

## Pretreatment of magnesium sulphate accelerates neuromuscular block as compared to vecuronium priming – A randomized trial

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### Abstract

**Background:** Action of non depolarising neuromuscular relaxants can be potentiated by small dose of priming. Priming reduces the time of onset of muscle relaxants by binding and occupying the choline receptors. Whereas magnesium decreases the release of acetylcholine in the presynaptic junction at the neuromuscular junction, hastening the effect of non-depolarising muscle relaxants. So we investigated whether pre- administration of magnesium reduces the time of onset of neuromuscular blockade compared to priming with vecuronium.

**Method:** 120 patients posted for surgery under general anaesthesia were recruited for this study. They were randomly allocated to control (group N), vecuronium priming (group P) or magnesium (group M) group. Group N (n = 40) received 100mcg/kg vecuronium after saline infusion, group P (n=40) received 10 mcg/kg vecuronium followed by 90 mcg/kg vecuronium. In group M (n=40) patients were infused with 40 mg/kg magnesium sulphate followed by 100 mcg/kg vecuronium. At the interval of 20 seconds, the train-of-four (TOF) responses to stimuli were recorded. Endotracheal intubation was done when one twitch was seen on the TOF stimulus. Time taken to intubation from the vecuronium intubating dose, time for reappearance of the 4<sup>th</sup> twitch, tracheal intubating conditions and side effects were noted.

**Results:** Onset time for intubation was significantly shortest in the group M as compared to other groups with mean time of 126.4 ± 23.3 seconds (p < 0.01). The reappearance of the 4<sup>th</sup> twitch was significantly prolonged in Group M as compared to other groups. The mean time for reappearance of 4<sup>th</sup> twitch was 77.5±10.4 minutes (p < 0.01) in group M. In the magnesium preloaded group, few patients had adverse events which was clinically not significant.

**Conclusion:** We conclude that pretreatment of magnesium infusion accelerates the onset of action of neuromuscular blockers and prolongs their duration of action.

**Keywords:** Magnesium infusion, Onset of neuromuscular blockade, Priming, Intubation

### Introduction

Competitive neuromuscular inhibiting drugs have slower onset of action.<sup>(1)</sup> Vecuronium is a cardiac stable, non-depolarising neuromuscular blocking drug with stable hemodynamics.<sup>(1,2)</sup> It also has a slower onset of action of more than 3 minutes which is one of the main disadvantage. Priming is administration of one tenth of the intubating dose of the non-depolarizing blockers few minutes before the full intubating dose.<sup>(3)</sup> Many studies have proved that this approach hastens the onset of non-depolarising muscle relaxants.<sup>(4)</sup> Even in paediatric group it has been proved that priming accelerates neuromuscular blockade.<sup>(5)</sup> Magnesium acts at the motor end plate, inhibiting the release of acetylcholine at the presynaptic junction and has a direct calcium antagonist action.<sup>(6)</sup> Thus magnesium has been shown to reduce the onset time of action of non-depolarizing drugs by potentiating their effect.<sup>(7)</sup> Though there are many side effects reported on the magnesium, they are all mild and self-limiting.

Thus, this study compared the vecuronium priming versus magnesium pre-treatment for rapid tracheal intubation.

### Methodology

This was a prospective randomized controlled study done in our hospital. After taking ethical committee clearance, one hundred twenty patients scheduled for surgery under general anaesthesia with intubation were recruited for this study. Patients aged between 18-60 years of age, belonging to American society of Anaesthesiologists physical status 1 and 2, posted for elective surgery under general anaesthesia were included. Patients with anticipated difficult airway, risk of aspiration, reactive airway disease, renal or cardiac disease, and medication which affects muscle relaxation were excluded from this study.

After taking informed consent, patients were randomized using a random number generator to one of the group. The investigator who recorded the onset time of intubation, time for reappearance of the 4<sup>th</sup> twitch and hemodynamics was blinded to the drugs used. All patients were kept nil by mouth for 6 hours prior to the surgery and were premedicated with tablet pantoprazole 40 mg and tablet metoclopramide 10 mg two hours prior to the surgery. On arrival to operation theatre electrocardiogram (ECG), Noninvasive blood pressure (NIBP) and pulse oximetry monitors were connected. TOF watch was connected in the wrist to look for the adductor pollicis action.

