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COMPARISON OF INTUBATING CONDITIONS BETWEEN ATRACURIUM PRIMING, MAGNESIUM SULPHATE PRE-TREATMENT AND COMBINATION OF TWO METHODS ON ONSET AND DURATION OF NEUROMUSCULAR BLOCKADE: A RANDOMIZED DOUBLE BLIND CONTROLLED STUDY

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Abstract

Introduction: Magnesium inhibits acetylcholine release from the presynaptic membrane at the motor end plate; and thus it enhances the effect of non-depolarising muscle relaxants. Priming technique shortens the time of onset of non depolarising neuromuscular relaxants. Thus, the combination of magnesium pre-treatment and priming may be an effective method for achieving an early tracheal intubating condition. We studied the effect of magnesium sulphate pretreatment in combination with atracurium priming on onset and duration of neuromuscular blockade, compared with these methods when used alone.

Materials and Methods: 100 patients scheduled for elective surgical procedures under general anaesthesia were divided into 4 groups. Group A (n=25) recieved priming with 0.05 mg/kg atracurium, three minutes before the intubating dose of atracurium 0.5 mg/kg, group M (n=25) was given 50 mg/kg magnesium sulphate as infusion over 10 mins before intubating dose of atracurium, group MA (n=25) received both the magnesium sulphate pretreatment and the priming dose of atracurium. Group N (n = 25) were given 0.5mg/kg atracurium alone as part of general anaesthesia. Tracheal intubation was done when the TOF stimulation showed single twitch which was measured at intervals of every 30 seconds. Parameters studied were the time to onset of neuromuscular blockade and the duration of neuromuscular blockade.

Results: The MA group had the shortest onset time (mean±SD) 114.30±20.19 sec ($p < 0.001$) compared to the other groups. The duration of blockade was prolonged in both Group MA and Group M compared to other groups ($P<0.001$). Few adverse effects were reported in groups receiving magnesium, but were clinically not significant.

Conclusion: Magnesium sulphate pretreatment in combination with atracurium priming shortens the time of onset of neuromuscular blockade when compared to magnesium sulphate pretreatment or priming used alone.

Keywords: Atracurium priming, magnesium sulphate, neuromuscular blockade

Introduction

Atracurium, a benzylisoquinolinium compound, is a nondepolarizing neuromuscular relaxant drug. The drug and its stereoisomer are commonly used in anaesthesia practice. Hoffman's elimination, which is an organ independent pathway, enables its safe usage in patients with renal and hepatic disease, but its late onset of action hinders its usage for rapid sequence induction and intubation.[1,2]

Magnesium acts as a calcium antagonist at the motor end plate by inhibiting presynaptic acetylcholine release. Magnesium has been found to shorten the onset time of non-depolarising muscle relaxants and thus potentiates their effect.[3,4]

The concept of priming refers to administration of one tenth the intubating dose of non depolarising neuromuscular relaxant, 3-5 minutes before the intubating dose is given. It is hypothesized that this approach will shorten the time of onset of non depolarising neuromuscular relaxant drugs [5,6]. The administration of the second larger dose at the time of the development of the maximal effect of the priming dose increasesthe receptor occupancy to over 90% which is required for profound neuromuscular blockade[5]

Thus, the combination of magnesium pre-treatment and priming with a non depolarising neuromuscular relaxant may be an effective alternative method for accomplishing early tracheal intubation. There are studies with rocuronium and vecuronium priming and magnesium pretreatment[12,13].

In this study we tested the hypothesis that combination of priming with atracurium and magnesium pretreatment is an effective method in accomplishing early tracheal intubation

Materials and Methods

After getting approval from the institutional ethical committee, the present study was undertaken in Department of Anaesthesiology, J.A Group of Hospitals, G.R. Medical College, Gwalior (M.P). This prospective, randomized double blind controlled study included 100 patients with inclusion criteria of– patients undergoing elective surgery under general anesthesia with endotracheal intubation, ASA Physical Grade I and II, age group 20 to 60 years of either sex of average height and weight, Mallampati class 1-2. The exclusion criteria included of- body mass index <18.5 or >25.0 kg/m^2, anticipated difficult airway, any cardiovascular/renal/neuromuscular or hepatic disease, patient on calcium channel blocker treatment, patient on medication affecting muscle relaxation.

Methodology

Well informed and written consent was taken from the patients and all patients were kept nil per oral from 12 midnight. Patients were allocated to the 4 groups (n=25each) by computer generated random number table. Group A: receiving priming with atracurium, Group M: receiving magnesium sulphate, Group MA: receiving both priming with atracurium and magnesium sulphate and Group N: receiving normal saline only.

On arrival in the operating room, standard intraoperative monitoring included electrocardiogram, noninvasive blood pressure measurement, pulse oximetry, end tidal CO_2 and neuromuscular monitioring. Neuromuscular monitoring was performed continuously using acceleromyography (TOF- Infinity® Trident® NMT SmartPod®) at the adductor pollicis muscle[9]. The acceleration transducer was attached on the volar side of the thumb and the electrodes were placed over the ulnar nerve on the volar side of the wrist. Calibration of Acceleromyography was done using the automated calibration mode, and train-of-four (TOF) signal were stabilized.

