ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 09 | September - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MAGNESIUM SULPHATE ATTENUATES SUCCINYL CHOLINE INDUCED FASCICULATIONS AND POST-OPERATIVE MYALGIA

Anaesthesiology

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ABSTRACT

Background: Succinyl Choline (Sch) is one of the most commonly used muscle relaxant because of its faster onset, excellent muscle relaxation suitable for intubation with rapid recovery. Complications of using Sch include muscle fasciculatons, and post-operative myalgia. A prospective randomized double-blind controlled study was designed to assess the effect of a combination of magnesium sulfate with Propofol for induction of anesthesia on Sch-induced fasciculations and myalgia. **Materials and Methods:** After approval by ASRAMS Institutional Ethics Committee, the procedures in the study were clearly explained to patients and informed written consent was obtained. The study was conducted during the period, October 2020-November 2022 at ASRAM General and Super-Specialty Hospital, Eluru, Andhra Pradesh. Patients were randomly allocated into 2 groups namely MG group and NS group. Patients in MG group received MgSO4 at a dose of 40mg/kg diluted to 10 ml with distilled water over 10 minutes, whereas, patients in NS group received 10ml of 0.9% isotonic saline in 10 minutes. This was followed by induction with Fentanyl 1.0 µg/kg and Propofol 2mg/kg in both the groups. Then Sch was administered at a dose of 1mg/kg. Patients were then observed for muscle fasciculations and post-operative myalgia and graded as none, mild, moderate and severe. **Results:** Fifteen patients had none, 8 had mild, 7 had moderate degree of fasciculations in MG group. 7 patients had mild, 20 had moderate, 3 had severe degree of fasciculations in NS group. p-value is 0.0001, which is statistically significant. None of the patients had post-operative myalgia in MG group. 7 patients had mild and 3 patients had moderate degree of post-operative myalgia in NS group. p-value is 0.002, which is statistically significant. **Conclusions:** From our study, we conclude that MgSO4 at a dose of 40mg/kg effectively reduces Sch-induced muscle fasciculations and Sch-induced post-operative myalgia.

KEYWORDS

Magnesium sulphate, Muscle fasciculation, Succinylcholine, postoperative myalgia.

INTRODUCTION

The neuromuscular transmission has fascinated the anaesthesiologist ever since the usage of curare as a muscle relaxant in anaesthesia practice. Claude Bernard(1) in his series of the effects of curare on nerve muscle preparations suggested the electrical transmission in the nerve and the presence of chemical molecule which is critical for the transfer of information between nerve and muscle. Vulpain (2) suggested the presence of a junction between terminal nerve and muscle and his suggestions were later confirmed from experimental studies. Langley (3) in 1905 explained and proved that a chemical molecule is present between nerve and the muscle to initiate a muscle contraction. Sch is still one of the most commonly used muscle relaxant in clinical practice, since its introduction by Theslaff and colleagues. Though being the fastest and short - acting muscle relaxant, it is not free of complications.

Sch induced muscle fasciculations cause hyperkalemia, increased intra-ocular pressure, increased intra-cranial pressure, increased intra-gastric pressure and myalgia. All the above mentioned complications of Sch can be avoided by blunting these fasciculations. Several drugs have been used to blunt Sch-induced muscle fasciculations. They are Rocuronium, Atracurium, Ketorolac, Lignocaine, Diazepam, MgSO4, Thiopentone, Diclofenac, small doses of Sch itself, Vecuronium, Pancuronium, and d-tubocurare. In our study, we used MgSO4 at a dose of 40mg/kg to blunt Sch-induced muscle fasciculations.

We used Propofol as an induction agent in our study because it has been shown in various studies that Propofol is a better agent than Thiopentone in reducing Sch-induced muscle fasciculations.

MATERIALS AND METHODS

After approval of our single-center study designed according to the CONSORT statement (Figure 1), by ASRAM Institutional Ethics Committee, the study was conducted during the period, October 2020-November 2022, in 60 ASA grade I or II patients undergoing elective surgeries under general anaesthesia. The age of the patients ranged from 18–60 years weighing 50-75 kg. All patients were thoroughly evaluated preoperatively. Informed written consent was obtained and the procedures were clearly explained. In the preoperative assessment room, vital parameters like pulse rate, blood pressure and baseline investigations like hemoglobin, blood sugar, urea and creatinine, CXR and ECG were checked. Thorough examination of all the systems and airway assessment was done.

