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Synergism Between Muscle Relaxant

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ABSTRACT

Muscle relaxants are essential in balanced anesthesia as adjuncts to analgesic and hypnotic drugs. Several maneouvers have been utilized to increase their speed of onset. They have included the use of 'priming doses', large doses and more recently combinations of two drugs. In this study the combination of atracurium and vecuronium was compared with either of the drug alone, in regard to intubating condition, onset of action, duration of action, quality of muscle relaxation ,time for reversal and complications if any. GROUP A patients received intubating dose of injection Atracurium, GROUP B received intubating dose of injection Vecuronium, GROUP C received combination of 3/4th of the intubating dose of both the injection Atracurium and injection Vecuronium. Three fourth combination of atracurium and vecuronium provided shorter onset time, excellent intubation condition, good hemodynamic stability and excellent muscle relaxation but with moderate prolongation of duration of action.

KEYWORDS neuromuscular blockade, Atracurium , Vecuronium, relaxant combination

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, a more rapid recovery, faster and complete antagonism of residual block than the case of the longer lasting drugs. It has made more convenient to provide paralysis by continuous infusion of relaxants. However neither drug is able to provide optimal intubating conditions as rapidly as succinylcholine. Several maneouvers have been utilized to increase their speed of onset. They have included 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).

Advantages offered by use of a combination of atracurium and vecuronium, would be that it would decrease the expense of producing conditions suitable for intubation and avoid the use of suxamethonium. In addition more rapid recovery time, in some instances allow for use of smaller than usual doses of relaxant antagonists and occasionally obviate the need for their use. Also incidence of cardio-vascular side effect will be diminished by the use of the combined regimen.

Hence the combinations of atracurium and vecuronium was compared with either of the drug alone, in regard to intubating condition, onset of action, duration of action, quality of muscle relaxation time for reversal and complications if any.

AIMS AND OBJECTIVES

The aims and objectives of the present study were to compare the following using combination of atacurium-vecuronium (three fourth of intubating dose) with either atacurium & 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 anaesthetist 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.

Patients were allocated to any of the four of groups of equal sizes as in table1

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 3/4th of the intubating dose of both the injection Atracurium(0.375 mg per kg body weight) and injection Vecuronium(0.075 mg per kg body weight) for intubation.

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

METHODOLOGY –

PRE-STUDY EVALUATION-

All patients underwent thorough pre-anaesthetic evaluation prior to surgery. All patients belonging to ASA I or II. On pre-operative visit, clinical examination of patients was done, procedure of anaesthesia was explained to the patient. Valid written consent was taken.

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, eletrocardiogram and chest roentero-gram(PA view).

Equipments for general anesthesia were kept ready. Baseline recording of pulse rate, arterial blood pressure were carried out.

Before entering the operation theatre, patients were premedicated with intramuscular injection gyclopyrolate (0.04 mg per kg body weight) half an hour before operation. Patients also received injection pentazocine 0.6mg per kg body weight via intravenous route.

All patients were induced with injection penthothal sodium 0.4 to 0.5 mg per kg body weight. 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. This was followed by assisted ventilation with 50% 0_2 in N_2O for 90 seconds. Meanwhile, TOF response was studied at 30 seconds interval. The intubating condition was assessed and direct larygoscopy was performed. The jaw tone was assessed as either good or inadequate to allow larygoscopy and intubating conditions were scored as excellent, good, poor or impossible according to parameters described by Goldberg and colleagues as in table2. If intubation was not successful at the first attempt, assisted ventilation was reinstituted until conditions were favourable.

TABLE 2

GRADE	DESCRIPTION
Excellent	Easy passage of the tracheal tube with no reactive coughing and with relaxed vocal cords.
Good	Slight reactive coughing but with relaxed vocal cords.
Poor	Moderate reactive coughing or bucking with some vocal cord movement.
Impossible	Vocal cords adducted or uncontrolled coughing and bucking.

After intubation, anaesthesia 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 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 table3

TABLE 3

INTUBATING SCORE	TOF 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 ⊠ =1.96 , ⊠ =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

TABLE 4

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 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.

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

Onset time 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 . **D**uration 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.

TABLE 6

	GRADES OF INTUBATING CONDITION				TOTAL
GROUP	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)	18(90%)	2(10%)	-	-	20

S – significant (P<0.05)

NS – not significant

It was observed that in Group A, maximum number of patients had poor intubating condition at the time of larygoscopy.

In Group B, most of patients i.e. 85% patients had excellent intubating condition and rest i.e. 15% patients had good intubating condition..

Group C had about 90% patients with excellent intubating conditions.

MUSCLE RELAXATION TOLD BY SURGEON:
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

Muscel relaxation was poor in most of the patients i.e. 71.5% patients in Group A while in Group B 100% patients had excellent muscle relaxation as in table7 .Muscle relaxation was excellent in majority of patients ie 90% in Group C.

