Comparison of neuromuscular blockade effects of a combination of Atracurium and Vecuronium with Vecuronium or Atracurium used Alone

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Abstract

Muscle relaxants are necessary for intubation of patients during anesthesia. Many such agents are available with various degrees of efficacy regarding intubation conditions, onset of actions and complications. In this study, effects of atracurium and vecuronium were analysed both singly and in various combinations. Eighty adult patients of ASA Grade I and II posted for elective surgery were randomly divided in 4 groups. Group A patients received intubating dose of injection Atracurium (0.5 mg/kg body weight), Group B received intubating dose of injection Vecuronium (0.1 mg/kg body weight), Group C received combination of half of the intubating dose of both injection Atracurium (0.25 mg/kg body weight) and injection Vecuronium (0.05mg/kg body weight) and Group D received combination of ¾ th of the intubating dose of both the injection Atracurium (0.375 mg/kg body weight) and injection Vecuronium (0.075 mg/kg body weight). It was concluded that ¾ combination of atracurium and vecuronium provided the shortest onset time with moderate prolongation of duration of neuromuscular blockade as compared to use of either drug or any single other ratios of the two drug combinations.

Key words: *neuromuscular blockade, Atracurium, Vecuronium*

Introduction

Muscle relaxants are essential in balanced anesthesia as adjuncts to analgesic and hypnotic drugs. The simultaneous introduction of the two muscle relaxants of intermediate action; 'Atracurium and Vecuronium' in the early 1980's revolutionized clinical practice by providing relaxation with little dependence on the kidney for elimination, faster onset of action, a relatively rapid recovery and faster and complete antagonism of residual block as compared to the longer lasting drugs. This led to a more convenient method to provide paralysis by continuous infusion of relaxants. However neither drug is able to provide optimal intubating conditions as rapidly as succinylcholine. Several maneuvers have been utilized to increase their speed of onset. These include the use of 'priming doses', large doses and more recently combinations of two drugs.[1] Synergism between atracurium and vecuronium has been demonstrated both in vivo and vitro.[2] The advantages offered by use of a combination of atracurium and vecuronium are a decrease in the expenses of producing conditions suitable for intubation and avoiding the use of suxamethonium. In addition, a more rapid recovery time, in some instances allows for use of smaller than usual doses of relaxant antagonists. The incidence of cardio vascular side effect are also diminished by the use of the combined regimen. Hence the combinations of atracurium and vecuronium were compared with either of the drug used alone and effects regarding intubation condition, onset of action, duration of action and complications if any, were studied.

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Aims and Objectives

To compare the effects of :

a) Atracurium used alone
b) Vecuronium used alone
c) Atracurium and Vecuronium used in the following combinations
   i) ½ of the intubating dose of Atracurium (0.25 mg/kg body weight) and Vecuronium (0.05 mg / kg body weight) and

ii) ¾ of the intubating dose of Atracurium (0.375 mg/kg body weight) and Vecuronium (0.075 mg/kg body weight).

The following effects were monitored :

1. Intubating conditions
2. Onset of action.
3. Duration of action.
4. Hemodynamic effects.

Methods :

This was a randomized, double-blind controlled study consisting of 80 patients undergoing routine elective surgery requiring endotracheal intubation as one of the anesthetic procedures. Neither the anaesthetist involved in the administration of anesthesia nor the investigator was aware of the group to which the patient had been assigned. All the patients were between the ages of 15 years to 65 years and were grouped as ASA (American Society of Anaesthesiologis) Grade I or II. Patients requiring general anaesthesia with endotracheal intubation and an estimated duration of surgery of atleast sixty minutes were chosen for the study. Patient who had neuromuscular disease, oesophageal reflux and difficult airway were excluded. Patients were allocated to one of the four groups of equal sizes.

All patients belonging to ASA I or II underwent thorough pre-anaesthetic evaluation prior to surgery in the form of clinical examination and investigations like blood sugar, blood urea nitrogen, serum creatinine, serum electrolytes, electrocardiogram and chest roentgenogram.

