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Original article

Neuromuscular Blocking Effect of Inhalational Anesthetic Agents- A Comparative Study

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ABSTRACT

Introduction: Volatile anesthetics enhance the action of neuromuscular blockade (NMB) by various degrees. The purpose of this study is to compare the muscle relaxant effects of isoflurane and sevoflurane, in the context of routinely used muscle relaxants viz. vecuronium and rocuronium. **Material and methods**: 80 patients were divided in a randomized manner into 4 groups of 20 each to receive a combination of an inhalational agent with a muscle relaxant. The time required for intubation and extubation were calculated using Train of Four (TOF) monitoring. **Result**: The group with vecuronium as muscle relaxant had significantly longer time for intubation and extubation with both inhalational agents. The group with sevoflurane as inhalational agent with vecuronium had significantly lower intubation and extubation time as compared to the group with isoflurane as inhalational agent with vecuronium as muscle relaxant. Isoflurane and sevoflurane equally affected intubation and extubation times of rocuronium.**Conclusion**: This study suggests that a combination of rocuronium with both isoflurane and sevoflurane is equally effective for early intubation as well as for early extubation as compared to vecuronium with isoflurane and sevoflurane. Vecuronium with sevoflurane had better results as compared with vecuronium with isoflurane.

KEYWORDS: Neuromuscular Blockade, Neuromuscular Blocking Agents (Vecuronium, Rocuronium), Anesthetics, Inhalational (Isoflurane, Sevoflurane).

INTRODUCTION

General anesthesia stands on the pillars of analgesia, amnesia, loss of autonomic reflexes and muscle relaxation. The first use of skeletal muscle relaxation during general anesthesia using d- Tubocurarine was reported in 1942. In a report from 1954, Henry Beecher and D.P Todd concluded that the use of curare led to a nearly six fold increase in postoperative complications and deaths [1]. Similar cautionary articles followed soon after. Churchill-Davidson advised in 1955 that a useful technique for monitoring the degree of neuromuscular blockade was to stimulate a peripheral nerve and observe the resulting muscle contraction [2-3]. A significant step forward occurred in 1970 with the introduction of the Train-of-Four (TOF) by Ali *et al* [4-5]. Recently, monitoring of the neuromuscular function has become more and more a part of the routine observations on the anaesthetized patient.

Clinically, a common method in determining the type, speed of onset, magnitude and duration of neuromuscular blockade present is to observe or record the skeletal muscle response that is evoked by a supramaximal electrical stimulus delivered by a peripheral nerve stimulator. Neuromuscular blocking drugs affect small rapidly moving skeletal muscles (eyes and digits) before those of the abdomen (diaphragm).

The characteristics of Neuromuscular blockade (NMB) is affected by the synergistic combination of NMBA with other drugs administered during general anesthesia like opioids, volatile agents and induction agents.

The volatile anesthetic agents "potentiate" the action of Neuromuscular blocking agents (NMBA) [6-11]. The effect is associated with almost all routinely used volatile agents - from halothane to more recently introduced agents like sevoflurane and desflurane. The degree of enhancement varies with the volatile agent and the neuromuscular blocking drug [6] [12-14].

Inhaled anesthetics decrease the dose of NMBA needed, as well as prolong the duration of recovery from NMB [15], depending on the duration of anesthesia [16-18] [20-22],the specific inhaled anesthetic [6], and the concentration (dose given) [19].Studies investigating the interaction between NMBAs and volatile anesthetics are typically realized during steady-state conditions, i.e. stable end-tidal concentration of the anesthetic vapor [7-11] and therefore do not allow conclusions to be drawn on this interaction during the wash-in and wash-out period of the volatile anesthetic. However, during the induction and towards the end of anesthesia this information may be of particular clinical interest [23].

This prospective, randomized study focuses on and tries to ascertain the best possible drug combination for optimal effect – both with conventionally available drugs as well as with the newly introduced and not so widely available drugs, both inhalational agents and NMBAs. Not acknowledging this effect of volatile anesthetics can result in prolonged duration of relaxation; which has potential implications for both the patient and anesthesiologist in terms of medical, legal and financial issues.

