RESEARCH ARTICLE

PRE-TREATMENT WITH MAGNESIUM SULPHATE BEFORE NON-DEPOLARIZING MUSCLE RELAXANTS: EFFECT ON SPEED ON ONSET, INDUCTION AND RECOVERY

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ABSTRACT
Background: Magnesium sulphate is used during anaesthesia for its antihypertensive/ antiarrhythmic properties and attenuating the response to endotrachial intubation and as an anticonvulsant for women with eclampsia. At the motor nerve terminal, $MgSO_4$ inhibits acetylcholine release. Thus, it enhances the effect of neuromuscular blocking agents.
Aims & Objectives: To determine the effect of magnesium sulphate pre-treatment on the onset, duration and recovery of non-depolarizing muscle relaxant and to quantify the haemodynamic effects of administration of $MgSO_4$ on the arterial blood pressure.
Materials and Methods: One year old prospective, randomized, double blinded, controlled clinical study was conducted on randomly selected 45 patients of either sex, aged between 18-55 years, of grade I or II of American Society of Anaesthesiologists, undergoing elective surgery at a Medical College of eastern Uttar Pradesh. Patients were divided into three groups according to the doses of $MgSO_4$ used for pre-treatment. Statistical evaluation was done by using student's 't' test for paired data.
Results: The Mean Arterial Blood Pressure response to laryngoscopy, tracheal intubation, was almost abolished in Group A ($p<0.05$) followed by Group B ($p<0.05$) and maximum pressure response occurred in Group C where $MgSO_4$ was not used ($p<0.05$). The speed of onset of neuromuscular block was accelerated by pre-treatment with $MgSO_4$ before non-depolarizing muscle relaxants. The mean onset time was 144.3 ± 12.08 seconds ($p<0.001$) in Group A, 192.66 ± 19.81 second ($p<0.001$) in Group B and 286.33 ± 34.20 seconds in Group C. The clinical duration was prolonged in $MgSO_4$ group as compared with control group. Mean value was 52.4 ± 8.97 minutes ($p<0.001$), 44.86 ± 6.59 minutes ($p<0.01$), and 34.2±8.05 minutes respectively in Group A, B and C. Pre-treatment with $MgSO_4$ before non-depolarizing muscle relaxant, accelerated speed of onset of neuromuscular block, necessary for intubation of trachea. $MgSO_4$, in the presence of non-depolarizing muscle relaxant, intensified and prolonged the neuromuscular blockade and recovery.
Conclusion: Monitoring of neuromuscular function and reduction in dose of vecuronium are required when using these two drugs in combination.
Key Words: Magnesium Sulphate ($MgSO_4$); Pre-treatment; Non-Depolarizing Muscle Relaxant

Introduction

Laryngoscopy and endotracheal intubation are associated with an increase in heart rate (HR), systemic arterial pressure (SAP), pulmonary arterial pressure (PAP) and capillary wedge pressure. Many pharmacological techniques using adrenoreceptor blockers, calcium channel blockers, opioids and vasodilators have been used to attenuate these responses, which indicate the lack of an ideal drug for this purpose.[1-3]

Magnesium sulphate inhibits catecholamine release from the adrenergic nerve terminals and from the adrenal medulla in vitro and magnesium sulphate has been used to attenuate adverse cardiovascular effects during laryngoscopy and intubation.[4-5] Magnesium sulphate is used during anaesthesia for its antihypertensive, arrhythmic properties and attenuating the response to endotracheal intubation and as an anticonvulsant for women with eclampsia.[6-8]

