bar{X} \pm SD$)		
	Rocuronium	Vecuronium	p value (Betn Grps)
Baseline	126.20 \pm 08.06	129.73 \pm 08.27	0.100
Sedation	127.20 \pm 05.40	127.87 \pm 04.73	0.611
Induction	130.67 \pm 07.62	129.93 \pm 07.67	0.712
Laryngoscopy	*143.87 \pm 08.42	*144.70 \pm 06.84	0.676
Intubation	*140.87 \pm 11.70	*137.40 \pm 07.85	0.182
1 minute	124.07 \pm 06.80	122.70 \pm 06.78	0.437
2 minutes	121.67 \pm 06.28	120.47 \pm 07.82	0.514
3 minutes	122.27 \pm 05.43	121.13 \pm 06.84	0.477
4 minutes	121.67 \pm 05.33	119.33 \pm 07.01	0.150
5 minutes	120.47 \pm 06.25	113.60 \pm 19.58	0.072
10 minutes	121.93 \pm 05.50	122.60 \pm 06.89	0.678
20 minutes	122.36 \pm 06.28	121.67 \pm 06.38	0.674
30 minutes	125.00 \pm 04.39	124.48 \pm 07.70	0.749

By Student't' test *p < 0.05 Significant Between Groups p > 0.05 Not Significant

Table 7- comparison of changes in mean diastolic blood pressure between two groups

Duration in minutes	Mean Diastolic blood pressure ($\bar{X} \pm SD$)		
	Rocuronium	Vecuronium	p value (Betn Grps)
Baseline	86.60 ± 07.70	85.80 ± 07.84	0.691
Sedation	83.27 ± 06.82	82.63 ± 06.69	0.715
Induction	86.83 ± 07.98	84.00 ± 07.11	0.182
Laryngoscopy	*91.20 ± 06.53	*90.63 ± 06.06	0.727
Intubation	86.27 ± 08.71	85.40 ± 06.11	0.655
1 minute	*79.47 ± 05.58	*78.20 ± 05.34	0.371
2 minutes	*76.53 ± 05.92	*75.67 ± 04.74	0.536
3 minutes	*77.03 ± 06.14	*76.10 ± 07.11	0.589
4 minutes	*75.03 ± 04.30	*74.80 ± 03.50	0.821
5 minutes	*76.80 ± 05.45	*75.37 ± 06.12	0.343
10 minutes	*76.00 ± 05.68	*74.87 ± 05.24	0.426
20 minutes	*78.56 ± 05.34	*77.10 ± 06.16	0.330
30 minutes	*77.82 ± 06.60	*76.40 ± 04.44	0.332

By Student 't' test *p < 0.05 Significant Between Groups p > 0.05 Not Significant

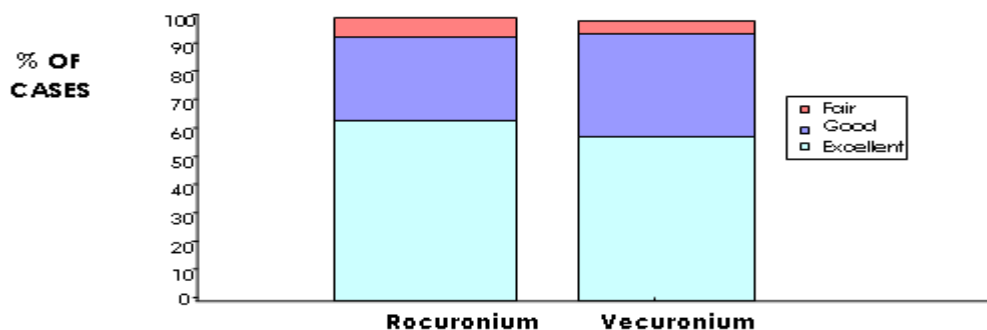


Fig. 2- profile of intubating conditions between two groups