Equipments for general anesthesia were kept ready. Baseline recording of pulse rate and arterial blood pressure was carried out. The following preanesthetic medications were instituted :

1. Injection glycopyrrolate:.04 mg/kg body weight, intramuscular
2. Injection pentazocine: 0.6 mg/kg body weight, intravenous
3. Injection promethazine: 0.5 mg/kg , intravenous.

All the patients were induced with injection penthothal sodium 0.4 to 0.5 mg/kg body weight. Train of four (TOF)responses was studied by visual means by pressing TOF button of the peripheral nerve stimulator. This was followed by intravenous administration of the muscle relaxant to be studied for intubation in the appropriate dose.

Table 1: Intubating dose of study drug among four Groups in mg/kg body weight

Intubating drug	Group A	Group B	Group C	Group D
Inj. Atracurium	0.5	--	--	--
Inj. Vecuronium	--	0.1	--	--
Inj.Atracurium + Inj. Vecuronium	--	--	0.25+ 0.05	-- --
Inj.Atracurium + Inj. Vecuronium	--	--	--	0.375+ 0.075

Assisted ventilation with 50% Oxygen in Nitrous oxide for ninety seconds was rendered subsequently. Meanwhile, TOF response was studied at 30 seconds intervals. The intubating condition was assessed and direct laryngoscopy performed. The jaw tone was assessed as either good or inadequate to allow laryngoscopy and intubating conditions were scored as excellent, good, poor or impossible according to parameters described by Goldberg and colleagues (Table 2). If intubation was not successful at the first attempt, assisted ventilation was reinstituted until conditions were favorable.

Table 2: Jaw tone assessment (Goldberg et al)

Grade	Description
I - Excellent	Easy passage of the tracheal tube with no reactive coughing and with relaxed vocal cords.
II - Good	Slight reactive coughing but with relaxed vocal cords.
III - Poor	Moderate reactive coughing or bucking with some vocal cord movement.
IV - Impossible	Vocal cords adducted or uncontrolled coughing and bucking.

After intubation, anesthesia was maintained with O_2 and N_2O and one-fourth of the loading dose of the muscle relaxant, volatile anaesthetic was used only if needed. At the end of the surgery residual neuromuscular

blockade was reversed with injection neostigmine 0.08 mg/kg body weight and injection atropine 0.02 mg/kg body weight by intravenous route. There was correlation between visual estimation of TOF response and clinical scores during intubation (Table 3).

Table 3: Intubating score according to TOF response at intubation

Intubating score	TOF Response at Intubation
3	4/4
2	3/4
1	2/4
0	1/4

Method of Analysis

To calculate the sample size, a power analysis of á =1.96 and â =1.64 at 5% level showed that 19 patients per study group were needed. Therefore we included 20 patients per group. The various data obtained, which included time of onset and duration of neuromuscular blockade in group A were calculated and compared to the corresponding times in group C and D using 't' test. Similarly time of onset and duration in group B were compared to the corresponding times in group C and D. Level of significance was chosen as p-value <0.05. Pulse rate and blood pressure changes were compared statistically with p-value >0.05 being not significant.

Results

Table 4 shows that all groups were comparable in respect of patients characteristics i.e.sex and age (p>0.05).

Table 4: Sex and Age Distribution of Study Group

Distribution	Group A	Group B	Group C	Group D
Male:Female Ratio	15:5	6:14	8:12	7:13
Mean Age (Years)	31.1	34.85	39.45	32.2
± S.D.	±7.7	±13.2	±10.9	±13.1

As is evident from Table 5, the onset time in Group D (combination of ¾th intubating dose) was significantly shorter(3.6±2.11min.) as compared to onset time in Group A (8.1±4.40 min.) and Group C (6.6±2.27 min.) with p<0.05 . The onset time (6.6±2.27 min.) in Group C was significantly shorter than Group A (8.1±4.40 min.) but longer than that in Group B(4.1±2.72 min.) . As evident in Figure 2, the duration of neuromuscular blockade in Group D (44.25±12.00 min.) was longer than Group B(33.25±5.86min.) and Group C (33.85±6.89 min.) which was statistically significant (p<0.05). The duration in Group C was comparable with that in Group B but longer than that in Group A(22.52±7.28 min.) which was statistically significant (p<0.05).