At the motor nerve terminal, $MgSO_4$ inhibits acetylcholine release, thus it enhances the effect of neuromuscular blocking agents.[9] It has been demonstrated that pretreatment with $MgSO_4$ increases the clinical duration and recovery index of neuromuscular blocking agents.[10-15] This may have clinical consequences, leading to incomplete neuromuscular recovery and residual paralysis at the end of surgery.[16-18] Thus quantitative data on the effect of anti-cholinesterase drugs in patients receiving $MgSO_4$ are needed for safe management of neuromuscular block. Research from the early 1950s first elucidated the nature of the effects of calcium and magnesium ions at the neuromuscular junction. By making allowance for some minor post-junctional effects of magnesium, studies of endplate potentials showed that it competed for prejunctional site with calcium ions.[19] The ions antagonized each other; high magnesium concentrations inhibited release of acetylcholine and high calcium

concentrations increased release from the presynaptic nerve terminal. These studies also showed that magnesium ions had an inhibitory effect on post-junctional potentials and caused a decrease in muscle fibre membrane excitability, although these effects were relatively minor in comparison with presynaptic inhibition of acetylcholine release. The nature of the presynaptic channel has been elucidated further in the past 20 years. The aim of the present study was to determine the effect of magnesium sulphate pre-treatment on the onset, duration and recovery of non-depolarizing muscle relaxant and to quantify the haemodynamic effects of administration of $MgSO_4$ on the arterial blood pressure.

Materials and Methods

This one year prospective randomized double blinded controlled clinical study was conducted on randomly selected 45 patients of either sex, aged between 18-55 years, grade I or II of American Society of Anesthesiologists (ASA), undergoing elective surgery at a hospital of a Medical College of eastern Uttar Pradesh, India after obtaining approval from institutional ethical committee. Patients suffering from neuromuscular/ cardiovascular/ central nervous system disorder, endocrinal anomalies, metabolic disease, and electrolyte imbalance were excluded from the study. Informed consents from all the patients were taken. A thorough preoperative clinical assessment was done in all patients soon after admission in the hospital. All the patients were divided into three groups according to dosage of $MgSO_4$ used for pretreatment.

Group-A consisted of 15 patients receiving $MgSO_4$- 60 mg/kg. Group-B consisted of 15 patients receiving $MgSO_4$- 40 mg/kg. Group-C consisted of 15 patients receiving normal saline.

All the patients were pre-medicated with tablet lorazepam 1 mg at night before the day of surgery.
All patients were pre-medicated with 0.2 mg Glycopyro1ate, 2-5mg midazolam and 50-150 µg fentanyl intravenously.

Fifteen minutes before induction of anaesthesia, patients in Group-A received $MgSO_4$ 60mg/kg in saline as an intravenous infusion over 15 minutes, patients in Group-B received $MgSO_4$ 40mg/kg in saline as an intravenous infusion over 15 minutes, and Group-C received same volume of saline without $MgSO_4$.

In all groups, anaesthesia was induced with thiopentone 5 mg/kg and fentanyl 2 µg/kg. Then, relaxograph was set to deliver supramaximal train-of-four (TOF) stimulus at 2 Hz frequency to get control twitch height. Patients in all groups received vecuronium bromide 100 µg/kg and intubation was done when maximum twitch depression occurred and anesthesia was maintained with 1% isoflurane and 60% nitrous oxide in oxygen.

After the end of surgery, when the amplitude of T1 had recovered to 10%, patients in all groups received neostigmine 0.05 mg/kg and glycopyrolate 0.02mg/kg. After neostigmin-glycopyrolate administration, T_1 was measured every minute for 10 minutes, in all groups.

Neuromuscular transmission was assessed by electromyography on the left hypothenar muscle, using trans-cutaneous electrodes. The measurement commenced after induction of anaesthesia. The relaxograph was set to deliver supramaximal train-of-four (TOF) stimuli (0.1 mg duration) at 2 Hz every 20th second. The first of the four responses was considered at twitch height (T_1); TOF ratio was noted. Patients hand was fixed carefully in a splint. Body temperature was maintained (36.0-36.5°C) constant during the study.

The following parameters were measured in all the groups:

- Arterial blood pressure
- Onset time = Time between administration of vecuronium and maximal twitch depression.
- Clinical duration of action = Time between administration of vecuronium and 25% recovery of T1
- Recovery index = Time from 25% to 75% recovery of T_1
- Clinical sign of neuromuscular recovery after reversal of neuromuscular block.

Statistical Analysis: It was done by using student's 't' test for paired data. The results were presented as mean ± S.D. and $p < 0.05$ was regarded as statistically significant.

