# NEUROMUSULAR BLOCKADE OF INJ. ATRACURIUM AND INJ. VECURONIUM

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**ABSTRACT**

**BACKGROUND**

Rapid onset of action, short duration of action and no cardiovascular side effects are the properties of ideal neuromuscular blocking agents. Both inj. Atracurium and Vecuronium are used for facilitating endotracheal intubation. It has been shown that synergism exists between them. In this study we evaluated the pharmacodynamic interaction of combination of injection atracurium and injection vecuronium. Our objective was to study quality of neuromuscular block.

**METHOD**

Sixty patients belonging to ASA-I category received either intubating dose of injection Atracurium (0.5mg/kg ) or intubating dose of injection Vecuronium ( 0.1mg/kg) or combination of 1/2 of the intubating dose of both drugs. Endotracheal intubation was attempted after injection of relaxant. We analyzed intubating condition, onset of action, duration of action, quality of muscle relaxation and complications if any. Pulse rate and blood pressure were monitored during endotracheal intubation and during maintenance.

**CONCLUSION**

The combination of atracurium and vecuronium provided shorter onset time (3.6±2.11). There was excellent intubation condition in 90% patients. There was excellent muscle relaxation but with moderate prolongation of duration of action (44.25±12.00). There was good hemodynamic stability and no side effects. Combination of two drugs was synergistic and more potent favoring either drug alone.

**KEYWORDS**

Neuromuscular Blockade, Atracurium, Vecuronium, Relaxant Combination.

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**INTRODUCTION:** There was clinical evidence of greater muscle relaxation with combination of d-tubocurarine and pancuronium or metocurine than equivalent doses of either drug alone. Thus it was proved that there exists synergism between non-depolarising muscle relaxant. (1)

Vecuronium was introduced in 1980 as non-depolarising muscle relaxant. It is an aminosteroid compound with intermediate duration of action and medium potency. Atracurium is bisquaternary ammonium compound with intermediate duration of action and minimal cardiovascular effect. Both the drugs are widely used for endotracheal intubation.

There are several studies demonstrating synergism between atracurium and vecuronium. They have reported faster onset of action and faster intubating condition.

Our hypothesis is that ½ intubation dose combination of atracurium and vecuronium, might confer advantage of synergism that would result in rapid onset of action in addition to more rapid recovery time.

Hence we analysed the pharmacodynamic interaction of combination of atracurium and vecuronium, by analysing quality of endotracheal intubating condition, onset of action, duration of action, quality of muscle relaxation, time for reversal and complications if any in comparison to individual drugs alone in a randomized comparative study.

**AIMS AND OBJECTIVES:** The aims and objectives of the present study were to compare the following using combination of atracurium-vecuronium (1/2 of intubating dose) with either atracurium & vecuronium alone.

1) Intubating Condition.
2) Onset of action.
3) Duration of action.
4) Quality of muscle relaxation.
5) Haemodynamic effects.

The randomized, double blinded controlled study group consisted of eighty patients undergoing routine elective surgery. Neither the anaesthetists involved in the administration of anesthesia nor the investigator, was aware of the group to which the patient had been assigned. All patients belonging to ASA I or II while the age of the patients varied between 15 years to 65 years. Patients requiring general anaesthesia with endotracheal intubation and an estimated duration of surgery of at least sixty minutes were studied. Patient who had neuromuscular disease, oesophageal reflux and difficult airway were excluded from the study.

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Patients were allocated to any of the four of groups of equal sizes as in Table 1.

| | |
|---|---|
| Group A | Twenty patients received injection Atracurium (0.5 mg per kg body weight) intravenous for intubation. |
| Group B | Twenty patients received injection Vecuronium (0.1 mg per kg body weight) for intubation. |
| Group C | Twenty patients received combination of the injection Atracurium (0.25 mg per kg body weight) and injection Vecuronium (0.05 mg per kg body weight) for intubation. |
| ***Table 1*** | |

All groups were comparable with respect to age, weight and method of anaesthesia.

**METHODOLOGY: PRE-STUDY EVALUATION:** All patients belonging to ASA I or II. underwent thorough pre-anaesthetic evaluation prior to surgery. All patients were investigated. For patients less than forty years of age, complete blood count, urine routine and microscopic examination were done and for patients above forty years of age, investigations in addition to above were carried out like blood sugar, blood urea nitrogen, serum creatinine, serum electrolytes, electrocardiogram and chest roentgenogram (PA view). Baseline recording of pulse rate, arterial blood pressure were carried out. Large peripheral venous line was secured.

