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Effects of Magnesium Sulphate on the Onset and Duration of Neuromuscular Blockade by Cisatracurium in Adult Patients Undergoing Transpedicular Screw Fixation Surgery Under General Anesthesia

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ABSTRACT

Background: In the past, various drugs have been used to potentiate the effects of non-depolarizing neuromuscular blocking agents. Among these agents, Magnesium Sulphate has been found to be effective and safe. In our part of the world, Cisatracurium had not been used commonly until recently when its availability has made possible its use as a long-term non-depolarizing neuromuscular blocking agent. So, we decided to use MgSo4 with cisatracurium to see its effectiveness in patients undergoing transpedicular screw fixation surgery. **Objective:** To compare the onset, duration of action and mean intraoperative consumption of Cisatracurium in adult patients undergoing Transpedicular screw fixation (TPSF) surgery under general anesthesia with and without pretreatment as well as intraoperative use of Magnesium sulphate. **Study Design:** A Randomized Controlled study. **Settings:** Department of Orthopedics & spine Centre, Ghurki Trust Teaching Hospital (GTTH), Lahore Pakistan. **Duration:** Six months from 1st June 2019 to 30th November 2019. **Methodology:** In this study, 46 patients were randomly divided into two groups by lottery method (23 in each group). In both groups, patients either received magnesium sulphate (Mgso4) 50 mg/kg in 100 ml of 0.9% Normal saline or 100 ml of only 0.9% Normal saline intravenously 20 minutes before induction of general anesthesia with Propofol, Fentanyl and Cisatracurium. After induction of general anesthesia, group M received continuous infusion of Mgso4 (20 mg/kg/hr) until the beginning of skin closure. Maintenance dose of Cisatracurium was given when first twitch was noted by Train-of-Four. Time of onset, duration of neuromuscular blockade and total intra-operative consumption of Cisatracurium were noted. Heart rate, mean arterial blood pressure and serum ionized Magnesium levels were also measured. **Results:** Time of onset was significantly shorter in the group M than group N ($P < 0.05$). Duration of neuromuscular block was significantly prolonged in group M as compared to group N ($P< 0.05$) and the total consumption of Cisatracurium during surgery was significantly lesser in group M when compared with group N ($P< 0.05$). Serum ionized Magnesium levels were significantly more in group M comparatively ($P<0.05$). There were no significant difference in heart rate and mean arterial blood pressure changes in two groups ($P>0.05$). **Conclusion:** Magnesium impairs neuromuscular transmission at blood levels that did not affect hemodynamics and significantly augments the neuromuscular blockade by Cisatracurium.

Keywords: *Cisatracurium, Magnesium sulphate, Neuromuscular blockade, Onset.*

INTRODUCTION

Among the non-depolarizing Neuromuscular Blocking Agents (NMBAs), Atracurium has been a preferred choice for many years in our institution. Cisatracurium has also been used frequently in anesthesia that facilitates endotracheal intubation and provides muscle relaxation for surgery.[1] Among many factors justifying the use of non-depolarizing NMBAs, one desire was to replace depolarizing NMBA, Succinylcholine having many undesired effects.[2] Cisatracurium releases lesser histamine than suxamethonium and causes less skin flushing, hypotension, and tachycardia.[3] Cisatracurium is a stereoisomer of atracurium having same molecular weight.[4] Cisatracurium is metabolized by hofmann

elimination independent of body temperature and pH.[5] Among the non-depolarizing NMBAs, Cisatracurium has a longer time of onset making it unsuitable for rapid sequence induction.[6] Cisatracurium is one of the commonly used muscle relaxant in general anesthesia with duration of neuromuscular blockade, hemodynamic and recovery profiles comparable with atracurium.[7] It has lesser hemodynamic effects and almost no accumulations in body even after massive usage.[8]

Since 1996, when the role of Magnesium sulphate (MgSo4) was studied in clinical anesthesia, it has gained remarkable importance in the field of anesthesiology and pain medicine.[9] It was used initially peri-operatively in the management of preeclampsia, cardiac arrhythmias, bronchial asthma and respiratory failure.[10] In recent times, it has been studied and used as an anesthetic and analgesic adjuvant in anesthesia.[11] MgSo4 is vital for a wide number of physiological processes in body. Magnesium is critical in human physiology as it blocks calcium channel channels at smooth muscle, skeletal muscle and conducting systems. Analgesic actions of MgSo4 are attributed to its antagonism for N-methyl-D-aspartate (NMDA) receptors.[12] MgSo4 significantly impairs neuromuscular transmission as well. MgSo4 attenuates the excitation of muscle fibers and decrease the end plate potential amplitude by decreasing acetylcholine release from the terminals of motor nerve fibers. Hence, it augments the neuromuscular transmission blocking by non-depolarizing neuromuscular blocking drugs.[13]