Results

Out of 45 patients studied, 17 were males and 28 were females. The male to female ratio was found to be 1:1.64. Minimum age in the study group was 18 years and maximum age was 55 years. Number of patient was maximum (35.56%) i.e. 16 patients, in age group of 29-38 years.

Table-1: Change in mean arterial blood pressure in different groups of various stage and statistical evaluation

Time interval (in minutes)	Group-A			Group-B			Group-C		
	Mean ± S.D.	"t"	"p"	Mean ± S.D.	"t"	"p"	Mean ± S.D.	"t"	"p"
Pre-operative	94.60 ± 04.81			103.53 ± 05.21			94.26 ± 07.08		
Before induction	90.07 ± 06.01	2.279	0.05	96.86 ± 08.46	2.598	<0.05	101.66 ± 10.06	2.331	<0.05
Just after intubation	98.27 ± 11.65	1.127	>0.05	110.00 ± 11.29	2.015	>0.05	108.53 ± 09.50	4.665	<0.001
5 minutes after intubation	93.73 ± 15.68	0.205	>0.05	99.47 ± 10.70	1.314	>0.05	103.33 ± 11.05	2.667	<0.05
30 minutes after intubation	92.73 ± 06.17	0.924	>0.05	95.00 ± 08.05	3.462	<0.01	95.53 ± 10.43	0.39	>0.05
60 minutes after intubation	96.80 ± 06.49	1.055	>0.05	96.87 ± 08.47	2.593	<0.05	97.40 ± 06.35	1.28	>0.05
Before reversal	102.93 ± 10.67	2.769	<0.05	108.20 ± 08.41	1.827	>0.05	101.53 ± 10.84	2.175	<0.05
Just after extubation	109.07 ± 08.87	5.554	<0.001	113.73 ± 09.35	3.691	<0.01	107.13 ± 06.41	5.219	<0.001
5 minutes after extubation	100.73 ± 08.29	2.479	<0.05	108.53 ± 09.50	1.788	>0.05	101.33 ± 06.96	2.762	<0.05
10 minutes after extubation	96.07 ± 06.07	0.736	>0.05	106.00 ± 06.71	1.126	<0.05	96.73 ± 06.27	1.011	>0.05

Table-2: Onset time of neuromuscular block (Time between administration of vecuronium and maximum twitch depression)

Time interval (in second)	Group-A (n=15)		Group-B (n-15)		Group-C (n=15)		Total (n=45)	
	N	%	N	%	N	%	N	%
120-140	9	60.6	0	0	0	0	9	20
140-160	5	33.33	0	0	0	0	5	11.11
160-180	1	6.67	7	46.67	0	0	8	17.78
180-200	0	0	4	26.67	1	6.66	5	11.11
200-220	0	0	4	26.66	1	6.67	5	11.11
220-240	0	0	0	0	0	0	0	0
240-260	0	0	0	0	1	6.67	1	2.22
260-280	0	0	0	0	6	40	6	13.33
280-300	0	0	0	0	3	20	3	6.67
300-320	0	0	0	0	3	20	3	6.67
Total	15	100	15	100	15	100	45	100
Mean ± S.D.	144.33±112.08		192.66±119.81		286.33±134.20			
't' value	15.163		9.179					
`p' value	<0.001		<0.001					

Table-3: Showing clinical duration of neuromuscular block (time between administration of vecuronium and 25% recovery of T1 height)

Time interval (in minutes)	Group-A (n--15)		Group-B (n-15)		Group-C (n=15)		Total (n-45)	
	N	%	N	%	N	%	N	%
20-30	0	0	0	0	5	33.33	5	11.11
30-40	1	6.67	4	26.66	6	40	11	24.44
40-50	5	33.33	9	60	4	26.67	19	42.22
50-60	6	40	2	13.34	0	0	8	17.78
60-70	2	13.33	0	0	0	0	1	2.22
70-80	1	6.67	0	0	0	0	1	2.22
Total	15	100	15	100	15	100	45	100
Mean ± S.D.	52.4 ± 8.97		44.86 ± 6.59		34.2 ± 8.05			
`p' value	<0.001		<0.01					

