Influence of magnesium sulfate on the pharmacodynamic characteristics of rocuronium. A randomized clinical trial

Guilherme Benette[1,2], Angelica Braga[2], Carla Ribeiro[2], Ana Paula Fernandez[2], Vanessa Henriques Carvalho[2]

[1]University of Campinas, Campinas, Brazil
[2]Department of Anesthesiology, State University of Campinas (Unicamp), Campinas, Brazil

Abstract

Background: As a multimodal anesthesia adjuvant, magnesium sulfate ($MgSO_4$) plays an important role in the anesthetic arsenal, due to its properties and substantial synergistic effects with other drugs such as opioids, hypnotics and neuromuscular blocking drugs (NMBD). Rocuronium is a non-depolarizing NMBD used widely in general anesthesia, and its association with $MgSO_4$ is still a concern. This study aimed to evaluate the influence of $MgSO_4$ at a dose of 30 mg kg^{-1} on the pharmacodynamic characteristics of rocuronium.

Methods: It was a double-blinded, randomized controlled trial in adult female patients scheduled for open hysterectomies with total intravenous anesthesia. Patients were allocated randomly to receive $MgSO_4$ (30 mg kg^{-1}) diluted in 100 mL of saline, 10 minutes before induction, or 100 mL of saline. Primary outcome: Influence of $MgSO_4$ on latency (onset time), clinical duration (CD25%) and time to recover 90% of T4/T1 – train of four (TOF = 0.9). In total, 70 patients were enrolled, 35 per group.

Results: The baseline characteristics were similar. A comparative analysis showed a significant difference between the groups regarding latency in seconds (lower with $MgSO_4$) 40.00 (35–45 [30–68]) compared to saline 53.00 (50–60 [40–90]) ($P < 0.001$), CD25% in minutes (longer with $MgSO_4$) 61.00 (53–70 [30–110]), saline 38.00 (35–48 [30–87] ($P < 0.001$), and TOF = 0.9 in minutes, longer with $MgSO_4$ 98.00 (88–111 [53–176]), saline 60.00 (55–78 [44–130]) ($P < 0.001$). $MgSO_4$ was found to reduce opioid consumption in the postanesthetic care unit.

Conclusions: The strong impact of $MgSO_4$ on the pharmacodynamics of rocuronium confirms the indispensable role of quantitative neuromuscular blockade monitoring to guide reversal.

Key words: magnesium, anesthesia, rocuronium.

CORRESPONDING AUTHOR:

Vanessa Henriques Carvalho, Departamento de Anestesiologia, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (Unicamp), Campinas, Brasil (2018), Brazil, e-mail: vanessahcarvalho74@gmail.com

In the era of multimodal anesthesia, magnesium sulfate ($MgSO_4$) has proven to be an important adjuvant in the anesthetic arsenal due to its properties and substantial synergistic effects with other drugs commonly used in anesthetic practice, highlighting its effect on NMDA (*N*-methyl-*D*-aspartate) receptors, contributing to analgesia, reducing arousal and preventing chronic pain when used at high doses in intravenous infusion [1, 2].

Because of these properties, it has an important role in reducing the consumption of some anesthetics, such as opioids, in the intraoperative and postoperative period, and consequently avoiding their adverse effects, such as nausea, vomiting, respiratory depression, hyperalgesia, and possibly significant changes in the immune system [1, 2].

However, due to its effects on the neuromuscular junction, there are reports of dose-dependent residual neuromuscular block when combined with neuromuscular blockers intraoperatively and immediately after general anesthesia [3–5]. High plasma concentrations of magnesium inhibit the release of acetylcholine from the presynaptic nerve terminal and potentiate the effect of neuromuscular blocking agents (NMBs) [4, 5]. Nevertheless, there are limited data on the usual dose of rocuronium, safety concerns, and pharmacodynamic properties when combined with a single dose of $MgSO_4$ for general anesthesia as an adjuvant to multimodal anesthesia.