Many studies have shown that MgSo4 prolongs the duration of non-depolarizing Neuromuscular Blocking Agents (NMBAs) after induction of general anesthesia. Relatively lesser data is available regarding the use of MgSo4 prior to induction of anesthesia with Cisatracurium as well as after induction and its effects on the onset time and duration of neuromuscular blockade by Cisatracurium. SH Kim and colleagues have shown that pretreatment of MgSo4 results in 29% quickening of onset time of action of Cisatracurium 0.15mg/kg with no significant effect on duration of neuromuscular block.[10] Prior to this, AM Pinard and colleagues showed that use MgSo4 prior to induction and after induction of general anesthesia potentiated the duration of neuromuscular block by cisatracurium during cardiac surgeries.[13]

The effects of intravenous MgSo4 prior to induction (pretreatment) and after induction of anesthesia (continuous iv infusion) on the onset as well as duration of neuromuscular blockade by cisatracurium were not studied in a single setting. So, we aimed to study these effects in adult patients undergoing transpedicular screw fixation (TPSF) surgery with general anesthesia.

METHODOLOGY

Study Design: Randomized controlled trial.

Settings: Department of Orthopedics & spine Centre, Ghurki Trust Teaching Hospital (GTTH), Lahore Pakistan by a combined team of Anesthetists and Orthopedic surgeons.

Duration: Six months from June 01, 2019 to November 30, 2019.

Sample Technique: Simple random probability sampling.

Sample Size: 46 patients.

Inclusion Criteria: 18-60 years of age, consent (written and informed), Both genders, ASA scores I and II, Patients for elective transpedicular screw fixation (TPSF) with general anesthesia and TPSF surgery lasting at least 2 hours were included.

Exclusion Criteria: ASA score III and IV, neuromuscular diseases, anticipated difficult airway, patients on beta blockers, patients using medications that influence neuromuscular functions (e.g., calcium channel blockers, phenytoin, aminoglycosides), Electrolyte's abnormalities, hepatic or renal insufficiency, patients taking magnesium supplements, patients with body mass index < 19 or > 28, pregnancy, breast feeding and allergy to study drugs.

Data Collection Procedure: All adult patients (N=46) fulfilling the inclusion criteria were selected and consent was taken. Blood samples for magnesium levels were drawn from all patients about 12 hours before surgery apart from other routine investigations. Detailed pre-operative assessment of all the patients was done. They received intravenous midazolam (0.05 mg/kg) half an hour before induction of general anesthesia. Standard monitors including non-invasive Blood pressure, Pulse oximetry, ECG and End-tidal carbon dioxide were applied to the patients in operation rooms (ORs). Two IV cannulas of 20 G were secured on the same side (opposite to side selected for neuromuscular monitoring) in all patients prior to administration of study drugs. Calibration of the neuromuscular monitor was done before the administration of MgSO4 and induction of general anesthesia (GA).

As the patients were randomized by using lottery method, 46 patients allocated to one of the two groups (M&N), 23 patients in each group. 20 minutes prior to induction of GA, group M received intravenous Mgso4 50 mg/kg in 100 ml of 0.9% Normal saline through a calibrated and designated syringe pump. Group N received the same volume of only 0.9% normal saline intravenously. After transfusing MgSo4, GA was induced with intravenous propofol (1-2 mg/kg), fentanyl (2-3 µg/kg) while maintaining the airway with facemasks receiving 50 percent of oxygen in air in both groups. Electromyography on the adductor pollicis of the hand (opposite to the side of non-invasive blood pressure (NIBP) monitoring and intravenous lines) was used for assessment of neuromuscular function, using train of four with neuromuscular transmission mode. After applying antiseptics on skin, electrodes were attached to ulnar

nerve on volar side of wrist. After injecting fentanyl, it was possible to automatically determine the stimulus current for maximal response of adductor pollicis muscle in all patients. After determining the supramaximal current and induction of GA, 0.2mg/kg of Cisatracurium (bolus dose) was given in both groups. Maintenance dose of 0.02mg/kg of Cisatracurium was given when neuromuscular function returned to 25% of T1 until the start of skin closure. Timefrom bolus dose of Cisatracurium to 95% depression of T1 response (single twitch) i.e. onset time and the time from bolus dose of Cisatracurium until T1 of the train of four (TOF) had recovered to 25% of control T1 value i.e. duration of action were noted. Anesthesia was maintained by 50% of nitrous oxide in oxygen along with isoflurane at 0.6 Mac in both groups. Heart rate and mean arterial blood pressure were noted at 15 minutes interval (before and after administration of drugs under study). Serum magnesium levels were also obtained in both groups 12 hours before surgery, 2 hours after start of surgery and 24 hours post-operatively. All patients were extubated with in ORs and shifted to post-operative care unit (PACU) for monitoring. Hospital laboratory was requested to get serum Magnesium levels after 2 and 24 hours to the end of surgery. Statistical data analyzed by using SPSS 26.0. P-Value <0.05 was taken as significant.