Table-4: Recovery of T1 height (recovery was assessed when T1 reached 10%)

Time (at minute)	Recovery of Ti height during 10 minutes (Mean ± S.D.)		
	Group-A	Group-B	Group-C
0	12 ± 2	13 ± 3	16 ± 6
1st	18 ± 3**	22 ± 4	27 ± 8
2nd	26 ± 3***	30 ± 4*	36 ± 7
3rd	31 ± 5***	40 ± 5***	53 ± 9
4th	37 ± 6***	49+8***	68 ± 8
5th	44 ± 7***	58 ± 8***	78 ± 6
6th	52 ± 8***	69+9***	84 ± 6
7th	60 ± 7***	77 ± 8***	90 ± 5
8th	66 ± 7***	83 ± 6***	92 ± 4
9th	70 ± 8***	88 ± 6*	94 ± 3
10th	75 ± 8***	92 ± 6	96 ± 2

** p < 0.05; ** p < 0.01; *** p < 0.001*

Table-5: Recovery characteristic after neuromuscular block reversal (recovery index (RI) = Time from 25% to 75% recovery of T1 height)

Recovery Characteristic	Group-A	Group-B	Group-C
	Mean ± S.D.	Mean ± S.D.	Mean + S.D.
Recovery index (RI) (T4/T1=25%)(min.)	10+02.0***	06+01.0***	05+01.0
Trainee of four (TOF) at 5th minutes	45+06.0***	60±08.0***	78+06.0
Trainee of four (TOF) at 10th minutes	75±09.0***	91+06.0*	96+02.0

** p < 0.05; ** p < 0.01; *** p < 0.001*

Table-6: Clinical sign of neuromuscular recovery (head lift for 5 seconds)

Time interval	Group-A (n=15)		Group-B (n=15)		Group-C (n=15)		Total (n=45)	
(in minutes)	N	%	N	%	N	%	N	%
1 – 5	0	0	0	0	3	20	3	6.67
5 – 10	3	20	12	80	12	80	27	60
10 – 15	11	73.33	3	20	0	0	14	31.11
15 – 20	1	6.67	0	0	0	0	1	2.22
Total	15	100	15	100	15	100	45	100
Mean ± S.D.	12.13 ± 1.99		8.8 ± 1.92		6.93 ± 1.34			
`p' value	<0.001		<0.01					

Abdominal hysterectomy and cholecystectomy were the most common operations performed and each constituted 18 out of 45 cases, i.e. 17.78%, followed by iliostomy closure constituting 6 out of 45 cases, i.e. 13.33%.

Mean arterial blood pressure decreased significantly in Group-A and B and increased significantly in Group-C before induction. After intubation, blood pressure rose in all the groups but significant increase was found only in group C. After extubation, mean arterial blood pressure rose significantly in all three groups and after 10 minutes from extubation, returned to near preoperative value in all 3 groups. [Table-1]

In Group-A, maximum number of patients had onset time in between 120-140 seconds, with mean onset time 144.3 ± 12.08 seconds (p<0.001), In Group-B, maximum number of patients had onset time between 160-180 seconds, with mean onset time is 192.66 ± 19.81 second (p<0.001). In Group-C, maximum number of patient had onset time in between 260-280 seconds, with mean onset time is 286.33±34.20 seconds. [Table-2]

In Group-A and Group-B, maximum number of patients had clinical duration in between 50-60 minutes and 40-50 minutes respectively, with mean clinical duration time was 52.4 ± 8.97 minutes (p<0.001) and 44.86 ± 6.59 minutes (p<0.01) respectively. In Group-C, maximum number of patients had clinical duration time in between 30-40 minutes, with mean clinical duration time was 34.2 ± 8.05 minutes [Table-3]. Recovery of T1 during 10 minutes period after reversal of neuromuscular block was slow in pre-treated with $MgSO_4$ Group-A and B compared with control Group-C [Table-4].