In the control group (group N), patients were infused with 100 ml of normal saline (NS) intravenously for 10 minutes and at 8<sup>th</sup> minute of infusion, they were induced with fentanyl 2 µg/ kg and propofol 2 mg/ kg after preoxygenation. At the 10<sup>th</sup> minute, vecuronium 100mcg/ kg was administered. In the priming group (group P) patients were given 100 ml NS intravenously over 10 min and at 8<sup>th</sup> minute of infusion, one tenth of the intubation dose of vecuronium that is 10 mcg/ kg was given followed by fentanyl 2 µg/ kg and propofol 2 mg/ kg. At the 10<sup>th</sup> minute, vecuronium 90 mcg/ kg was administered. In magnesium group (group M) 100 ml of magnesium sulphate of 40 mg/ kg was infused intravenously over 10 min followed by induction with fentanyl 2 µg/ kg and propofol 2 mg/ kg at 8<sup>th</sup> minute. At the 10<sup>th</sup> minute vecuronium 100mcg/ kg was administered.

In all the three groups TOF twitches were monitored every 20 seconds. All patients were intubated using an appropriate size endotracheal tube, at a point of single twitch on the TOF monitor. Time taken from injection of intubating dose of vecuronium to the time of intubation was the onset time of neuromuscular blockade. According to cooper scoring system (Table 1), intubating condition was scored as excellent (8-9), good (6-7), fair (3-5), and poor (0-2).

**Table 1: Cooper scoring system**

Score	Jaw relaxation	Vocal cords	Response to intubation
0	Impossible to open	Closed/bucking	Severe coughing
1	Opens with difficulty	Closing	Mild coughing
2	Moderate opening	Moving	Slight diaphragmatic movement
3	Easy opening	Open	No movement

Heart rate, blood pressure and oxygen saturation were recorded at baseline, one, five and ten minutes after intubation. Anaesthesia was maintained with sevoflurane 2-2.5% in oxygen and nitrous oxide. After a successful endotracheal intubation, twitches on TOF stimulation were recorded every 5 minutes. The time taken for reappearance of the 4<sup>th</sup> twitch from the time of administration of vecuronium is noted. Side effects like flushing, difficulty in swallowing and weakness were noted after extubation.

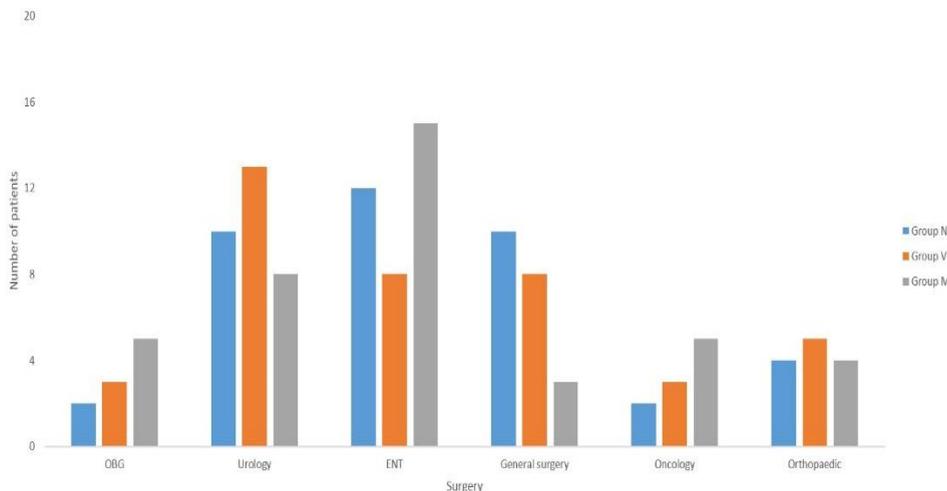
**Statistical analysis:** In the previous published study<sup>(3)</sup> the onset of neuromuscular blockade for intubation with vecuronium priming was 70 seconds. Based on this, accepting 15 seconds difference in onset time of neuromuscular blockade, assuming type 1 error (two-tailed test) to be 5% and power of 0.8, we got a minimum sample size of 35 patients for each group. Therefore, 40 patients were taken per group to compensate for any possible dropouts. The primary outcome was the time of intubation from the time of administration of intubating dose of vecuronium. Secondary outcomes were conditions of intubation as per cooper score, the time for reappearance of 4<sup>th</sup> twitch (duration of action) and any side effects. Analysis of variance (ANOVA) was used to find the significance of study parameters between the groups of patients. For categorical parameters Chi-square or Fisher Exact test was used.  $P < 0.05$  was considered significant. Statistical Package for Social Sciences version 15 was used for statistical analysis.