Study objectives:

The aim of this study is comparison of characteristics of neuro-muscular blockade of vecuronium and rocuronium with propofol- isofluraneanaesthesia compared with propofol - sevofluraneanaesthesia. And the Objectives are to compare, Time to optimal relaxation for intubation as determined by NMB monitoring and Time to recovery from the neuro-muscular blockade as determined by NMB monitoring.

MATERIALS AND METHODS

80 patients between 21-60 years in ASA (American Society of Anesthesiologist) class I or II requiring muscle relaxation for elective surgery were selected and allotted the groups randomly by closed envelope method. The exclusion criteria were presence of hepatorenal, cardiovascular, metabolic or neuromuscular diseases, allergy to the drugs to be used and unwillingness of the patient. All patients were premedicated with Tab Diazepam 10 mg orally at night, InjGlycopyrrolate 0.2 mg and InjOndansetron 4 mg intravenously 10-15 min before induction.

The ulnar nerve was tested for the estimation of the muscular relaxation. Neuromuscular monitoring was applied before the start of the operation with attachment on the thumb and the index finger of the selected hand. An informed consent was taken from each patient. The electrodes were placed on the forearm on the flexor surface over the nerve at the wrist 2cm to 3cm apart between the tendons of Flexor Carpi Ulnaris and Flexor DigitorumProfundus where the ulnar nerve passes before entering the hand. Induction was done with InjPropofol 2 mg/ kg and oxygen-nitrous oxide 50:50 started simultaneously. After induction the Supramaximal stimulus was calculated with single twitch method. Then the calculation of TOF was started at a frequency of 20 sec.

The inhalational agents as per the group allotted was started to achieve end-tidal concentration of 1 MAC (Standard for sevoflurane and isoflurane. i.e.1.7% and 1.2% respectively) [24-25] simultaneously with administration of the muscle relaxant allotted to the group. The time required for the TOF count 0 was taken as the end point for intubation. The concentration of the anesthetic agent was measured with multigas monitor.

The dosages used for muscle relaxant were also standard both for vecuronium and rocuronium viz. 0.1 mg/ kg and 0.6 mg/kg respectively for intubation and $1/10^{th}$ of the initial dose for maintenance depending on the TOF response of count 2. The level of muscle relaxation was maintained with the respective muscle relaxant in the form of intermittent boluses, the frequency of dose was determined by NMB monitoring.

The last dose of muscle relaxant was given minimum 20 min before the expected time of completion of the surgery. The supply of the volatile anesthetic was shut off as soon as the skin closure started and the cutting off of nitrous oxide followed soon thereafter. The effects of NMB were reversed by administering Inj Neostigmine 50-60 micrograms/ kg and InjGlycopyrrolate 4-5 micrograms/ kg intravenously after the twitch response corresponding to count 4 was attained. Extubation was carried out when a TOF of 0.7 was attained. During this period the patient was administered 100% oxygen.

Intraoperative monitoring included temperature (maintaining normothermia), pulse oximetry, electrocardiogram, noninvasive blood pressure and end tidal carbon dioxide monitoring (maintained between 30-35 mm Hg monitored with multigas monitor).

Allotment of groups - A total of 80 patients were studied, 20 in each of the following four groups:

Group 1. Propofol and Isoflurane with Muscle Relaxation by Vecuronium.

Group 2. Propofol and Sevoflurane with Muscle Relaxation by Vecuronium.

Group 3. Propofol and Isoflurane with Muscle Relaxation by Rocuronium.

Group 4. Propofol and Sevoflurane with Muscle Relaxation by Rocuronium.

The equipment used for all the monitoring was modular monitor S/ 5TM Compact critical care monitor, Datex-Ohmeda, with softwares S-00C03 and S-00C04 of Datex-Ohmeda, Finland.

(i) Automatic NMG monitoring equipment with standard attachments consisting of a mechano-sensor.

(ii) The degree of block is given as a percentage of control and as a TOF ratio. Bars imitating twitch heights and the compound EMG response curve are given in the Relaxograph.