Table 5 : Onset of action and duration of neuromuscular blockade (all values in minutes)

	Group A	Group B	Group C	Group D
Onset Time (Mean)	8.1	4.1	6.6	3.6
± S.D.	±4.40	±2.72	±2.27	±2.11
Duration of Action (Mean)	22.52	33.25	33.85	44.25
± S.D.	±7.28	±5.86	±6.89	±12.00

As is evident from Table 6, about 90% patients in Group D had excellent intubating conditions which was significant (p<0.05) when compared to that in Group A (15%) and Group C (25%) but not significant when compared to that in Group B (85%, p>0.05). In Group C, majority of the patients (65%) had good intubating condition which was significant (p<0.05) when compared to that in Group A (30%) and Group B (15%).

Hemodynamic effects

Cardiovascular status of all patients remained stable. Changes in pulse rate (82.27±14.2 / min) in Group D were statistically significant unlike in Group A (96.02±8.6 / min) and Group B (94.3±14.06 min) (P>0.05) as shown in Table 7. Also changes in blood pressure values (111.08±11.08 mmHg) in Group D were statistically significant unlike in Group A (127±9.2 mmHg) (Table 8).

Table 6 : Intubation condition grades

	Grades of Intubating Condition				Total
Groups	**I (Excellent)**	**II (Good)**	**III (Poor)**	**IV (Impossible)**	
A (n=20)	3 (15%)	6 (30%)	9 (45%)	2 (10%)	20
B (n=20)	17 (85%)	3 (15%)	-	-	20
C (n=20)	5 (25%)	13 (65%)	2 (10%)	-	20
D (n=20)	18 (90%)	2 (10%)	-	-	20

Table 7: Comparison of Pulse Rate/Min. (Mean ±S.D.)

Distribution	Group A	Group B	Group C	Group D
Preoperative	83.4 (±9.0)	91.5 (±12.2)	84.9 (±10.6)	83.9 (±8.5)
Intraoperative	96.0 (±8.6)	94.3 (±14.6)	91.4 (±15.2)	82.27 (±14.2)
Postoperative	94.4 (±8.8)	92.7 (±9.3)	86.4 (±10.0)	82.2 (±9.7)

Table 8: Blood Pressure (BP mm of Hg) Changes (Mean ±S.D.)

Distribution	Group A	Group B	Group C	Group D
Preoperative	111.5 (±10.7)	118.4 (±9.8)	112.2 (±13.2)	113 (±11.9)
Intraoperative	127 (±9.2)	119 (±13.0)	114.7 (±13.2)	111.08 (±11.1)
Postoperative	129.6 (±4.6)	122.3 (±8.7)	119.5 (±11.6)	119.3 (±11.0)

Side effects

1. Two patients in Group C developed bradycardia.
2. One patient in Group B developed ventricular premature beats.
3. No residual recurarization was seen post operatively.

Discussion

Rapid onset of action, permitting early tracheal intubation is one of the desirable properties of neuromuscular blocking agents. With the current method of administration of muscle relaxants this can be achieved with succinylcholine. Succinylcholine however, has numerous side effects and occasionally may cause serious complications like prolonged apnoea and hyperkalemia (resulting in cardiac arrest). With reasonable doses of non-depolarised muscle relaxants, conditions suitable for tracheal intubation cannot be achieved in less than 2 to 3 minutes and the onset time required for the development of maximal effect is 5 to 6 minutes. Several maneuvers have been utilized to increase this speed.