This study aims to evaluate the influence of $MgSO_4$ at a dose of 30 mg kg^{-1} as a single injection on the pharmacodynamic characteristics of rocuronium

in patients undergoing total intravenous general anesthesia.

Primary outcome: Influence of $MgSO_4$ on latency (onset time) measured as the time in seconds from the start of injection of rocuronium until 95% depression of the first twitch (T1) of the TOF [6]; clinical duration (CD25%) – the time in minutes (min) from the start of injection of rocuronium until T1 of the TOF had recovered to 25% of the final T1 value; and recovery time of 90% of T4/T1 – train of four (TOF = 0.9) [6].

Secondary outcomes: Clinical conditions of tracheal intubation [7]; hemodynamic repercussions of laryngoscopy and tracheal intubation maneuvers, assessed at different time points: control – before intervention; M1 – pre-induction; M2 – post-induction and pre-tracheal intubation (TI); and M3 – one minute post-TI. Consumption of propofol and remifentanil intraoperatively; duration of surgery, duration of anesthesia, time to recovery of consciousness, consumption of opioids during hospitalization in the post-anesthetic care unit (PACU); length of stay (LOS) in the PACU.

METHODS

This randomized study was conducted in a tertiary hospital in Campinas, Brazil. The study protocol was approved by the local Research Ethics Committees (Campinas – SP, Brazil Ref: CAAE 50852714.7.0000.5404) and registered in the Brazilian Registry of Clinical Trials (ReBEC-U1111-1253-2766, RBR-79j38k).

The present study is a prospective, randomized-controlled, parallel, two-arm, double-blind clinical trial, following the CONSORT (Consolidated Standards of Reporting Trials) specifications. After obtaining written informed consent, 70 female patients, ASA (American Society of Anesthesiologists) physical status 1 and 2, undergoing abdominal gynecological surgery (open hysterectomies) under general anesthesia, were included in the study. The inclusion criteria were: patients with ASA physical status 1 and 2, undergoing general anesthesia using NMBs. Non-inclusion criteria were: neuromuscular, hepatic or renal diseases, hydroelectrolytic or acid-base disorders, difficult airway (Mallampati III and IV), gastroesophageal reflux, peripheral temperature lower than 32ºC and BMI > 35 or < 18.5 kg m^{-2}.

Study protocol

Following the strategy of simple randomization (1 : 1) and respecting the confidentiality of allocation, the research subjects were distributed into two groups, using sealed brown envelopes, according to whether or not they would use $MgSO_4$ (30 mg kg^{-1}),

based on a computer-generated list of random numbers: Group 1 ($MgSO_4$) and Group 2 (saline).

All anesthetic procedures were performed by one of the two anesthesiologists participating in the study (C.J.R. and A.F.A.B.) and data was collected by the principal investigators (V.H.C. and G.B.). Members of the research team who were in the operating room (OR) were unaware of the randomization of the group, as well as of the intervention, since both disposables were identical and had been previously prepared by (A.P.C.F.) outside the OR.

On admission to the operating room, venous access was made with an 18G intravenous cannula to administer fluids and drugs. In the operating room, they were continuously monitored with a cardio monitor, pulse oximeter, non-invasive blood pressure monitor, capnograph, bispectral index, thermometer and neuromuscular junction monitor (TOF-GUARD). The subjects were fasting, and the pre-anesthetic medication was midazolam at a dose of 1 to 3 mg intravenously 5 min before entering the operating room. Group 1 was given $MgSO_4$ (30 mg kg^{-1}) at a maximum dose of 2 g, diluted in 100 mL of 0.9% saline 10 min before induction of anesthesia and Group 2 was given 100 mL of 0.9% saline without $MgSO_4$. This $MgSO_4$ infusion 10 min before induction can be justified by the fact that the effect of the magnesium ion on the neuromuscular end-plate is both concentration- and time-dependent. A bolus injection cannot reach the motor nerve terminal in a concentration that could interfere with rocuronium. Also, an *in vitro* study showed that 4 to 6 min were necessary to establish a new frequency of miniature end-plate potentials after administration of increasing magnesium concentrations [6].

