Original Article

EVALUATION OF ATRACURIUM BESYLATE AND VECURONIUM BROMIDE IN COMBINATION TO FACILITATE RAPID TRACHEAL INTUBATION

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Financial Support: None declared
Conflict of interest: None declared

How to cite this article:
Patel KB, Sharma AS, Patel HS, Patel RD, Parekh BC, Modi TM. Evaluation of Atracurium Besylate and Vecuronium Bromide in Combination to Facilitate Rapid Tracheal Intubation. Natl J Community Med 2014; 5(2):240-244.

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Date of Submission: 15-04-14
Date of Acceptance: 28-06-14
Date of Publication: 30-6-14

ABSTRACT

Background: Combination of atracurium and vecuronium is a good alternative for rapid tracheal intubation in certain conditions where one has to avoid giving succinylcholine as a muscle relaxant. It has been shown good synergism between two drugs for mechanism of action, duration of action, haemodynamic stability, and recovery from anaesthesia.

Materials and Methods: A total of 75 patients were studied in 3 groups having 25 patients in each. Intubating conditions were studied after 75 seconds and 90 seconds in combination of atracurium and vecuronium with same dose. Pulse rate and systolic blood pressures were monitored during intubation and subsequently during maintenance.

Results: Combination of atracurium and vecuronium gave clinically acceptable intubating condition in majority of patients in 75 seconds but in 90 seconds, it gave similar results to that of suxamethonium at the cost of longer duration. Alone vecuronium is not a suitable non depolarizing muscle relaxant for rapid sequence induction. No significant difference in haemodynamic data were noted in all three groups. Good and early recovery was noted in combination of atracurium and vecuronium. Combination of two drugs was synergistic and more potent in an equipotent dose ratio favouring one parent drug so maximum reduction of drug requirement would be about 40%.

KEY WORDS: Atracurium Besylate, Neuromuscular Block, Rapid Tracheal Intubation, Vecuronium Bromide

INTRODUCTION

The need for a rapid acting non depolarizing neuromuscular blocking agent has been eloquently stated by Savareseet al[1]. When used in recommended doses for intubation neither atracurium 0.5 mg/kg nor vecuronium 0.1 mg/kg achieve suitable conditions until 2.5 – 3.5 minutes. Attempts have been made to speed the onset of twitch suppression by atracurium and vecuronium utilizing the "Priming Technique".[2] Although adequate twitch suppression for intubation was obtained in 1.4 minutes and 1.1 minutes interval was required between the priming and larger dose. Combinations of pancuronium with d-tubocurarine or metocurarine were found to result in greater muscle relaxation than equivalent doses of each drug alone. This led to the conclusion that the synergism observed with these combinations was due to different mechanisms of action (pre and post junctional).[2]

The present study was undertaken to determine if a combination of atracurium and vecuronium will hasten the development of condition necessary for intubation. With the introduction of vecuronium in early 80's, many of the postulated ideal properties of neuromuscular blocking agents were realised.[3] These are non depolarizing mechanism of action, rapid onset of action, short duration of action, rapid recovery, non cumulative, no cardiovascular side effects, no histamine release, reversible with cholinesterase inhibitors, high potency, pharmacologically inactive metabolites.

Vecuronium, an aminosteroidal compound has intermediate duration of action and medium potency. Atracurium, a bisquarternary ammonium benzylisoquinoline compound having minimal cardiovascular effect and because spontaneous hofmann degradation at body pH and temperature, produced an agent whose intermediate duration of action was independent of the liver and kidney. So, keeping these properties in mind, it was decided to evaluate the feasibility or effectiveness of atracurium and vecuronium in combination to facilitate rapid tracheal intubation.

MATERIALS AND METHODS

The study was conducted in a prospective, randomized, double blinded manner on patients who had

been operated for various kind of surgeries in tertiary care hospital. Ethical clearance was obtained from the institutional research and ethical committee. In this study, after informed consent, 75 patients were studied. Patients with ASA risk I and II from either sex and between the age group of 5–60 years with mallampatti grade I and II were selected and were categorized according to muscle relaxant received in group I, II, and III. In this study, if patients had evidence of neuromuscular diseases or were receiving no medications known to influence neuromuscular function or having contraindications for undergoing a rapid sequence induction of anaesthesia were excluded.