Recovery of T1 during the 10 minutes period was less in patients who were pre-treated with MgSO4 compared to controls. Recovery index was 10 ± 2, 6 ± 1 and 5 ± 1 (p<0.001) in Group-A, B and C respectively [table-5]. The maximum number of patients showed the clinical sign of neuromuscular recovery between 10-15 minutes in Group-A, and 5-10 minutes in Group-B and C [Table-6].

Discussion

The present study showed that pre-treatment with $MgSO_4$ before non-depolarizing muscle relaxant resulted in the delayed recovery from neuromuscular block. Reversal of neuromuscular block was done by neostigmine and glycopyolate. This study reveals that,

- $MgSO_4$ pre-treatment before non-depolarizing muscle relaxant, accelerated speed of onset of neuromuscular block necessary for intubation of trachea,
- $MgSO_4$ in the presence of non-depolarizing muscle relaxant intensified and prolonged the nueromuscular blockade and recovery.

Magnesium sulphate is increasingly used as an adjuvant to general anesthesia, mainly for haemodynamic control and nociception modulation.[20] Two major problems may arise with the use of $MgSo_4$ in patients undergoing general anaesthesia. Firstly, $MgSO_4$ may enhance the action of non-depolarizing neuromuscular blockers by reducing end plate sensitivity and decreasing muscle fibers excitability. Secondly, Mg^{2+} may interact with calcium at vascular membranes and decrease peripheral vascular resistance.[21]

The increasing interest in therapeutic uses of $MgSO_4$ in anaesthesia and intensive care unit mandate an independent study for its neuromuscular effect and its possible interaction with non-depolarizing muscle relaxants. The pressure response (mean arterial blood pressure) to laryngoscopy, tracheal intubation and extubation was almost abolished in Group-A, followed by in Group-B, and maximum pressure response occurred in control Group-C where $MgSO_4$ was not used in our study.

Allen et al reported that magnesium sulphate obtunded the hypertensive response to intubation in patients with pre-eclampsia.[22] They reported no increase in arterial pressure for 5 minutes after intubation, in women pre-treated with $MgSO_4$ 40mg/kg or alfentanyl 10 µg/kg, but a significant increase in women pretreated with lidocaine 1.5 mg/kg. This is similar to the findings of our study,

where an insignificant increase in the arterial blood pressure after intubation, in patients pre-treated with $MgSO_4$, was observed – but, a highly significant increase was seen in the control group.

Puri et al studied the effect of $MgSO_4$ on haemodynamics and efficacy in attenuating the response to endotracheal intubation in patients with coronary artery disease, and concluded that mean arterial pressure decreased ($p<0.001$) after magnesium administration alone, compared with control group ($p<0.05$) at pre-induction stage.[3] Our findings are similar to their findings.

In the present study, we observed that recovery of T_1 was significantly slower in patients pre-treated with $MgSO_4$ compared with controls. James et al (1991) studied the priming of pancuronium with $MgSO_4$, and concluded that pre-treatment with magnesium does not usefully increase the speed of onset of action of pancuronium.[23] But in our study, the speed of onset was increased significantly after pre-treatment with $MgSO_4$ before vecuronium. One possible explanation to this is that, the effects of a bolus dose of $MgSO_4$ are diminished by the time that spontaneous recovery from the longer acting pancuronium begins to take place.

Fuchs-Buder et al (1996) concluded that pre-treatment with $MgS0_4$ before vecuronium accelerated the onset time, and prolonged the clinical duration of neuromuscular block. Our finding is also comparable with this study, as pre-treatment with $MgSO_4$ before vecuronium accelerated the onset time, and prolonged the clinical duration of neuromuscular block.[12]

Kaussman et al (1997) determined the effects of prior administration of $MgSO_4$ 60 mg/kg intravenous, on the onset and duration of rocuronium induced neuromuscular block.[14] They found that mean onset time were similar in $MgSO_4$ group (71 ± 20 seconds) and in normal saline group (75 ± 23 seconds), but times to initial, 10% and 25% recovery from neuromuscular block were significantly longer in the $MgSO_4$ group 42.1 ± 16.3, 49.0 ± 12.4 and 56.5 ± 13.2 minutes respectively, than in the saline group 25.1 ± 9.1, 33.0 ± 11.1 and 35.6 ± 13.2 minutes, respectively ($p<0.05$) in all three cases.