Combinations of the drugs, atracurium and vecuroniun have been utilized to increase the onset of action. Several investigators have demonstrated synergism between atracurium and vecuronium, both in vivo and in vitro.[2] The mechanism by which different non-depolarizing neuromuscular blocking drugs interact to produce a supra-additive effect is unclear. However the interaction appears to be pharmacodynamic rather than pharmacokinetic. Although the precise mechanism underlying synergistic interactions are not known, hypothesis that have been put forward include :

a) The existence of multiple binding sites at the neuromuscular junction (pre and post synaptic receptors).
b) Alteration of the pharmacokinetic behavior of one drug by the other (Martin et al).[3]

It has been shown that concomitant administration of some mixtures of non-depolarizing compounds (d-tubocurarine and gallamine; pancuronium and gallamine; pipecuronium and rocuronium) does result in additive effects. Other combinations of non-depolarizing agents (pancuronium and metocurine, gallamine and metocurine or d-tubocurarine and pancuranium) clearly demonstrate synergistic effects [4,5]. Although Waud and Waud have suggested that synergistic action can be entirely of postsynaptic origin, others have attributed synergism to both presynaptic and motor end plate effects.[6, 7] Adequate intubating conditions are dependent on depth of anaesthesia, skill of endoscopist and muscle relaxation. In our study, excellent intubating conditions were achieved in 90% of patient who received ¾th of intubating dose of combination of atracurium and vecuroniun, 25% of patient who received ½ of intubating dose of combination of atracurium and vecuroniun, 85% of patient who received

vecuronium alone and 6.6% of patient who received atracurium alone. This was statistically significant and this also suggests that excellent intubating condition can be achieved with three fourth dose combination compared to other groups.

J.A.Berman, M.Sesking etc., studied combination of atracurium and vecuronium to facilitate rapid endotracheal intubation. They found that 90% of patient, who received ¾th of intubating dose of combination of atracurium and vecuronium, facilitated rapid intubation. They also found that depression of twitch height could be achieved rapidly with combination of atracurium and vecuronium in 90% of patients.[8]

Silverman D.G., Swift C.A. and Hartman K.A. found that the onset of blockade with combination of atracurium and vecuronium was faster compared to vecuronium alone.[9] In the current study combinations of atracurium and vecuronium produced a significantly shorter onset time than would be expected from simple additivity. Our study shows that onset time was shortest in the group which received three fourth combination (3.6 minutes ±2.11) ($p<0.05$ significant), which was statistically significant, compared to other groups. In Group C, onset of action was 6.6 minutes and in Group B it was 4.1 minutes. It was longest in the Group which received atracurium alone i.e. 8.1 minutes. It is presumed that differences in onset in various patients are because of difference in muscle blood flow, and relaxant binding between central and peripheral muscle groups.[10]

J.A. Berman, K.K. Suh, W.Bleiweiss, M. Seskin found that onset was faster with a combination of atracurium and vecuronium.[8] Similar studies done by Naguib.[11] Kim and Cho[12] also had the same conclusion. A review of their results suggests that the onset times of mixtures of mivacurium and rocuronium are shorter than would be anticipated if the two drugs had an additive action.

In this study we found that the duration of neuromuscular blockade was longer in three-fourth dose combination i.e. 42.52(±12) $P<0.05$ which was significant and onset time was shorter compared to half dose combination as duration of action was 33.85 minutes(±6.89). J.A.Berman[8] found 50% combination did not result in prolongation of action but 70% to 80% of combination led to rapid onset time with prolongation of action. These results correspond with our study.

The number of patients in this study was small and therefore, the possibility of a type II error cannot be discounted which suggests that another study using a larger more number of patients in the future would be more valuable.

The results of this study has clinical implications. Large doses of atracurium or vecuronium can be used to facilitate rapid tracheal intubation. However, the size of the dose is limited by the duration of the resulting neuromuscular blockade. An ideal drug combination for tracheal intubation should reduce the onset time but should not prolong the duration of action. Our results suggest that though ¾th combination provides shorter onset time, it provides no advantage over using full doses of either drug alone, since it is associated with the disadvantage of longer duration of neuromuscular blockade.

Summary and Conclusion

In conclusion, three-fourth combination of atracurium and vecuronium provides shorter onset time but with moderate prolongation of duration of action when compared to half dose combination of atracurium and vecuronium. This combination also provides excellent intubating condition. Apart from providing shorter onset time and excellent intubating condition , this combination provides no other advantage in clinical practice .

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