Exclusion criteria included patients not fulfilling inclusion criteria, patients with systemic disorders, and patients taking analgesics. Patients were randomly allocated into 2 groups, namely MG group and NS group, by chit-picking method.

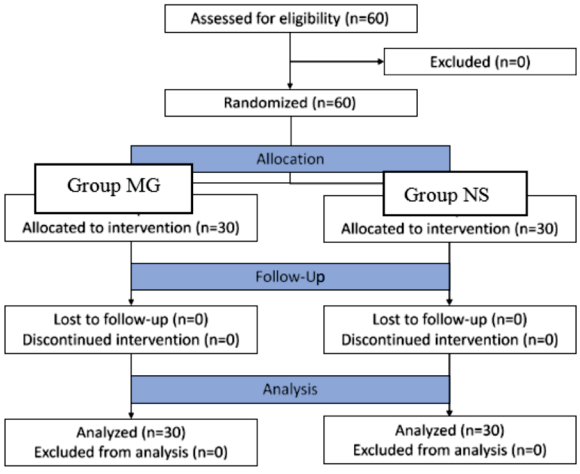

Figure 1: Consort Flow Diagram Of Randomized, Double-blind Study

The Materials And Methods Used In The 2 Groups Are Outlined Below:

- **MG GROUP:** Premedication: Inj. Glycopyrrolate 10µg/kg i.v, Inj. Midazolam 0.03mg/kg i.v, Inj. Fentanyl 1µg/kg i.v, Inj. Ondansetron 0.1mg/kg i.v; Propofol 2mg/kg i.v, Sch 1mg/kg i.v, iv MgSO4 @ 40mg/kg diluted to 10mL with distilled water over 10 minutes;
- **NS GROUP:** Premedication: Inj. Glycopyrrolate 10µg/kg i.v, Inj. Midazolam 0.03mg/kg i.v, Inj. Fentanyl 1µg/kg i.v, Inj. Ondansetron 0.1mg/kg i.v; Propofol 2mg/kg i.v, Sch 1mg/kg iv,

0.9% W/V isotonic saline of volume 10 ml over 10 minutes;
- Maintenance (in both GROUPS MG and NS): with controlled positive pressure ventilation using Oxygen and medical-grade air (50-50%), Sevoflurane (0.5-1.0%).
- Reversal (in both GROUPS MG and NS): Inj. Neostigmine 50µg/kg i.v, Inj. Glycopyrrolate 10µg/kg i.v.

Double-blinded randomization: Neither the patient or interventionist was aware of the specific materials used in procedure, and observations were recorded independently by primary investigator of the study. In the operating room, appropriate equipment for airway management and emergency drugs were kept ready. Patients were shifted to the operating room, non-invasive blood pressure monitor, pulse oximeter and ECG leads were connected, preoperative baseline systolic and diastolic blood pressure, pulse rate and oxygen saturation were recorded.

Patients in MG group received $MgSO_4$ at a dose of 40mg/kg diluted to 10 ml with distilled water over 10 minutes, whereas, patients in NS group received 10ml of 0.9% isotonic saline in 10 minutes. This was followed by induction with Fentanyl 1.0 µg/kg and Propofol 1mg/kg in both the groups. Then Sch was administered at a dose of 1mg/kg. Patients were then observed for muscle fasciculations and graded as none, mild, moderate and severe. The primary and secondary outcome measures of study are detailed below:

Primary Outcome measures: Fasciculations present or not, grading scale:
1. Nil (absent)
2. Mild (fine fasciculations of eyes, face, neck or fingers without movement of limbs)
3. Moderate (obvious muscle twitching at more than one site or movement of limbs)
4. Severe (vigorous, sustained and widespread fasciculations)

Secondary Outcome measures: Postoperative myalgia after 24 hours, grading scale.
1. Nil (absence of pain)
2. Mild (muscle stiffness or pain on specific questioning in nape of neck, shoulders and lower chest on deep breathing)
3. Moderate (muscle stiffness and pain complained by the patient spontaneously requesting analgesia)
4. Severe (incapacitating generalized muscle stiffness or pain)