Group I: Inj. Vecuronium 0.1 mg/kg I/V with intubation done at 120 sec.

Group II: Inj. Vecuronium 0.08 mg/kg I/V + Inj. Atracurium 0.4 mg/kg I/V with intubation done at 75 sec.

Group III: Inj. Vecuronium 0.08 mg/kg I/V + Inj. Atracurium 0.4 mg/kg I/V with intubation done at 90 sec.

All patients were thoroughly examined. Complete history of present illness, previous medical and surgical history, any previous anaesthesia exposure, drug allergy or other significant history was taken. General and Systemic examinations were done. Routine investigations were done which were mainly haemogram, urine examination, renal functions test, chest x-ray, ECG, blood sugar. All patients were premedicated with Inj. Glycopyrolate 0.2 mg, Inj. Fentanyl 100 mcg and Inj. Ondensetron 4 mg intravenously 15 minutes prior to induction. On operation table, baseline pulse rate and blood pressure were noted. ECG monitor was applied and large peripheral venous line was secured. All patients were pre oxygenated with 100% oxygen with mask for 3 min. Patients were induced with Inj. Pentothal sodium (2.5%) 5-7 mg/kg and muscle relaxant according to their group. Along with that, after giving muscle relaxant, with the use of peripheral nerve stimulator, TOF count and T1/TOF ratio measured and after 75 sec and 90 sec, intubation was performed and intubating condition was noted. Intubating conditions were noted as (according to Lund and Stovner, 1970)

Score	Definition	Class
0	Poor	Insertion of tube impossible, jaw not relaxed, vocal cords moving
1	Fair	Condition less favourable but insertion of tube possible, bucking on insertion of tube
2	Satisfactory	Slight movement on being touched, slight bucking after insertion of tube, jaw relaxed, vocal cords apart
3	Excellent	Vocal cords well abducted, not moving, absent bucking, jaw relaxed, no diaphragm movement or limb movement on insertion of tube

Pulse rate and blood pressure were taken before and after induction at 0, 1, 3 and 5 minutes. Duration of action of intubating dose was noted as the time interval between first dose and time of appearance of flickers clinically. Patients were maintained with nitrous oxide, oxygen, inhalation agent and respective muscle relaxants. After completion of surgery, on appearance of flickers clinically, effect of muscle relaxant was reversed with Inj. Glycopyrolate and Inj. Neostigmine. After satisfactory recovery, patients were extubated and observed in the recovery room. During recovery period, patients were observed for recovery score (acco. to Steward,1975) on 5, 10, 20 minutes, 4, 12 and 24 hours.

Consciousness	Ventilation	Movements	Score
Not responding	Required ventilation	Not moving	0
Responds to stimuli	Good airway maintained	Non purposeful movements	1
Awake	Coughing on command	Purposeful movements	2

Patients were also observed for 24 hours postoperatively for complications like bradycardia, hypotension, apnoea, skin allergic reactions and bronchospasm. During whole surgery, patients were given intravenous fluids according to their body weight and NBM hours and also maintenance fluids calculated and given to them. Patients were given blood transfusions if required whenever.

RESULTS

The demographic data for all three groups were studied and randomly classified according to concerned group, they received for intubation.[Table 1] Three groups were similar in respect of age and weight. It showed that patients were of younger age group with somewhat equal male and female patients and having moderate weight. Intubating conditions with vecuronium alone at 120 seconds and other two groups of combination of atracurium and vecuronium at 75 seconds and 90 seconds.[Table 2] As can be seen in Group I i.e. vecuronium 0.1 mg/kg, 36% patients had excellent and 24% had satisfactory intubating conditions at 120 seconds. In Group II, 32% patients had excellent and 56% had satisfactory intubating condition at 75 seconds whereas in Group III, 76% patients had excellent and 20% had satisfactory intubating conditions at 90 seconds. Here, Lund and Stovner class had been merged in sense of clinically acceptable(class 3 and 2) and unacceptable(class 1 and 0) intubating condition with all the groups.[Table 3] Comparing the result of two neuromuscular blocking agents, we observed that combination of atracurium and vecuronium in dose of 0.4 mg/kg and 0.08 mg/kg gave clinically acceptable intubating condition in 88% patients in 75 seconds compared to only vecuronium which gave 60% patients at 120 seconds while combi-

nation of both drugs gave clinically acceptable intubating condition in 96% at 90 seconds.