Group A: Patients received 100 ml normal saline as intravenous infusion over 10 min. At the 7th minute of infusion, a priming dose of atracurium 0.05mg/kg was administered followed by preoxygenation and induction of general anaesthesia (GA) with inj. glycopyrolate 0.01mg/kg, inj. fentanyl 2 µg/ kg and inj. Propofol 1.5-2 mg/ kg. At the 10th minute, after the infusion got completed, atracurium 0.5 mg/ kg was administered. TOF stimulus was monitored every 30 seconds and endotracheal intubation performed at the point when TOF count showed a single twitch.

Group M: patients received 100 ml normal saline with magnesium sulphate 50 mg/ kg as intravenous infusion over 10 min. At 7th minute after starting of infusion, pre-oxygenation was followed by induction of GA. At the 10th minute, after the infusion got completed, atracurium 0.5 mg/ kg was administered. TOF stimulus was monitored every 30 seconds and endotracheal intubation performed at the point when TOF count showed a single twitch.

Group MA: patients received 100 ml normal saline with magnesium sulphate 50 mg/ kg as intravenous infusion over 10 min. At 7th minute of infusion, a priming dose of atracurium 0.05 mg/ kg was administered followed by preoxygenation and induction of GA. At the 10th minute, after the infusion got completed, atracurium 0.5 mg/ kg was administered. TOF stimulus was monitored every 30 seconds and endotracheal intubation performed at the point when TOF count showed a single twitch..

Group N: Patients received 100 ml normal saline as intravenous infusion over 10 min. At 7th minute of infusion, pre-oxygenation was followed by induction of GA. At the 10th minute, after the infusion got completed, atracurium 0.5 mg/ kg was administered. TOF stimulus was monitored every 30 seconds and endotracheal intubation performed at the point when TOF count showed a single twitch.

Anaesthesia was maintained with O_2, N_2O (40:60) and isoflurane gas mixture. Endotracheal intubation was followed by recording of train of four stimulation every 5 minutes. Onset of neuromuscular blockade was calculated from the time of injection of intubatory dose of atracurium to the time when only one twitch was present on TOF stimulation. The duration of neuromuscular blockade was calculated from time of administration of intubatory dose atracurium to the time when fourth twitch reappears. At the end of surgery, patients were given 0.04 mg/kg of neostigmine and 10 µg/kg of glycopyrolate for the reversal of neuromuscular blockade.

Statistics

The Statistical software SPSS 17.0 was used for the analysis of the data. Analysis of variance (ANOVA) was used to find the significance of study parameters between the 4 groups. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups. $P < 0.05$ was considered significant and $P > 0.05$ was considered non-significant.

Results

Demographic data was comparable among groups (table1). Time of onset was shortest for group MA (114.30±20.19 sec) (Table 2) which was statistically significant compared to all groups except for Group M. Reappearance of 4th twitch i.e. duration of neuromuscular blockade was prolonged in both Group M and MA (Table 2) which was statistically not significant among themselves but significant when compared to other two groups (table 3).

Side effects reported in four groups are shown (table 4). None of the patients in control and prime group had side effects. 5(20%) patients in group M and 3(12%) patients in group MA experienced flushing, 3(12%) patients in group M and 4(16%) patients in group MA experienced generalized weakness. None of the adverse effects required interruption of the magnesium sulphate infusion or any treatment.

Table 1: Demographic data

Variables	Group A	Group M	Group MA	Group N	P value
Age (years) Mean ± SD	35.12±12.42	36.00±14.14	34.37±12.73	35.52±12.58	>0.05
Male: Female	14:11 35.12±12.42	12:13	13:12	11:14	>0.05
Weight (kg) Mean ± SD	55.84±6.74	55.34±6.82	56.44±5.34	54.14±6.13	>0.05

P<0.05 → significant p>0.05 → non significant

Table 2: Onset time for intubation and reappearnce of 4th twitch

	Group A	Group M	Group MA	Group N	P value
Onset time (sec) Mean ± SD	90±28.80	126.20±23.47	114.30±20.19	202.10±27.00	<0.01
Reappearance of 4th twitch (min) Mean ± SD	45.5±13.17	76.31±7.59	76.22±8.31	35.40±8.44	<0.01

P<0.05 → significant p>0.05 → non significant

Table 3: P value between the groups

	Group N vs Group A	Group N vs Group M	Group N vs Group MA	Group A vs Group M	Group A vs Group MA	Group M vs Group MA
Onset time	<0.05	<0.01	<0.01	<0.01	<0.01	**>0.05**
Reappearance of 4th twitch	<0.05	<0.01	<0.01	<0.01	<0.01	1.000

P<0.05 → significant p>0.05 → non significant

Table 4: Side Effects

Side effects	Group A	Group M	Group MA	Group N
Nausea vomiting	--	--	--	--
Flushing	--	5 (20%)	3 (12%)	--
Generalized weakness	--	3 (12%)	4 (16%)	--
Aspiration	--	--	--	--

Discussion

Atracurium, a benzylisoquinolinium compound, is a non-depolarizing neuromuscular relaxant. It is a competitive antagonist of the postsynaptic nicotinic receptor at the neuromuscular junction. It competes with acetylcholine for binding sites. Atracurium binds to the postsynaptic nicotinic receptor and prevents depolarization of the motor end plate, inhibiting skeletal muscle contraction. Atracurium is indicated to provide skeletal muscle relaxation and facilitate endotracheal intubation during surgery or mechanical ventilation.