Statistical Analysis

Statistical analysis was performed with SPSS version 22.0 (SPSS, Inc), and a value of $P<0.05$ was considered statistically significant. Sample size calculation was performed based on an α-value of 0.05 and power of 80%. Therefore, we chose 30 patients per group in the study. Sample size estimation with two means, wherein Null hypothesis H_o: $m_1 = m_2$ (Vs) Alternative hypothesis H_a: $m_1 = m_2 + d$, where, d is the difference between two means, and n1 and n2, are the sample sizes for Group I and Group II, such that, $N = n1 + n2$. The ratio, $r = n1/n2$; Then, the total sample size for the study is as follows:

$$N = \frac{(r+1)(Z\alpha/2 + Z1\text{-}\beta)^2 \sigma^2}{rd^2}$$

Where Z_α is the normal deviate at a level of significance (Z_α is 1.96 for 5% level of significance) and $Z_{1-\beta}$ is the normal deviate at 1-β% power with β% of type II error (0.84 at 80% power); $r = n1/n2$, is the ratio of sample size required for 2 groups; generally, it is one for keeping equal sample size for 2 groups; σ and d are the pooled standard deviation and difference of means of 2 groups;

$$Sd_{pooled} = \frac{\sqrt{SD1^2 + SD2^2}}{2}$$

X^2 test (Chi^2) was used for Qualitative analysis in non-parametric data like sex distribution, ASA grading, muscle fasciculations, post-operative myalgia and t-test (2 - sided) for Quantitative analysis in parametric data (Age & Weight distribution, heart rate and systolic BP data).

RESULTS

Patient demographics and General Characteristics-

The mean age of groups MG and NS are 39.97 and 39.47, respectively with a p-value of age distribution among NS and MG group being 0.87, which is statistically not significant. Therefore, both the groups are comparable in terms of Age. The percentage of male patients in MG group is 83.30% and in NS group is 76.7%. The percentage of female patients in MG group is 16.70% and in NS group is 23.3%, p-value is 0.52, which is statistically insignificant. Hence, both the groups are comparable in terms of sex. The mean weight of patients in MG group is 62.30 and the mean weight of patients in NS group is 66.65. The p-value for weight distribution statistics is 1.00 which is statistically insignificant. Hence, both the groups are comparable in terms of weight.

Twenty two patients in MG group and 20 patients in NS group belong to ASA I. Eight patients in MG group and 10 patients in NS group belong to ASA II. p-value is 0.57 which is statistically not significant. Both the groups are comparable in terms of ASA status.

Table 1: Distribution Data Of Fasciculations In MG And NS Groups, According To Severity Grade.

Fasciculations	MG Group		NS Group	
	N	%	N	%
None	15	50.00	0	0
Mild	8	26.70	7	23.30
Moderate	7	23.30	20	66.70
Severe	0	0	3	10.00
Chi square Value *	24.33			
Df	3			
Significance	0.0001 (Significant)			

In our study results (Table 1), 15 patients had none, 8 had mild, 7 had moderate degree of fasciculations in MG group. 7 patients had mild, 20 had moderate, 3 had severe degree of fasciculations in NS group. p-value is 0.0001, which is statistically significant.

Table 2: Distribution Data Of Post-operative Myalgia At 24 Hours, In MG And NS Groups, According To Severity Grade.

Post-Operative Myalgia	MG Group		NS Group	
	N	%	N	%
None	30	100.00	20	66.70
Mild	0	0	07	23.30
Moderate	0	0	03	10.00
Chi square Value *	12.00			
Df	2			
Significant	0.002 (Significant)			

None of the patients in our study (Table 2), had post-operative myalgia in MG group. 7 patients had mild and 3 patients had moderate degree of post-operative myalgia in NS group. p-value is 0.002, which is statistically significant.

Table 3: Peri-operative Hemodynamics (Heart Rate) In MG And NS Groups.