In our study the onset time was shorter in $MgSO_4$ group as compared to control group. This may be due to the difference in neuromuscular blocking drug used in our study. But duration of neuromuscular block was increased by pre-treatment with $MgSO_4$ in their study, which is similar to the observation of our study.

Fuchs-Buder et al (1999) investigated the dose-effect relationship of neostigmine, in antagonizing vecuronium induced neuromuscular block, with and without $MgSO_4$ pre-treatment, in 48 patients.[24] They found that neostigmine induced recovery of T_1 during the 10 minutes period, after administration of neostgmine 0.02 mg/kg and atropine 0.01 mg/kg, was less among patients pre-treated with $MgSO_4$, as compared with controls: respective value after 5 minutes were 43 ± 8% and 66 ± 6% ($p<0.01$), and after 10 minutes, 60+8% and 83±6%, respectively ($p<0.01$). TOF ratio, 5 minutes after neostigmine, was 29 ± 6% in Group-A and 29±5% in Group-B. The respective values after 10 minutes were 38 ± 11% and 51 ± 7% ($p<0.01$), and recovery index was 14 ± 4 ($p<0.001$) and 6±1. In the current study, we also observed that neostigmine induced recovery of T_1 was less in patients pre-treated with $MgSO_4$ compared with controls.

In our study, the effect of neostigmine in antagonizing $MgSO_4$ pre-treated vecuronium induced neuromuscular block was investigated during isoflurane anaesthesia. Isoflurane potentiates the action of vecuronium and stops volatile anaesthetic, induces some degree of recovery from neuromuscular block.[25] However, this is probably not relevant during pharmacologically induced reversal with neostigmine. McCourt et al demonstrated that stopping isoflurane at the time of administration of neostigmine did not shorten the recovery time after rocuronium.[26]

The result of this study demonstrated earlier onset time and longer clinical duration of atracurium induced neuromuscular block in $MgSO_4$ pre-treated group, compared to control group. These results were also in accordance with the study of Lamp et al (1993)[13], and Azer et al (2002)[27], where speed of onset of atracurium was increased markedly, when patients were pre-treated with $MgSO_4$. In our study, accelerated speed of onset, prolonged clinical duration, and delayed recovery of vecuronium induced neuromuscular block was found in patients pre-treated with $MgSO_4$ before vecuronium. Several studies have reported similar results, and proved the effect of $MgSO_4$ in prolongation of clinical duration of different neuromuscular blocking drugs.[28]

$MgSO_4$ resulted in about 29% shortening of onset time of cisatracurium (0.15 mg/kg), without prolongation on the recovery of neuromuscular block in the study by Kim et al.[29] In another study, although magnesium was able to hasten the muscle-relaxing effect of cisatracurium, in addition to providing a longer duration and increased

intensity of the neuromuscular blockade. This increase in speed to muscle relaxation was not significant enough to justify its routine use as a priming agent for cisatracurium in rapid sequence induction.[30]

The study shows that when $MgSO_4$ was used with vecuronium, the dose of vecuronium required was less for the same duration of surgery. Adequate neuromuscular blockade monitoring is mandatory in patients pre-treated with $MgSO_4$. Adjusting the dose of $MgSO_4$, to get desirable clinical response without adverse effect, is also mandatory. The dose of $MgSO_4$ used in the current study was considered safe by Tramer et al (1996).[31] Mg^{2+} is eliminated rapidly in the presence of normal renal function.[32]

Conclusion

$MgSO_4$ pre-treatment, before non-depolarizing muscle relaxant, accelerated the speed of onset of neuromuscular block necessary for intubation of the trachea. $MgSO_4$, in the presence of non-depolarising muscle relaxant, intensified and prolonged the neuromuscular blockade and recovery. So, monitoring of neuromuscular function and reduction in dose of vecuronium are required when using these two drugs in combination.

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