When an intubating dose is given, atracurium has an onset of action of approximately 2 minutes. It is an intermediate-acting non-depolarizing muscle relaxant with duration of action of approximately 30 to 35 minutes. Hofmann elimination which is a nonenzymatic degradation accounts for 45% of the metabolism of atracurium. The rest is metabolized by ester hydrolysis by non-specific esterases in the plasma.

Monitoring of neuromuscular blockade can be done by quantitative or qualitative methods. Nerve stimulation is frequently used for monitoring neuromuscular blockade intraoperatively. ECG electrodes are applied at either the ulnar, facial, or tibial nerve. Then a train of four stimulation is applied. Four stimuli are applied at the chosen nerve at a frequency of 2 Hz provoking a twitch response. When atracurium or another non-depolarizing neuromuscular blocking agent is given, there is a reduction in the amplitude of the evoked responses, T_4 (the final twitch of the train of 4 sequences) is affected first, then T_3, followed T_2, then T_1. This sequential decrease in twitch height is known as fade. As the intensity of the neuromuscular blockade increases, the twitches began to disappear in the same sequence as fade occurs, with T_4 disappearing first. As neuromuscular blockade is reversed, T_1 is the first to reappear. The ratio of twitch intensity when comparing T_4 to T_1 is an important value, a ratio of 0.9 is indicative of sufficient neuromuscular blockade reversal.[10]

Magnesium by acting as a calcium channel blocker, decreases acetylcholine release from the presynaptic nerve terminals, resulting in potentiation of neuromuscular blockade caused by nondepolarizing neuromuscular blocker[11]. The work done by Ryu JH et al, Lee DH et al, Na HS et al, Oguzhan N et al and Telci L et al have concluded that requirement for nondepolarizing neuromuscular blockers reduces by perioperative use of magnesium sulfate as an adjuvant[12-16]

Rao MH et al and Schmidt J et al have concluded in their study that onset of neuromuscular blockade is accelerated by priming technique[5,6].

Magnesium pretreatment and priming seem to effect neuromuscular transmission at different sites or stages which may be responsible for enhancing the effects of non depolarizing neuromuscular blockers in a synergistic way[17]. So this study was planned to assess the onset of action as well as the duration of neuromuscular blockade with atracurium priming and the combination of magnesium pretreatment with atracurium priming.

In our study, we found that the magnesium and prime group (Group MA) had the shortest onset time 114.30±20.19 sec followed by magnesium group (Group M), where it was 126.20±23.47 and these were statistically significant when compared to other two groups (p<0.01).This was similar to the study done by Kim MH et al[8] where he compared magnesium pre-treatment, rocuronium priming, and a combination of the two, and

found that the group with both magnesium pretreatment and priming had the shortest time of onset and best tracheal intubating conditions. The time of onset of neuromuscular blockade in magnesium pretreatment and priming technique group was significantlly shorter as compared to the control group(Group N). This finding is in concurrence with other studies[6,18]

The duration of blockade by non depolarizing muscle relaxant was determined by the reappearance of 4th twitch (in minutes) in all the groups. The groups receiving magnesium sulphate had a prolong duration of neuromuscular blockade which was statistically significant ($p<0.05$) compared to other two groups. The "intubating dose" of atracurium (0.5mg/kg) was used in the study and a clinical duration of action of about 30-35 min was found. However, after magnesium pre-treatment the duration of atracurium block was nearly doubled. Similar results were found in previous study where they investigated the interaction between magnesium sulphate and rocuronium[18,19].

In our study, 5(20%) patients in Group M and 3(12%) patients in Group MA experienced flushing. 3(12%) patients in Group M and 4(16%) patients in Group MA experienced generalized weakness. None of the adverse effects required interruption of the magnesium sulphate infusion or any treatment. None of the patient in any group had hypoxia, respiratory difficulty, or any sign of aspiration.

Our study had few limitations – 1. The sample size chosen may be small. 2. The onset of neuromuscular blockade may not have been detected very accurately as the train of four stimulus was given after every 30 seconds. 3. We did not took into account the intubating conditions.

Conclusion

Thus, in conclusion, magnesium sulphate pre-treatment in combination with atracurium priming provides faster onset of neuromuscular blockade as well as longer duration of blockade when compared with magnesium sulphate pre-treatment or atracurium priming alone without any critical adverse events.

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