Heart Rate	MG Group Mean ± SD	NS Group Mean ± SD	t-value	p-Value df=58
Base Line	86.90 ± 8.92	89.57 ± 11.70	0.99	0.33*
Before Induction	79.97 ± 8.68	87.67 ± 09.24	3.33	0.002
Post Induction	90.73 ± 7.88	97.43 ± 10.22	2.84	0.01
Post Intubation 1 Minute	100.33 ± 8.47	106.50 ± 11.14	2.41	0.02
Post Intubation 3 Minutes	90.73 ± 7.43	95.90 ± 09.52	2.34	0.02
Post Intubation 5 Minutes	85.30 ± 6.64	87.37 ± 07.52	1.13	0.26*

In our study, heart rate was measured at baseline, after giving $MgSO_4$ before induction, post induction, post intubation at 1st, 3rd and 5th minute (Table 3). Calculated p-values are 0.33, 0.002, 0.01, 0.02, 0.02, 0.26, respectively. Heart rate variation is statistically significant among the two groups during before induction, post induction, post intubation at 1st and 3rd minute.

Table 4: Peri-operative Hemodynamics (systolic Blood Pressures) In MG And NS Groups.

Blood Pressure	MG Group Mean ± SD	NS Group Mean ± SD	t-value	p-value df=58
Base Line	125.37 ± 8.48	126.83 ± 08.90	0.65	0.52*
Before Induction	121.00 ± 6.87	122.77 ± 06.93	0.99	0.33*

Post Induction	105.10 ± 7.88	103.57 ± 06.37	0.83	0.41*
Post Intubation 1 Minute	113.50 ± 9.41	119.10 ± 20.42	1.36	0.18*
Post Intubation 3 Minutes	112.93 ± 9.08	113.60 ± 09.43	0.28	0.78*
Post Intubation 5 Minutes	107.73 ± 5.91	107.73 ± 5.91	0.01	1.00*

Systolic blood pressure measurements at baseline, after giving $MgSO_4$ before induction, post induction, post intubation at 1st, 3rd and 5th minute are seen in Table 4. Calculated p-values are 0.52, 0.33, 0.41, 0.18, 0.78, 1.00, respectively. All the values are statistically not significant.

DISCUSSION

Sch is one of the most commonly used muscle relaxants in clinical practice. However, use of Sch causes complications namely muscle fasciculations, post-operative myalgia, hyperkalemia, increased intraocular pressure and increased intracranial pressure. In our study, we used MgSO4 to attenuate Sch-induced muscle fasciculations and post-operative myalgia.

Results from our study show that there is significant reduction of heart rate in MG group before induction, post induction, post-intubation at 1st and 3rd minute. Moreover, 50% of patients in MG group had no fasciculations, whereas, in NS group incidence of fasciculation was 100%.

All of the patients in MG group had no post-operative myalgia, whereas, 33.30% patients in NS group had post-operative myalgia.

Table 5: Comparison Of Our Study Results With Other Studies Having Similar Experimental Objectives.

Study (no of enrolled subjects=N)	Intervention group	Control group	Fasciculations +ve (Intervention Vs Control)	Post-operative myalgia +ve (Intervention Vs Control)
MF Hussain et al4 (2019); N=40+40	Lignocaine, 1.5mg/kg	Normal Saline	----------	20% Vs 70%
Kousar5 et al (2021); N=35+35	MgSO4,40 mg/kg	Normal Saline	52% Vs 100%	52 Vs 100%
Kumar6 et al (2012); N=30+30	MgSO4, 40mg/kg	Normal Saline	50% Vs 100%	0% Vs 30%
Mathur7 et al (2016); N=45+45	MgSO4, 6mg/kg	Normal Saline	7% Vs 100%	----------
Kothari8 et al (2022); N=50+50	Rocuroniu m 60µg/kg Vs Vecuronium 10µg/kg	---------- ---	26% Vs 64%	6% Vs 14%
Geetha9 et al (2020); N=30+30	MgSO4, 40mg/kg	Normal Saline	36% Vs 100%	7% Vs 40%
Our Study; N=30+30	MgSO4, 40mg/kg	Normal Saline	50% Vs 100%	0% Vs 33%

In a randomized controlled double-blind study conducted by Hussain et al (4) in 2019, 80 voluntarily consenting patients with ASA Class I and II, aged 20-50 years, were recruited for general anesthesia with oro-tracheal intubation and patients were divided into two groups of 40 each, one group received Lignocaine 1.5mg/kg (Intervention group) and another group Normal Saline (Control group). In the Lignocaine group, 20% of the patients had post-operative myalgia compared to 70% in the Normal Saline group. The baseline values of systolic, diastolic blood pressures and heart rate are comparable in both groups.