Intramuscular injection Glycopyrrolate (0.04 mg per kg body weight) and injection pentazocine 0.6mg per kg body weight via intravenous route was administered to all patients half an hour before operation. E.C.G. monitor was applied and peripheral nerve stimulator was attached.

All patients received injection pentothal sodium 0.4 to 0.5mg per kg body weight for induction. Train of four response 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 followed by assisted ventilation with 50% $0_2$ in $N_2O$ for 120 seconds. Meanwhile, TOF response was studied at 30 seconds interval. The intubating condition was assessed and direct laryngoscopy was 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 Lund and Stovner as in table 2. If intubation was not successful at the first attempt, assisted ventilation was reinstituted until conditions were favourable.

| Grade | Description |
|---|---|
| Excellent | Easy passage of the tracheal tube with no reactive coughing and with relaxed vocal cords. |
| Fair | Moderate reactive coughing / bucking but with relaxed vocal cords, insertion of tube possible |
| Satisfactory | Slight reactive coughing or bucking with some vocal cord movements |
| Poor | Vocal cords adducted or uncontrolled coughing and bucking, Insertion of tube impossible. |
| ***Table 2*** | |

After intubation $N_2O$ and $O_2$ (2:1) was used as fresh gas flow and neuromuscular block was maintained with one fourth of the loading dose of the muscle relaxant. Volatile anaesthetic gas was used only if needed. During anaesthesia electrocardiogram and hemoglobin oxygen saturation were monitored. At the end of the surgery residual neuromuscular blockade was reversed with injection neostigmine 0.08 mg per kg body weight and injection atropine 0.02 mg per kg body weight by intravenous route.

There is correlation between visual estimation of TOF and clinical scores during intubation as in Table 3.

| Intubating Score | TOF at Intubation |
|---|---|
| 3 | 4/4 |
| 2 | 3/4 |
| 1 | 2/4 |
| 0 | ¼ |
| ***Table 3*** | |

Patients were observed in the intraoperative and postoperative period for complications like hypotension, bradycardia, bronchospasm, apnoea, flushing erythema and ECG changes.

**METHOD OF ANALYSIS:** To calculate the sample size, a power analysis of $\alpha$=1.96, $\beta$ =1.64 at 5% level with standard deviation of 2.11 for size of the effect that is clinically worthwhile to detect to be 1.7, showed that 20 patients per study group were needed. The various data obtained, which included onset time and duration of neuromuscular blockade in group A, were calculated and compared to the corresponding times in group C, using t test. Similarly onset time and duration in group B were compared to the corresponding times in group C. 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:** In this study-Data regarding patient distribution in sex and age.

| Distribution | Group A | Group B | Group C |
|---|---|---|---|
| Sex Male: Female | 15:5 | 6:14 | 7:13 |
| Age Mean (Years) | 31.1 | 34.85 | 32.2 |
| +.S.D. | +7.7 | +13.2 | +13.1 |
| ***Table 4*** | | | |

Table 4 shows that all these groups were comparable in respect of patients characteristics i.e. sex and age. Their ages varied from 15yrs to 65yrs with mean age ranging around 30 years.

Onset of action and duration of neuromuscular blocked are displayed in table 5.

| | Group A | Group B | Group C |
|---|---|---|---|
| Onset Time Mean | 8.1 | 4.1 | 3.6 |
| +S.D. (Minutes) | +4.40 | +2.72 | +2.11 |
| Duration Of Action:Mean | 22.52 | 33.25 | 44.25 |
| +S.D. (Minutes) | +7.28 | +5.86 | +12.00 |

***Table 5***

Onset time for intubation in Group A was 8.1 minutes which is maximum time among all the three groups. Onset time in Group C was 3.6 minutes which is significant when compared to onset time in Group A. None of the patients required more than one attempt at intubation.

Duration of neuromuscular blockade in Group A was 22.52 minutes while in Group B, Group C it was 33.25 minutes and 44.25 minutes respectively.

| | Grades of intubating condition | | | | Total |
|---|---|---|---|---|---|
| Group | I (Excellent) | II (Satisfactory) | III (fair) | IV (poor) | |
| A (n=20) | 3(15%) | 6(30%) | 9(45%) | 2 (10%) | 20 |
| B (n=20) | 17(85%) | 3(15%) | - | - | 20 |
| C (n=20) | 18(90%) | 2(10%) | - | - | 20 |

***Table 6***

S–significant (P<0.05).
NS–not significant.