The general anesthesia technique used was the same in both groups. During induction of anesthesia, sufentanil (0.3 µg kg^{-1}), propofol (1.5 to 2.5 mg kg^{-1}) and rocuronium (0.6 mg kg^{-1}) were injected over 5 seconds. Patients were ventilated under a mask with 100% oxygen until a 75% reduction in the amplitude of the evoked muscle response to isolated stimulation was achieved, at which point laryngoscopy and tracheal intubation maneuvers were performed and assessed. Anesthesia was maintained with continuous infusions of propofol and remifentanil in controlled target pumps and a mixture of O_2 and air (50%). Ventilatory parameters were adjusted to maintain expired CO_2 (PETCO$_2$) between 30 and 33 mmHg. The skin temperature over the thenar region was monitored continuously and kept between 30 and 32ºC.

To assess neuromuscular transmission and the pharmacodynamic characteristics of rocuronium, a TOF-Guard monitor (Organon, Swords Co., Dublin, Ireland) was used. The surface electrodes were

installed in the path of the ulnar nerve, at wrist level on the side contralateral to the patient's motor dominance, and the acceleration transducer (piezoelectric) was attached to the distal phalanx of the thumb of the limb under study. The "control" muscle response was obtained through isolated supramaximal stimuli (1 Hz) for 3 min after induction of anesthesia. After the administration of rocuronium, neuromuscular function was monitored continuously with a sequence of 4 TOF stimuli until the neuromuscular variables were fully assessed. T4 : T1 = 0.9 (90%).

The procedures for setting up, calibrating and stabilizing the neuromuscular monitoring followed Good Clinical Research Practice in pharmacodynamic studies of NMB agents [8].

Data collection

Patients were identified by numbers, and data was collected in the operating room of the Hospital Prof. Dr. José Aristodemo Pinotti – CAISM – UNICAMP. The data were collected by one of the researchers inside the operating room, where there was another anesthesiologist responsible for patient care, and later in the PACU.

Data processing

The information contained in the forms was typed up and stored in a database. The distribution frequencies and the medians of the control variables in both groups were analyzed to check their comparability. The dependent variables were then statistically analyzed.

Statistical analysis

To calculate the sample size, we used the data obtained by Czarnetzki *et al*. [6] regarding the effects of $MgSO_4$ on the clinical duration of rocuronium. In the absence of $MgSO_4$, the clinical duration was 33.2 ± 8.1 min versus 44.7 ± 14 min in subjects exposed to $MgSO_4$. To detect a 50% difference in the increase in clinical duration (44.7 – 33.2/2 = 5.75), with a significance level of 5% (α error) and a power of 80% (β), the number of subjects needed in each group was 31. Thus, 70 patients were included in the study (margin of approximately 10%), distributed into two groups according to whether or not $MgSO_4$ was used.

The χ^2 or Fisher's exact test was used to analyze and compare categorical variables between the two groups. The Mann-Whitney test was used to compare numerical variables, due to the lack of normal distribution of the variables. The data are presented as mean, SD, minimum, median, maximum and quartiles 1 and 3.

The significance level adopted for the statistical tests was 5% ($P < 0.05$), with a statistical power of 80%. For the statistical analysis, the following computer program was used: SAS for Windows (Statistical Analysis System), version 9.2. SAS Institute Inc, 2002-2008, Cary, NC, USA.

RESULTS

All 70 patients were enrolled and randomized between August 2020 and October 2021. All of them were analyzed according to the protocol. No patients were lost to follow-up.

The $MgSO_4$ and saline control groups were well compared for baseline characteristics (Table 1).

A comparative analysis showed a statistically significant difference between the groups regarding latency (lower in the $MgSO_4$ group, 40.00 (35–45 [30–68]) compared to saline, 53.00 (50–60 [40–90]) ($P < 0.001$), CD25% (higher in $MgSO_4$, 61.00, compared to saline, 38.00 (35–48 [30–87]) ($P < 0.001$), and TOF = 0.9 longer in the $MgSO_4$ group, 98.00 (88–111 [53–176]) compared to saline, 60.00 (55–78 [44–130]) ($P < 0.001$) (Table 2).