RESULTS

Out of the 46 patients under study, there were no refusals and no patient was withdrawn from study due to adverse effects of the study drugs or any other mishap. No significant difference was noted in both groups considering age, weight, height, gender and supramaximal current. (Table 1)

Table 1: Demographical data of patients (both groups)

Gender	Group M (n=23)	Group N (n=23)	P-Value
Male	15 65.21%)	14 60.86%)	>0.05
Females	8 (34.78%)	9 (39.13%)	>0.05
Mean height (cm)	172 ± 10.16	169 ± 9.92	>0.05
Weight (kgs)	72 ± 6.36	69 ± 5.05	>0.05
Age (years)	55 ± 6.16	50 ± 7.23	>0.05
Supramaximal current (mA)	29.5± 9.4	30.2± 8.3	>0.05

Time of onset (seconds) was significantly shorter in group M (80-180) as compared to group N (101-235). Duration of neuromuscular blockade was also significantly prolonged in M group. Group M also consumed significantly less dose of cisatracurium compared to group N (Table 2)

Table 2: Pharmacodynamics of cisatracurium in both groups (mean ± SD)

Variable	Group M (n=23)	Group N (n=23)	p-value
Time to Onset (seconds)	112 ± 12.09	165 ± 10.09	P< 0.05
Time to first maintenance dose (min)i.e., duration of intubating dose of cisatracurium	86 ± 6.25	57 ± 8.15	P<0.05
Time to second maintenance dose (min)i.e., duration of 1st maintenance dose	58 ± 5.04	39 ± 3.37	P< 0.05

Serum magnesium levels were similar in two groups 6 hours before the surgery, but significantly higher in M group 2 hours after the start of surgery and 24 hours post-operatively when compared to N group. (Table 3)

Table 3: Serum Magnesium (ionized) levels in both groups (mean ± SD)

Mg (ionized) mg/dl	Group M (23)	Group N (23)	p-value
6 hours before surgery	1.73 ± 0.19	1.76 ± 0.22	0.670
2 hours after start of surgery	2.2 ± 0.24	1.76 ± 0.22	0.000
24 hours after surgery	2.3 ± 0.17	1.76 ± 0.22	0.000

Heart rate (beats/minute) and mean arterial blood pressure (mm Hg) were measured before and after induction of GA until the end of surgery and anesthesia with 15 minutes interval selected in Non-Invasive Blood Pressure (NIBP) monitor. No significant difference was noted in heart rate and mean arterial blood pressure in both groups (p-value > 0.05) For convenience, here we show the data up to 2 hours after the start of surgery (Table 4)

Table 4: Heart rate and Mean Arterial Blood Pressure in both groups at various interval

	Before GA Induction		At GA induction		15 min		30 min		45 min		60 min		75 min		90 min		120 min	
	Group N (23)	Group M (23)	N (23)	M (23)	N (23)	M (23)	N (23)	M (23)	N (23)	M (23)	N (23)	M (23)	N (23)	M (23)	N (23)	M (23)	N (23)	M (23)
MAP (mm hg)	72 ± 5.15	73 ± 4.22	73 ± 3.45	74 ± 3.12	72 ± 2.23	75 ± 4.25	74 ± 2.23	72 ± 3.45	73 ± 2.63	71 ± 4.14	73 ± 3.75	70 ± 3.60	71 ± 1.75	75± 3.05	72± 2.23	69± 3.71	70± 4.11	68± 3.73
HR (beats/min)	76± 3.75	75± 4.21	81± 3.36	79± 2.76	77± 4.45	78± 3.02	73± 2.73	74± 3.02	71± 4.12	69± 5.12	73± 2.24	72± 3.75	71± 4.04	68± 5.25	72± 3.71	73± 2.25	70± 3.15	72± 3.50

P<0.05 was considered as significant. At all the intervals mentioned in table, heart rate and mean arterial blood pressure were not significantly different in two groups under study. i.e. P >0.05

DISCUSSION

Our study has shown that administration of MgSo4 twenty minutes prior to before general anesthesia resulted in significantly (32%) quicker onset of action of Cisatracurium. We also noted that subsequent continuous intravenous infusion of MgSo4 prolongs the duration of neuromuscular blockade by Cisatracurium (duration of intubation dose, 86 ± 6.25 vs 57 ± 8.15 & duration of 1st maintenance dose, 58 ± 5.04 vs 39 ± 3.37) without any notable adverse effects on hemodynamics. Although, the serum levels of magnesium were significantly higher after MgSo4 administration (2.3 ± 0.17 vs 1.76 ± 0.22), it did not result in any harmful effects in patients that received MgSo4. It led to significantly lesser consumption of Cisatracurium (0.22 ± 0.00 vs 0.28 ± 0.02) in patients that received MgSo4, favoring its usage in surgical population that requires general anesthesia.