Table 1: Demographic Characteristics

	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)
Age(Years)Mean ± SD	33.76 ± 15.57	26.48 ± 13.24	36.52 ± 14.52
Weight (Kgs) Mean ± SD	51.28 ± 14.76	44.20 ± 15.58	53.52 ± 12.02
Gender(M/F)	11 / 14	14 / 11	15 / 10
ASA Risk I / II	2 / 23	16 / 9	3 / 22

• Group I = Inj. Vecuronium 0.1 mg/kg I/V with intubation done at 120 sec., Group II = Inj. Vecuronium 0.08 mg/kg I/V + Inj. Atracurium 0.4 mg/kg I/V with intubation done at 75 sec, Group III : Inj. Vecuronium 0.08 mg/kg I/V + Inj. Atracurium 0.4 mg/kg I/V with intubation done at 90 sec., M = Male, F = Female. There was no significant difference between groups

Table 2: Lund and Stovner classification of Intubating condition

Class(Score)	Group – I(n = 25)	Group – II (n = 25)	Group III (n = 25)
Excellent(3)	9(36%)	8(32%)	19(76%)
Satisfactory(2)	6(24%)	14(56%)	5(20%)
Fair(1)	8(32%)	3(12%)	1(4%)
Poor(0)	2(8%)	-	-

Comparing two groups of combination of atracurium and vecuronium at 75 and 90 seconds time for intubating condition which showed that 96% patients had clinically acceptable intubating condition at 90 seconds than 88% patients had at 75 seconds. Overall, results showed that combination of atracurium and vecuronium gave clinically good intubating condition at 90 seconds when used in ratio of 5:1 with dose of 0.4 mg/kg for atracurium and 0.08 mg/kg for vecuronium.

Table 3: Acceptability of Intubating condition and Duration of Recovery from Initial Dose of NDMR

Groups	Intubating condition		Duration of Recovery from initial dose of NDMR
	Clinically Acceptable	Clinically Un acceptable	
Group – I	15(60%)	10(40%)	37.48 min
Group – II	22(88%)	3(12%)	48.52 min
Group - III	24(96%)	1(4%)	48.32 min

† NDMR = Non depolarizing muscle relaxant

The clinical recovery of the initial dose of vecuronium was longer after using combination of atracurium and vecvuronium (in group II, it was 48.52 minutes and in group III, it was 48.32 minutes) than that of vecuronium 0.1 mg/kg, 37.48 minutes. Changes in mean pulse rate and systolic blood pressure in patients of different groups at different time interval after giving muscle relaxants were recorded.[Table 4] It can be seen that pulse rate was going to settle in just 3 minutes and reached about near to base line at 5 minutes after induction with combination of atracurium and vecuronium group rather than vecuronium alone. Changes were in mean systolic blood pressure in patients of different groups at different time interval after giving muscle relaxants. The result showed that increase in blood pressure in group II and group III was not as high as in group I, but the difference between these all groups were also not significant and almost in all 3 groups, the systolic blood pressure was going to settle within 3 minutes and gone less baseline at 5 minute due to drug induced effect after induction.