## Results

There was no difference in demographic data among groups (Table 2). Majority of the patients underwent otolaryngology surgery, followed by urology with no difference in types of surgery (Fig. 1).

**Table 2: Patient's demographics**

	Group N (n=40)	Group P (n=40)	Group M (n=40)	p
Age (years) mean ± SD	34.12±12.62	38.00±15.14	34.44±12.91	0.73
Male : Female	18:22	24:16	21:19	0.239
Weight (kg) Mean ± SD	56.84±7.44	58.44±5.92	55.24±4.44	0.147
ASA I:II	22:18	17:23	25:15	0.316



**Fig. 1: Types of surgery in three groups**

In group M time for onset of neuromuscular blockade for intubation was shortest with mean of (126.4±23.3) seconds (Table 3). This was statistically significant compared to both group P and group N. Reappearance of 4th twitch from the time of vecuronium was prolonged in Group M with mean of 77.5 ± 10.4 minutes (Table 3). Comparison between the groups for both onset and duration of neuromuscular blockade was statistically significant (Table 4). There was no significant change in haemodynamics among all the three groups. All patients in three groups had very good intubating conditions with cooper score of 8 to 9 (P =1.000). In all the group side effects were noted (Fig. 2). In both group N and group P nobody had side effects. In magnesium group 10 (25%) patients had flushing and 4 (10%) patients experienced generalized weakness. These side effects were statistically significant, but were not clinically significant.

**Table 3: Onset of time for intubation and reappearance of 4<sup>th</sup> twitch**

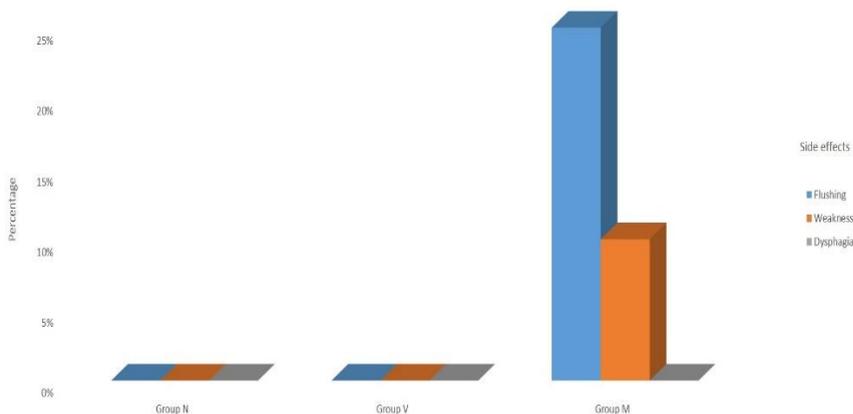
	Group N(n=40)	Group P (n=40)	Group M(n=40)	p
Onset time (seconds) Mean ± SD	218.00±30.1	202±30.9	126.4±23.3	<0.001
Reappearance of 4 <sup>th</sup> twitch (minutes) Mean ± SD	41.3±11.8	48.2±12.2	77.5±10.4	<0.001

p<0.05 – significant

**Table 4: p value between the groups**

	Group N vs P	Group N vs M	Group P vs M
Onset time (p)	0.038	<0.001	<0.001
Reappearance of 4 <sup>th</sup> twitch (p)	0.022	<0.001	<0.001

p<0.05 – significant



**Fig. 2: Adverse events**

## Discussion

Succamethonium chloride is a noncompetitive neuromuscular blocker with rapid onset of action with less than a minute. This depolarizing drug has many complications like bradyarrhythmias, malignant hyperthermia, raised intraocular pressure and intracranial pressure.<sup>(8)</sup> A nondepolarising muscle relaxant with faster onset of action similar to succinylcholine with lesser complications and adverse effects is needed.