The dose of MgSo4 used for this study resulted in serum concentrations that maintained hemodynamic stability. The normal range of serum magnesium level is 0.76–1.15 mmol/L (1.5–2 mEq/L or 1.7–2.4 mg/dL).[14] Previously, different doses of MgSo4 have been used prior to induction as well as after induction of general anesthesia with varying results regarding its effects on the onset of action as well as prolongation of neuromuscular blockade by non- depolarizing Neuromuscular Blocking Agents (NMBAs). Kim *et al*. reported about 29% quicker onset of action of Cisatracurium when 30 mg/kg of MgSo4 was given 15 minutes before induction of general anesthesia.[10] Contrary to our study, they showed that MgSo4 did not affect the clinical duration of neuromuscular blockade by Cisatracurium. It is noteworthy that they only gave the bolus dose of MgSo4 prior to induction of GA and did not continue it in the intra-operative period, as we did in our study. Mean arterial blood pressure was significantly higher immediately after MgSo4 administration but heart rate did not show any significant change.

Pinard *et al*. reported prolongation of neuromuscular blockade by Cisatracurium by 30 to 35 minutes when MgSo4 was given at 70 mg/kg 10 minutes before induction of general anesthesia in 10 patients that underwent cardiac surgery.[13] Similar to our study, they continued MgSo4 in the intra-operative period till the beginning of sternum closure and showed that MgSo4 led to significantly lesser intra-operative consumption of Cisatracurium. They did not studied the onset of action of Cisatracurium after MgSo4 administration. Later on, Kim *et al*. and now we noticed MgSo4 effects on the onset of Cisatracurium.

We noted that MgSo4 led to significant lesser dose requirement of Cisatracurium (0.22mg/kg vs 0.28 mg/kg) in GA. Zia *et al*. also showed that MgSo4 reduces the dose of Atracurium during general anesthesia.[15] Wu *et al*. showed that prior administration of 30 mg/kg MgSo4 in 5 minutes quickened the onset speed of Atracurium and increased the duration of neuromuscular blockade by Atracurium.[16] Similar to our study, Telci *et al* reported that pretreatment with 30 mg/kg of MgSo4 followed by IV infusion at 10 mg/kg/hr significantly quickened the onset time as well duration of neuromuscular blockade by vecuronium.[17] Schulz-Stubner *et al*. reported that dose of mivacurium decreased from 0.01 to 0.008 mg/kg/min in those patients who received infusion of MgSo4.[18] Contrary to our results, a study involving MgSo4 and rocuronium, Gupta *et al*. showed that time of onset of Rocuronium was not affected by 30 mg/kg MgSo4, but similar to our study, they reported significantly prolonged duration of neuromuscular blockade by rocuronium.[19]

Previously, high doses of cisatracurium have been used in an attempt to be used for rapid sequence induction. Bluestein *et al*. used 1.5 mg/kg of cisatracurium which provided intubation conditions within about 90 seconds with onset time (mean) of 3.4 minutes, which cannot be considered as a substitute for succinylcholine.[20] In our study, using MgSo4 with cisatracurium, we recorded mean onset time of 112 seconds, which is similar to study conducted by Kim *et al*.[10] This is significantly quicker as compared to 1.5mg/kg of cisatracurium.[21]

Magnesium lowers blood pressure by vasodilatation and relaxation of smooth muscles due to antagonizing effects on calcium channel receptors and channels.[22] We used 70 mg/kg of MgSo4 20 minutes prior to induction of general anesthesia and then continued at 20 mg/kg/hr as iv infusion till skin closure and we did not note any significant changes in blood pressure and heart rate at all stages. Adding magnesium to general anesthesia arsenal will not only reduce the dose of cisatracurium significantly, it will also provide good analgesia.

CONCLUSION

We conclude that magnesium impairs neuromuscular transmission at blood levels that did not affect hemodynamics and significantly augments the neuromuscular blockade by Cisatracurium.

LIMITATIONS

In our study include the lack of variety of surgeries that may need general anesthesia. Many patients in this study did not need more than two maintenance doses of Cisatracurium, longer duration of anesthesia may be more helpful in augmenting our conclusion

SUGGESTIONS / RECOMMENDATIONS

We suggest further studies on various other surgical patients undergoing general anesthesia as well to strengthen these arguments.

CONFLICT OF INTEREST / DISCLOSURE

None.

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