Figures 1 and 2 (boxplots) illustrate the analysis of the values observed for these variables.

TABLE 1. Characteristics and pre-operative data of patients receiving magnesium sulfate ($MgSO_4$) or saline. Values are median (IQR [range]) or number (proportion)

	MgSO$_4$ ($n = 35$)	Saline ($n = 35$)
Age (years)	43 (42–48 [23–54])	46 (43–52 [32–64])
Body mass (kg)	70 (62–77 [55–108])	66 (62–72 [51–97])
BMI (kg m^{-2})	7.69 (23.44–29.32 [22.38–34.87])	26.99 (23.73–29.86 [19.95–34.55])
ASA I, *n* (%)	221 (30%)	36 (51.4%)
ASA II, *n* (%)	49 (70%)	34 (48.5%)
Tracheal intubation conditions – satisfactory, *n* (%)		
Yes	35 (100%)	34 (97.14%)
No	0 (0%)	1 (2.86%)

Age, body mass, BMI (body mass index): Mann-Whitney test.
ASA (American Society of Anesthesiologists): χ^2 test = 0.07; GL = 1; $P = 0.794$
Tracheal intubation conditions: Fisher exact test: $P = 1.000$

TABLE 2. Influence of magnesium sulfate (MgSO₄) in the pharmacodynamic characteristics of rocuronium. Values are median (IQR [range])

	MgSO$_4$ (n = 35)	Saline (n = 35)	P-value*
Latency (s)	40.00 (35–45 [30–68])	53.00 (50–60 [40–90])	< 0.001
CD25% (min)	61.00 (53–70 [30–110])	38.00 (35–48 [30–87])	< 0.001
TOF = 0.9% (min)	98.00 (88–111 [53–176])	60.00 (55–78 [44–130])	< 0.001

*Mann-Whitney test

Enrollment

Assessed for eligibility (n = 70)

Excluded (n = 0)
- Not meeting inclusion criteria (n = 0)
- Declined to participate (n = 0)
- Other reasons (n = 0)

Randomized (n = 70)

Allocation

Allocated to intervention (n = 35)
- Received allocated intervention (n = 35)
- Did not receive allocated intervention (n = 0)

Allocated to intervention (n = 35)
- Received allocated intervention (n = 35)
- Did not receive allocated intervention (n = 0)

Follow-up

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

Analysis

Analysed (n = 35)
- Excluded from analysis (n = 0)

Analysed (n = 35)
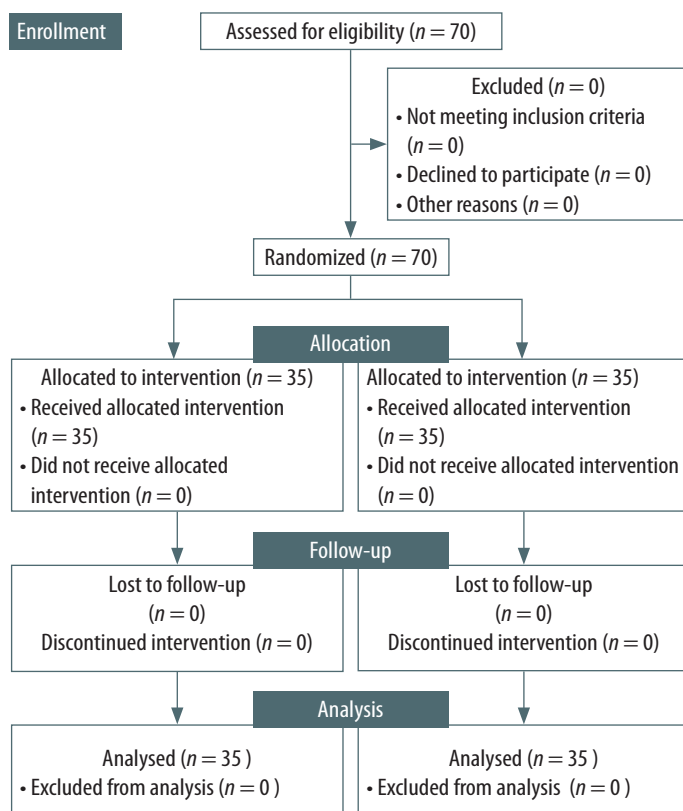- Excluded from analysis (n = 0)