Kousar et al (5) in 2021 conducted a study on 70 patients who were intubated with Sch. The patients were randomly divided into two groups: Group A received MgSO4 at 40mg/kg and Group B received 0.9% normal saline. In group-A, 48.6% cases had no fasciculations while in Group-B all cases had moderate fasciculations ($p<0.001$, significant). In group-A, 48.6% of patients did not develop myalgia, 51.4% had mild myalgia, while in Group-B, 20% and 80% of cases had mild and moderate myalgia ($p<0.001$). The study concluded that the use of MgSO4 at 40mg/kg before induction of anesthesia significantly reduces the incidence and severity of fasciculations and myalgias and decreases hospital stay.

Kumar et al (6) conducted a study in 2012, on 60 patients with comparable demographic data. All patients remained hemodynamically stable and none of them had prolonged neuromuscular blockade. There was no statistically significant difference between two groups for their heart rate and systolic blood pressure at any point of time ($p>0.05$). The overall incidence of muscle fasciculations was 50% in MgSO4 group compared to 100% of patients in normal saline group with a statistically significant difference between two groups ($p<0.001$). In MgSO4 group, 23.3% and 26.7% patients developed mild and moderate fasciculations, respectively. Observations of normal saline group revealed mild, moderate and severe fasciculations in 33.3%, 60%, and 6.7% patients, respectively. Additionally, none of the patients in MgSO4 group had post-operative myalgia compared to 30% of patients in the normal saline group after 24 hours (p-value<0.002).

Mathur et al (7) in 2016 conducted a study with 45 patients each in MgSO4 and Control (Normal Saline) groups with similar baseline characteristics. After experimental intervention, fasciculations were observed in 6.6% and 99.8% of cases and controls, respectively. Fasciculation grade in the intervention group was significantly lower than that in the control group ($p<0.001$). They concluded that MgSO4 can prevent and reduce the degree of fasciculations after Sch administration.

A study by Kothari et al (8) was conducted in 2022, to determine the effect of pretreatment with Rocuronium Vs Vecuronium on Sch-induced fasciculations and post-operative myalgia. The group found that fasciculations were absent in 74% of patients in the Rocuronium group as compared to 36% in the Vecuronium group ($p=0.001$), whereas fine fasciculations (grade I) were observed in 24% of patients in the Rocuronium group as compared to 50% in Vecuronium ($p=0.007$). Only 2% of the patients had moderate fasciculations (Grade II) in Rocuronium group as compared to 14% in Vecuronium group ($p=0.028$). None of the patients had vigorous fasciculations (grade III) in any group. They also found that on the 1st post-operative day, 94% and 86% of patients did not have any myalgia in Rocuronium group and Vecuronium groups, respectively. They concluded that Rocuronium and Vecuronium both are effective in attenuation of post-Sch fasciculations and post-operative myalgia, but Rocuronium is more effective as compared to Vecuronium.

In a prospective, randomized, double-blinded Case-Control Study, Geetha (9) et al in 2020, measured heart rate changes in Sch-treated patients, pre-treated with MgSO4 and normal saline. They observed that heart rate changes due to sympathetic over-activity were suppressed in MgSO4 group. Futhermore, 94% of patients had no post-operative myalgia in MgSO4 group in comparison to 60% of patients in control group (p-value=0.002), which is statistically significant.

Finally, from our prospective, randomized, double-blinded study which evaluated the effect of MgSO4 in attenuating Sch-induced muscle fasciculations and post-operative myalgia, we found that: The demographic profiles like Age, Sex, weight, ASA- PS status are comparable in both the groups. There was 50% reduction in the incidence of muscle fasciculations in the group pretreated with $MgSO_4$, whereas, the incidence of fasciculations was 100% in the control group. The incidence of post-operative Sch-induced myalgia was 0% in group pretreated with MgSO4, whereas, there was 33.30% incidence of post-operative myalgia in control group. Heart rate variations due to sympathetic overactivity was significantly suppressed in MgSO4 group compared to Control group, whereas no such difference was observed in systolic blood pressures between the two groups.

CONCLUSION

From our study, we conclude that $MgSO_4$ at a dose of 40mg/kg effectively reduces Sch-induced muscle fasciculations and Sch-induced post-operative myalgia.

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