Table 4: Haemodynamic changes during endotracheal intubation

Time after Induction	Group I (n = 25)		Group II (n = 25)		Group III (n = 25)	
	Pulse	SBP	Pulse	SBP	Pulse	SBP
B(Mean ± SD)	81 ± 4.37	122 ± 9.09	85 ± 8.20	120 ± 4.24	82 ± 5.19	118 ± 6.50
A/0(Mean ± SD)	101 ± 7.32	132 ± 7.48	100 ± 12.0	128 ± 12.52	98 ± 8.64	130 ± 5.22
A/1(Mean ± SD)	119 ± 9.84	140 ± 5.65	116 ± 8.61	136 ± 7.72	117 ± 5.50	137 ± 4.70
A/3(Mean ± SD)	102 ± 7.46	117 ± 11.04	92 ± 2.98	116 ± 5.85	91 ± 2.34	115 ± 9.11
A/5(Mean ± SD)	90 ± 5.51	106 ± 7.52	82 ± 6.21	101 ± 8.56	82 ± 2.70	99 ± 5.59

‡ B = Baseline pulse and blood pressure, A/0, 1, 3, 5 = Time after induction of o, 1, 3, 5 minutes, SBP = Systolic blood pressure

So, haemodynamic stability is good for vecuronium alone as well as combination of two drugs. In this study, recovery score more than 4 was noted in 100% patients in group II and group III in less than 5 minutes while in group I, 8% patients has got less than 4 recovery score in less than5 minutes and 4% patients had got less than 4 recovery score in less than 10 minutes. It was also noted in group II that 24% patients had got score 5 and 60% patients had got score 6 in less than 5 minutes and in group III, 20% patients had got score 5 and 64% patients had got score 6 in less than 5 minutes while in group I, only 28% patients had got score 5 and 44% patients had got score 6 in less than 5 minutes. It was also noted that in less than 10 minutes, almost good recovery score (> 3) was noted in 100% patients in group II and group III patients while 96% patients in group I. It was noted that incidence of complications in group I was hypotension which was only in 4% patients while group II, hypotension noted in 4%, bradycardia in 8% and allergic skin reaction in 4% while in group III, incidence of hypotension noted in 4%, bradycardia in 4% and al-

lergic skin reaction in 4%. There was not a single incidence of bronchospasm in any of three groups which showed that incidence of complication were negligible in group II and III as compared to benefits of the combination of drugs used.

DISCUSSION

Until now, suxamethonium remains the muscle relaxant of choice for rapid sequence induction in patient with full stomach because it offers a brief onset time, reliably optimal intubating condition and a brief duration of action. However, suxamethonium has a number of side effects mainly due to its depolarizing mode of action like severe bradycardia, prolonged apnoea and muscle pain. So, the search for ideal neuromuscular blocking agent has been focused on nondepolarizing muscle relaxants. The study has shown that a rapid onset of action is only produced by compounds of relatively low potency and a compromise between a potent neuromuscular blocking agent with a rapid onset time must be made to reduce side effects.[1] Berman IA et al studied atracurium and vecuronium in combination to facilitate rapid tracheal intubation by using 50%, 70% and 80% of the recommended intubating dose of each drug in the combination and found better intubating condition, by increasing the dose of each drug from 50% to 70% while increasing to 80% did not result in a more rapid onset of action.[8] In the present study, rapid tracheal intubation were compared in elective surgery patients in 75 seconds and 90 seconds after using combination of atracurium 0.4 mg/kg and vecuronium 0.08 mg/kg with control group of vecuronium alone in the dose of 0.1 mg/kg. In our study, there was almost equal number of gender patient with mean weight of 49.6 kg. Obese patients were omitted. Only mallampatti grade I and II patients were studied. All patients were premedicated with Inj. Glyco 0.004 mg/kg, Inj. Promethazine 0.25 mg/kg and Inj. Pentazocine 0.3 mg/kg intravenously prior to induction with Inj. Sodium Pentothal 5-7 mg/kg intravenously.