The concept of the priming technique is that the initial one tenth dose of non-depolarizing muscle relaxants occupies and blocks large number of the acetylcholine receptors before apparent clinical reduction in neuromuscular transmission. Hence second dose blocks the remaining receptors leading to rapid onset of intubating conditions.<sup>(3,9)</sup> Vecuronium is a competitive neuromuscular inhibitor which is routinely used for intubation and muscle relaxation for surgery.<sup>(1)</sup> It is an intermediate acting non depolarising muscle relaxant which maintains stable hemodynamics with lesser side effects.<sup>(2)</sup>

Magnesium is also one of the drug which facilitates neuromuscular blockade. It acts by decreasing the release of acetylcholine at the neuromuscular junction by inhibiting the calcium channels and also reduces the sensitivity of the motor endplate to acetylcholine. It also attenuates the direct excitability of the muscle fibres by altering the electrical threshold of the muscle membrane.<sup>(6,7,10)</sup> The site of action at the neuromuscular junction and stages of interruption of neuromuscular transmission appears to differ between the priming principle and magnesium.

So in this study we compared the vecuronium priming versus magnesium sulphate 40 mg/kg for the time of onset of neuromuscular blockade for intubation, duration of action of neuromuscular blockade and any adverse events in patients posted for surgery under general anaesthesia.

The variation in time of onset of action for vecuronium when pretreated with magnesium sulphate is lower as compared to that of controls.<sup>(10)</sup> The Standard Deviation value for the onset of time was smaller in the magnesium pretreated group as compared to the control group in our study. Magnesium hastens the onset of neuromuscular blockade as well as reduces the variability of onset time of neuromuscular blockade. This shows that magnesium provides a better predictable onset compared to the other groups.

In this study, we found that the mean onset time for intubation was shortest in group M with mean of 126.40 ± 23.3 secs (p<0.001). In a randomised controlled trial by Kim et al,<sup>(11)</sup> infusion of magnesium combined with rocuronium priming had the shortest onset time for intubation as compared to the magnesium infusion group and priming group. In another study by Czarnetzki et al<sup>(12)</sup> the onset of action with magnesium pretreatment was rapid as compared to saline (P<0.001), similar to our

study. In a study on 30 female patients by Schmidt J et al,<sup>(13)</sup> found the onset time was significantly shorter in the rocuronium priming group as compared to the bolus group measured at the laryngeal adductor muscles. But in our study we did not find statistically significant difference between the priming technique and the control group.

In this study the duration of blockade was prolonged in group M as compared to the control group and group P. The time taken for reappearance of the 4<sup>th</sup> twitch was taken as the duration of neuromuscular blockade. Magnesium decreases the recovery rate of vecuronium and prolongs the time to achieve safe extubation. A longer duration of action with slower recovery after an intubating dose of vecuronium when used with magnesium results in a change in the total duration of vecuronium-induced curarization. Intergroup comparison revealed P<0.001 with the magnesium group which was statistically significant. Fuchs-Buder et al,<sup>(14)</sup> in his study compared the effect of magnesium infusion on the duration of vecuronium blockade and found statistically significant prolongation of neuromuscular blockade similar to our results.

Czarnetzki et al,<sup>(12)</sup> in their study, found that the clinical duration was prolonged on average mean of 44.7 minutes with magnesium and 33.2 minutes with saline (p 0.0002), similar to our study. In a study by Kim et al,<sup>(11)</sup> there was statistically significant increase in duration of neuromuscular blockade in patients who received magnesium as compared to the rocuronium priming and the control group.

In our study, in magnesium group 10(25%) patients had flushing, 4(10%) patients experienced generalized weakness. None of our patients experienced dysphagia. In Kim's<sup>(11)</sup> study, patients who received magnesium infusion had burning sensation and pain at the cannula site, which was reported as tolerable and self-limiting. In our study patients had flushing and weakness which was also self-limiting and didn't require interruption of the magnesium infusion. In the vecuronium priming group none of the adverse events like dyspnea or dysphagia with aspiration were observed similar to previous studies.<sup>(3)</sup>

## Conclusion

Thus to conclude the magnesium pre-treated patients had a rapid onset of neuromuscular blockade with prolongation of vecuronium induced neuromuscular blockade as compared to the vecuronium priming.

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