(iii) Monitoring equipment for Temperature monitoring, electrocardiogram, pulse oxymeter, noninvasive bloodpressure and end tidal carbon dioxide and end tidal volatile anesthetic agent concentration monitoring.

The Parameters monitored were supramaximal single twitch response at 1 Hz frequency at the start of the surgery and TOF before induction, during induction, during maintenance phase of the surgery and during recovery. Times for all TOF responses were measured with a standard stop watch.

RESULTS

There was no statistically significant difference in all four groups with respect to age, sex and weight. Both the intubation and extubation times calculated as an average showed significant results. The average intubation and extubation times for the four groups were calculated and in both instances the times obtained in the group in which rocuronium was used along with sevoflurane were found to be significantly less as compared to other groups.[Table1][Table 3]

Table 1: Intubation time (In sec) for various groups

Group	N	Mean	Std. Deviation	Std. Error
1	20	190.75	5.684	1.271
2	20	177.05	6.386	1.428
3	20	118.65	6.037	1.350
4	20	115.30	6.062	1.355

Table 2: Multiple inter group comparison of Intubation time (In sec)

Group Vs	Group	Mean Difference	Std. Error	Sig.
1	2	13.700(*)	1.912	.000
	3	72.100(*)	1.912	.000
	4	75.450(*)	1.912	.000
2	1	-13.700(*)	1.912	.000
	3	58.400(*)	1.912	.000
	4	61.750(*)	1.912	.000
3	1	-72.100(*)	1.912	.000
	2	-58.400(*)	1.912	.000
	4	3.350	1.912	.503
4	1	-75.450(*)	1.912	.000
	2	-61.750(*)	1.912	.000
	3	-3.350	1.912	.503

Table 3:Extubation time (In sec) for various groups

Group	N	Mean	Std. Deviation
1	20	258.05	10.425
2	20	210.75	9.182
3	20	194.70	14.582
4	20	188.65	10.282

Group 1 had significantly higher time of intubation as compared to all other groups. Thus it is found that the combination of Isoflurane with vecuronium requires significantly higher time 190.75 sec (180 – 208 sec) vis-a-vis other groups. Similarly in group 2, a combination of Sevoflurane with vecuronium also takes statistically significantly more time of 177.05 sec (164 – 188 sec) as compared to group 3 and group 4, but it is better than the results for group 1. The intubation time for group 3 was 118.65 sec (108 – 126 sec) and for group 4, 115.30 sec (106 – 126 sec), when compared with each other was similar, i.e. the results are not significant statistically. But both these groups have results which are significant as compared with the groups 1 and 2. [Table 4]

Thus it was seen that the groups in which vecuronium was the muscle relaxant required more time for intubation as compared to those with groups with rocuronium. But the addition of sevoflurane to the group 2 improves the intubation time of the group with vecuronium as compared to group 1 which has isoflurane as inhalational agent. Thus it is likely that sevoflurane helps achieve muscle relaxation faster as compared to isoflurane.

Group 1 had significantly higher time to extubation as compared to all other groups. Thus it is found that the combination of Isoflurane with vecuronium requires significantly higher time 258.05 sec (239 – 271 sec) vis-a-vis other groups. Similarly in group 2, a combination of

Sevoflurane with vecuronium also takes statistically significantly more time of 210.75 sec (194 – 231 sec) as compared to group 3 and group 4, but it is significantly lesser than the results of group 1.

The extubation time for group 3 was 194.7 sec (170 – 214 sec) and for group 4, 188.65 sec (168 – 204 sec), when compared with each other was similar, i.e. the results are not significant statistically. But both these groups have results which are statistically significant as compared with the groups 1 and 2. [Table 4]

Thus it was seen that the groups in which vecuronium was the muscle relaxant required more time for extubation as compared to those with groups with rocuronium. But the addition of sevoflurane to the group 2 improves the extubation time of the group with vecuronium as compared to group 1 which has isoflurane as inhalational agent. Thus it is likely that action of sevoflurane on muscle relaxants is reversed faster as compared to isoflurane.