It was observed that in Group A, maximum number of patients had fair and poor intubating condition at the time of laryngoscopy. In Group B, most of patients i.e. 85% patients had excellent intubating condition and rest i.e. 15% patients had satisfactory intubating condition. Group C had about 90% patients with excellent intubating conditions.

**MUSCLE RELAXATION TOLD BY SURGEON:** Muscle relaxation was excellent in 90% of patients in Group C. Muscle relaxation was poor in 71.5% patients in Group A while in Group B 100% patients had excellent muscle relaxation as in Table 7.

| Group | Excellent | Good | Poor | Total |
|---|---|---|---|---|
| A | - | 7(28.55%) | 13(71.5%) | 20 |
| B | 20(100%) | - | - | 20 |
| C | 18(90%) | 2(10%) | - | 20 |

***Table 7***

**HEMODYNAMIC EFFECTS:** Cardiovascular status of all patients remained stable. Changes in pulse rate and blood pressure values in Group C were statistically significant than in Group A and Group B (P>0.05) Pulse rate changes are shown in following Table 8.

| | Group A | Group B | Group C |
|---|---|---|---|
| Preoperative | 83.40(±9.0) | 91.5(±12.2) | 83.85(±8.5) |
| Intraoperative | 96.02(±8.6) | 94.3(±14.06) | 82.27(±14.2) |
| Post-operative | 94.4(±8.8) | 92.7(±9.3) | 82.2(±9.7) |

***Table 8: Pulse Rate Changes Mean±SD***

| | Group A | Group B | Group C |
|---|---|---|---|
| Preop | 111.5(±10.7) | 118.4(±9.8) | 113(±11.9) |
| Intraop | 127(±9.2) | 119(±13.04) | 111.08(±11.08) |
| Postop | 129.6(±4.6) | 122.3(±8.7) | 119.3(±11.0) |

***Table 9: Blood pressure changes mean (+S.D)***

**SIDE EFFECTS:** Among the side effects two patients in Group C developed bradycardia. Also patient in Group B developed VPC's. All patients were reversed completely. No residual recurarisation was seen post operatively.

**DISCUSSION:** It was first observed in 1969 that d-tubocurarine–gallamine combination produced potentiation of neuromuscular blockade. It has been shown that concomitant administration of some mixtures of non-depolarizing compounds (pancuronium and gallamine; pipecuronium and rocuronium) does result in additive effect. Other combinations of nondepolarizing agents (pancuronium and metocurine, gallamine and metocurine or d-tubocurarine and pancuronium) clearly demonstrate synergistic effects. [(2)] More recently, combinations of the drugs, atracurium and vecuronium have been utilized to increase the onset of action. Several investigators have demonstrated synergism between atracurium and vecuronium, both in vivo and in vitro.[(1)] The mechanism by which different non-depolarising neuromuscular blocking drugs interact to produce a supra-additive effect is unclear. However the interaction appears to be pharmacodynamic rather than pharmacokinetic. Although waud and Waud have attributed that potentiation can be entirely of postsynaptic origin; others synergism to both presynaptic and motor end plate effects.[(3,4)] Although the precise mechanism underlying synergistic interaction are not known, hypothesis that has been put forward include;

a) The existence of multiple binding sites at the neuromuscular junction (pre and post synaptic receptors).
b) Alternate of the pharmacokinetic behaviour of one drugs by the other a hypothesis by Martin et al.[(5)]
c) Non-equivalence of binding sites in the regions of the alpha–chain responsible for ligand recognition,[(6,7)]
d) Presence of one molecule of non-depolarising drug at one of the two alpha subunits of the acetylcholine receptors.[(8)]
e) Multiple receptor sites and different modes of action of competitive neuromuscular blocking agents.

Silverman D. G, Swift C. A, and Hartman K. A, found that onset of blockade with combination of atracurium and vecuronium is faster compared to vecuronium alone.[(9)] Our study showed that onset time was shortest in group which received is 3.6 minutes (+-2.11) (p<0.05 significant), which

was statistically significant compared to other groups. In Group A onset of action was 8.1 minutes and in Group B it was 4.1 minute. It was longest in Group which received atracurium alone i.e. 8.1 minutes. We presume that differences in onset in various patients are because of difference in muscle blood flow, and relaxant binding between central and peripheral muscle group.