Study states combination of atracurium and vecuronium is a suitable alternative to suxamethonium for rapid tracheal intubation when using thiopentone and sufentanil or fentanyl as a induction agent.[8] Study by Donati F et al showed and stated that onset time of neuromuscular block in the adductor pollicis is not a meaningful, quantifiable and point defining optimal intubating conditions and satisfactory intubating conditions might be present before the development of complete block of adductor pollicis muscle.[4,5] This is also we noted because we have used peripheral nerve stimulator for the onset time of muscle relaxant at adductor pollicis. The complete blockage of muscle fibre occurred after average two or three minutes when train of four counts would be 0. While intubation conditions were good to excellent at 75 and 90 seconds also.[10]

In the present study, we found the following result: In group I i.evecuronium 0.1 mg/kg, only 60% patients had excellent intubating conditions as compared to 88% patients in group I i.e. combination of atracurium 0.4 mg/kg and vecuronium 0.08 mg/kg at 75 seconds and 96% patients in group III i.evecuronium 0.08 mg/kg and atracurium 0.4 mg/kg at 90 seconds. Studying the results of combination at 90 seconds and vecuronium alone, we observed that 96% patients receiving combination had clinically acceptable intubating conditions as compared to only 60% patients receiving vecuronium alone. This difference is highly significant. Thus, as compared to vecuronium alone, combination of atracurium and vecuronium provides far better intubating conditions after 90 seconds. Rautoma P, Erkola O et al studied that significant potentiation was maintained also during the course of anaesthesia.[21]

A combination of atracurium and vecuronium had an effect like one intermediate acting agent. If a combination is used instead of using atracurium or vecuronium alone, maximum reduction of drug consumption would be approximately 30%.[21]Sloan MH, Lerman J et al studied the interaction of vecuronium and atracurium which showed that the slopes of the dose response curve relationships were significantly different($P<0.001$). With vecuronium alone, speed of onset of neuromuscular blockade was significantly slower($P<0.001$) and the duration of action less(0.001) than that with atracurium alone or with combination.[24] There were no differences between atracurium and combination of both medications. The recovery index was similar for all groups.[22]They concluded that dose response relationships of vecuronium and atracurium in children were not parallel and the neuromuscular effects of vecuronium and atracurium were neither additive nor synergistic while vecuronium had a slower duration of action than atracurium, this feature was not apparent when it was combined with atracurium in equipotent doses. Recovery was rapid and not prolonged when these two drugs were combined. Berman IA et al had found that increasing the percentage of both drugs to 70% and 80% caused a prolongation of a recovery of neuromuscular block.[8]Stir JA et al had found similar results with atracurium 0.125 mg/kg and vecuronium 0.025 mg/kg(5:1 ratio).[22] From results of our study, we concluded that clinically acceptable intubating conditions may be obtained in all patients. With combination of atracurium 0.4 mg/kg with vecuronium 0.08 mg/kg after 90 seconds. It can be provided by combination of both drugs after 75 seconds but increasing the time interval to 90 seconds, it must be possible to achieve good results.

In our study, we found mean duration of combination group around 48 minutes that is due to using high dose of both parent drugs while vecuronium alone group had duration of around 37 minutes. This finding showed that dose ratio for intubation increasing caused prolongation of recovery from the neuromuscular block which may be undesirable in short proce-

dures, day care surgeries and could present a potentially difficult situations if intubation proved to be difficult. This possibility must be taken into consideration prior to using higher dose. Stirt JF et al had found that the cardiovascular effects produced by atracurium could be decreased by using the combination in equipotent doses. The haemodynamic stability of combination group is same as that of the vecuronium alone group.[26] In our study, we do not found clinical evidence of hypotension, flushing even using combination of atracurium and vecuronium as atracurium used to produce hypotension, flushing, erythema due to histamine release. Meretoja OA had observed spontaneous recovery of neuromuscular junction in the combination group of atracurium and vecuronium in 66% patients which was at the same rate as that of parent drug while slight delayed recovery was noted in pipecuronium group.[2] Stirt JA had found that recovery significantly faster in the group recovering the combination of atracurium and vecuronium than single drug used.[22]

During our study, we found that the post operative recovery was quite early and had a good recovery score in the combination of vecuronium and atracurium group. Recovery was slightly delayed in a few patients in vecuronium group alone so this was one positive feedback of combination group. We had also noticed few complications like hypotension, bradycardia, skin allergic reactions in combination groups but it was statistically insignificant. We had not noticed post operative apnoea in a single patient of all three groups.

ACKNOWLEDGEMENT

We would like to acknowledge the whole Department of Anaesthesiology for their timely help in completing this study.

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