Table 4: Multiple inter group comparison of Extubation time (In sec)

GroupVs	Group	Mean Difference	Std. Error	Sig.
1	2	47.300(*)	3.575	.000
	3	63.350(*)	3.575	.000
	4	69.400(*)	3.575	.000
2	1	-47.300(*)	3.575	.000
	3	16.050(*)	3.575	.000
	4	22.100(*)	3.575	.000
3	1	-63.350(*)	3.575	.000
	2	-16.050(*)	3.575	.000
	4	6.050	3.575	.568
4	1	-69.400(*)	3.575	.000
	2	-22.100(*)	3.575	.000
	3	-6.050	3.575	.568

DISCUSSION

The intubation time required by the group containing vecuronium as muscle relaxant (group 1 and group 2) requires significantly longer time for intubation as compared with other groups but when sevoflurane replaced isoflurane as the inhalational agent in the group 2 the intubation time improved significantly as compared to group 1.Thus implying faster intubating conditions with sevoflurane when vecuronium was the muscle relaxant used.

The groups containing rocuronium as muscle relaxant (group 3 and group 4) shows no statistically significant changes in the intubating times with both inhalational agents. But when these groups (group 3 and group4) were compared with the groups containing vecuronium as muscle relaxant (group 1 and group 2), the intubating time for groups 3 and 4 was found to be significantly less.

These findings imply that the time required for achieving intubating conditions are achieved better with sevoflurane when vecuronium is used as the muscle relaxant vis-à-vis isoflurane. It also suggests that rocuronium has faster action as compared to vecuronium irrespective of the inhalational agent used. The muscle relaxant activity of the rocuronium is equally affected with both isoflurane and sevoflurane.

Similarly for extubation time the group containing vecuronium as muscle relaxant (group 1 and group 2) requires significantly longer time for extubation as compared with other groups but when sevoflurane replaced isoflurane as the inhalational agent in the group 2 the extubation time improved significantly as compared to group 1.Thus implying faster extubating conditions with sevoflurane when vecuronium was the muscle relaxant used.

The groups containing rocuronium as muscle relaxant (group 3 and group 4) shows no statistically significant changes in the extubating times with both inhalational agents. But when these groups (group 3 and group4) were compared with the groups containing vecuronium as muscle relaxant (group 1 and group 2), the extubating time for groups 3 and 4 was found to be significantly reduced.

CONCLUSION

These findings imply that the time required for achieving extubating conditions are achieved better with sevoflurane when vecuronium is used as the muscle relaxant vis-à-vis isoflurane. It also suggests that rocuronium has faster action as compared to vecuronium irrespective of the inhalational agent used. The muscle relaxant activity of the rocuronium is equally improved with both isoflurane and sevoflurane.

Thus if Rocuronium is used for cases requiring muscle relaxant along with the inhalational agents the turnaround and anesthesia time for the cases can be improved upon. However if rocuronium is not available, than vecuronium along with sevoflurane gives a faster turnaround and faster intubation and extubation times when compared to vecuronium with isoflurane.

Limitations of the study:

The duration of the surgeries were not taken into consideration. It has been observed that the duration of the surgery does influence the duration of the neuromuscular blocking effect of the inhalational agent, especially after the fourth dose of muscle relaxant.

The cut-off point for stopping of the inhalational agent has been taken arbitrarily as the start of the closure of the skin, which is a subjective parameter. The duration of skin closure will be dependent on the type of surgery i.e. length of incision, location of incision and also the level of skill of the surgeon. Thus the duration of skin closure will vary from patient to patient. The end -tidal concentration of the inhalational agent in the circuit will depend on the flow of the fresh gas flow primarily, among other variables.

The maintenance of the muscle relaxation was achieved with intermittent bolus doses, which is subject to individual assessment. Though the decision to give bolus doses was determined by the TOF, the maintenance is better achieved with continuous infusion. The study fails to take into account the effects of propofol and nitrous oxide on muscle relaxant. But this may not be important as it is a common feature for all the groups.

Competing interest: The authors declare that they have no competing interests.

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