P. Rautoma et al found synergism between atracurium & vecuronium. They concluded that combination had an effect like one intermediate acting agent. They also found that if a combination is used instead of using either drug alone, the maximal reduction of drug consumption would be approximately 30%.[10]

O. A. Meretoja et al studied synergism between atracurium with vecuronium in 30 children & found that a combination of atracurium & vecuronium is supra additive compared with the effects of each drug alone. [11]

Sloan M.H., Lerman J et al studied the interaction of atracurium with vecuronium which showed that there were no differences between atracurium and combination of both the drugs. Onset of neuromuscular blockade was significantly slower with Vecuronium than that with Atracurium or combination ($p<0.001$). There was no difference in the recovery index among all groups. The duration of action was less in Vecuronium group than with other groups ($p<0.001$).[12] Recovery of neuromuscular blockade was rapid and not prolonged when two drugs were combined.

Stir J et al studied combination of Atracurium 0.125mg/kg and Vecuronium 0.025mg/kg (5:1 ratio).[13]

J. A. Berman, K. K. Suh, W. Bleiweiss, M. Seskin studied that onset is faster in combination of atracurium and vecuronium. They studied combination of atracurium and vecuronium to facilitate rapid endotracheal intubation. [14] They found that 90% of patient who received 1/2 of intubating dose of combination of atracurium and vecuronium, facilitate rapid intubation. They studied 50%, 70% and 80% of the recommended intubating dose of each drug in the combination. There was 90% of depression of twitch height with combination of atracurium and vecuronium. They noted better intubating condition by increasing the dose of each drug from 50% to 70%.

Apart from faster onset time, good intubation condition is also essential feature.

In our study we found that duration of neuromuscular blockade was longer in combination of relaxant i.e. 44.25(+_ 12) $p<0.05$significant and onset time was shorter compared to either drug alone. Duration of action in vecuronium group was 33.25 (+_5.86) minutes where onset time was longer and duration of action (22.52+_7.28) was shorter in the patients who received atracurium. An ideal drug combination for tracheal intubation would reliably reduce the onset time but would not prolong the duration of action. Unfortunately, 1/2 dose combination reduced onset time but prolonged the duration of action moderately. This may be undesirable in providing anesthesia for day care surgeries. This must be taken into account while using this combination. J.A. Berman found 50% of combination doses not result in prolongation of action but 70% to 80% of combination leads to rapid onset time with prolongation of action. These results corresponded with our study.

A.J. England, M. F. Morgarson and S. A. Feldman studied comparison of mixture of vecuronium and rocuronium with either vecuronium or rocuronium for quality of condition for tracheal intubation at one minute. [15] Excellent intubation conditions were achieved in 57% of the rocuronium group, 70% of mixture group and 27% of rocuronium group. Adequate intubating conditions are dependent on depth of anaesthesia, skill of endoscopist and muscle relaxation. Thus our study correlates with their findings. In this study excellent intubating conditions were achieved in 90% of patient who received 1/2 of intubating dose of combination of atracurium and vecuronium, 85% of patient who received vecuronium alone, 6.6% of patient who received atracurium alone. This was statistically significant and this also suggest that excellent intubating condition can be achieved with ½ dose combination compared to either drug alone.

The hemodynamic stability of combination group was significant than either drug alone. There was no clinical evidence of hypotension with combination of drugs. It was observed that hemodynamic changes were similar to that of vecuronium group in one study. [16]

Similar studies done by Naguib [17] suggests that the onset times of mixtures of mivacurium and rocuronium are shorter that would be anticipated if the two drugs had an additive action.

The quality of muscle relaxation as told by surgeons was excellent in 20% patients who received vecuronium as compared to 90% in the group which received 1/2 dose combination, which was statistically significant. However, surgeons were not satisfied with muscle relaxation in only atracurium group while muscle relaxation in patients who received only vecuronium was 100%.

This result has clinical implication that combination of two different non-depolarising drugs can be used in case of rapid endotracheal intubation.

We did not notice any allergic reaction or postoperative apnoea. There was only episode of bradycardia in 2 patients in combination group.

**SUMMARY AND CONCLUSION:** This study shows that the combination of atracurium-vecuronium (1/2 of intubating dose) was synergistic. The onset of intubation condition of the combination of the two drugs was comparable to that of vecuronium. Early onset of action, permitting early tracheal intubation is one of the desirable properties of neuromuscular blocking agents Excellent intubation condition has been achieved with the 1/2 dose combination. This result has clinical implication that this combination can be used in case of rapid endotracheal intubation. Also the muscle relaxation according to surgeons was excellent in most of the patients who received 1/2 dose combination compared to Atracurium alone. There was no detrimental effect of combination.

In conclusion, combination of atracurium and vecuronium provides shorter onset time, excellent intubation condition, good hemodynamic stability and excellent muscle relaxation but with moderate prolongation of duration of action.

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