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:-
TABLE 8
PULSE RATE CHANGES MEAN + S.D

	Group A	Group B	Group C
Preperative	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 9
BLOOD PRESSURE CHANGES MEAN (+S.D)

	Group A	Group B	Group C
Pre0p	111.5(±10.7)	118.4(±9.8)	113(±11.9)
Intraop	127(±9.2)	119(±13.04)	111.08(±11.08)
Post op	129.6(±4.6)	122.3(±8.7)	119.3(±11.0)

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
Fast 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. 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 if maximal affect is 5 to 6 minutes. Several maneouvers have been utilized to increase their speed.

More recently, 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-depolarising 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 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 (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 effect. Other combinations of non-depolarizing agents (pipecuronium and rocuronium) does result in additive effect. Other combinations of nondepolarizing agents (pancuronium and metocurine, gallamine and metocurine or d-turbocurarine and pancurranium) clearly demonstrate synergistic effects(4,5) Although waud and Waud have attributted that potentiation can be entirely of postsynaptic origin; others 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 3/4th of intubating dose of combination of atracurium and vecuroniun, 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 three fourth dose combination compared to other groups.

J.A.Berman, M.Sesking, studied combination of atracurium and vecuronium to facilitate rapid endotracheal intubation (8) They found that 90% of patient who received 3/4th of intubating dose of combination of atracurium and vecuronium, facilitate rapid intubation. They found 90% of depression of twitch height are achieved rapidly with combination of atracurium and vecuronium.

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(9). Excellent intubation conditions were achieved in 57% of the rocuronium group, 70% of mixture group and 27% of rocuronium group. Thus our study correlates with their findings.

Silverman D.G, Swift C.A, and Hartman K.A, found that onset of blockade with combination of atracuriun and vecuronium is faster compared to vecuronium alone(10). Our study showed that onset time was shortest in group which received three fourth combination 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(11).

J.A. Berman, K.K. Suh, W.Bleiweiss, M. Seskin studied that onset is faster in combination of atracurium and vecuronium. Similar studies done by Naguib(12), Kim and Cho also have studied the interaction of rocuronium and mivacurium(13). A review of their results 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. So all these studies supported our result. In our study we found that duration of neuromuscular blockade was longer in three fourth dose combination i.e. 42.52(+_ 12) p<0.05significant 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. 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 corresponds with our study.

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 three fourth 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% .There was no stastically significant hemodynamic changes among all the groups.

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%(14).

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(15).

SUMMARY AND CONCLUSION

Excellent intubation condition has been achieved in 90 seconds with the Group C where three fourth dose combination was used. This result has clinical implication that combination of two different non-depolarising drugs can be used in case of rapid endotracheal intubation . An ideal drug combination for tracheal intuabation would reliably reduce the onset time but would not prolong the duration of action. Unfortunately, three fourth dose combination reduced onset time but prolonged the duration of action moderately. Also the muscle relaxation according to surgeons was excellent in most of the patients who received three fourth doses combination compared to Atracurium alone.

In conclusion, three fourth 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.

REFERENCES

1) Saverese JJ, Kitz R.J. Priming principle, Anesthesiology 1975;42:236 2)Ghoneim M M, Long J P. The interaction between d-tubocurarine and gallamine .Canadian J of Anesthesia 1972;19:66-74 3) Martyn JA. Leibel WS, Competitive non- specific binding does not explain the potentiating effect of muscle relaxant combination. Anaesthesia and analgesia 1983;62:160-163. 4)Saverese J.J., Lebowitz P W. Combination of pancuronium and metocurine, Anesthesia and Analgesia1980;59:12-17 50Saverese J.J., Lebowitz P W. Potentiation of neuromuscular blockade by combination of pancuronium and d-tubocurarine. Anesthesia and Analgesia1980;59:604-9 6) B.E. Waud and D.R. Waud. Interaction among agents that block end plate depolarization competitively. Anaesthesiology 1985;63:4-15. 7). B.E.Waud and D.R. Waud. Quantitative examination of interaction of competitive neuromuscular blocking agents.Anaesthesiology1984;61:420-427 8) J.A.Barman, K.K. Suh, M.Seskin Evaluation of Atracurium and Vecuronium in combination to facilitate rapid tracheal intubation. Anaesthesialogy vol-63; A342 9) A.J. England, M.P. Margarson, S.A.Feldman. Tracheal intubation condition after one minute, rocuronium, alone in combination. Anaesthesia 1997;52:336-340. 10). Silvernam D.G., Swift C.A., Hartman K.A. Dubow H.D., Accelerated recovery from combined atracurium and vecuronium. Neromuscular block British Journal of Anaesthesia 1989; 62:699. 11) Wylie –Practice of anesthesia 12) Mohammed Naguib. Neuromuscular effects of rocuronium bromide and mivacurium chloride alone and in combination. Anaesthesiology 1994;81:338-395. 13) Kim SY, Cho MH. Neuromuscular and Cardiovascular advantage of combination of Mivacurium and rocuronium over either drug alone. Anaesthesia 1996;51:929-931. 14) P. Rautoma , O. Erkula. Potency & maintenance requirement of Atracurium & vecuronium given alone or together. Acta Anaesthesiologica Scandinavica 1995;39(2):220-223. 15)O.A.Meretoja, B. W. Brandom, T. Taivainen. Synergism between atracurium & vecuronium in children. British Journal of Anesthesia1993;71(3):440-442