FIGURE 1. Consort flow diagram

There was no significant difference between the groups in the distribution of patients in terms of physical status (ASA) ($P = 0.79$), or in terms of satisfaction with tracheal intubation (TI) ($P = 1.00$), as well as the hemodynamic repercussions of laryngoscopy and TI, shown by heart rate, 75 (69–78 [58–104]) in the MgSO$_4$ group compared to the saline group 78 (71–84 [47–105]), $P = 0.095$, and mean arterial pressure, 77.33 (65.67–80.67 [43.67–91.67]) in the MgSO$_4$ group compared to saline, 79.33 (67.67–88.00 [44.33–108.00]), $P = 0.28$, at M3.

Surgical duration in minutes in MgSO$_4$ group: 118.00 (90–150 [70–252]) compared to saline: 113.00 (85–130 [25–250]), $P = 0.306$; duration of anesthesia in minutes: 155.00 (135–190 [109–290]) in MgSO$_4$ compared to saline, 150.00 (130–165 [50–269]), $P = 0.190$. Also, intraoperative propofol consumption (mg kg^{-1} min^{-1}): 0.10 (0.09–0.11 [0.04–0.36]) in the MgSO$_4$ group compared to saline, 0.10 (0.08–0.11 [0.03–0.14]), $P = 0.30$, and intraoperative remifentanil consumption in the MgSO$_4$ group:

0.08 (0.06–0.12 [0.01–0.36]) compared to saline, 0.10 (0.08–0.12 [0.03–0.18]), $P = 0.07$, showed no difference between the groups. There was also no difference between the groups concerning length of stay in the PACU, 155.00 (120–186 [95–420]) in MgSO$_4$ and 130.00 (101–200 [60–317]) in saline, $P = 0.125$.

There was a statistically significant difference between the groups in the time taken to recover consciousness (awake time in minutes – eyes opening spontaneously and confirming name and place), which was prolonged with MgSO$_4$, 15.00 (10–21 [5–35]), compared to saline, 13.00 (9–15 [1–45]), $P = 0.014$, and opioid consumption in the PACU, measured by morphine equivalents, which was lower in the MgSO$_4$ group 0.00 (0–0.66 [0–1.33]) compared to saline, 0.33 (0–1.00 [0–1.33]), $P = 0.03$ (Table 3).

DISCUSSION

The evidence from this randomized controlled study provides a substantial understanding of the synergy between MgSO$_4$, in the dosage of anesthetic adjuvant (30 mg kg^{-1}), and the usual clinical dosage of rocuronium (0.6 mg kg^{-1}). A significant interaction was observed between these substances, which could significantly influence clinical practice. It demonstrated that MgSO$_4$ alters the pharmacological properties of rocuronium, resulting in a statistically significant reduction in latency (onset of action), a statistically significant prolongation of its clinical duration (CD25%) and a statistically significant increase in the time taken to re-establish neuromuscular transmission (TOF = 0.9%). Some authors have only observed a reduction in the latency of rocuronium with a dosage of 0.3 mg kg^{-1} and 0.6 mg kg^{-1} when combined with 60 mg kg^{-1} of MgSO$_4$ [3]. Such findings highlight the potential of MgSO$_4$ as an effective anesthetic adjuvant, capable of optimizing the conduction of anesthesia, not only the onset time of rocuronium. In times of shortage of medications such as neuromuscular blocking drugs (NMBD), in COVID-19, MgSO$_4$ was found to be a good alternative as an anesthetic adjuvant, reducing the need for higher NMBD doses [4]. However, it must be taken into consideration that the safety margin of neuromuscular transmission may be altered due to the increase
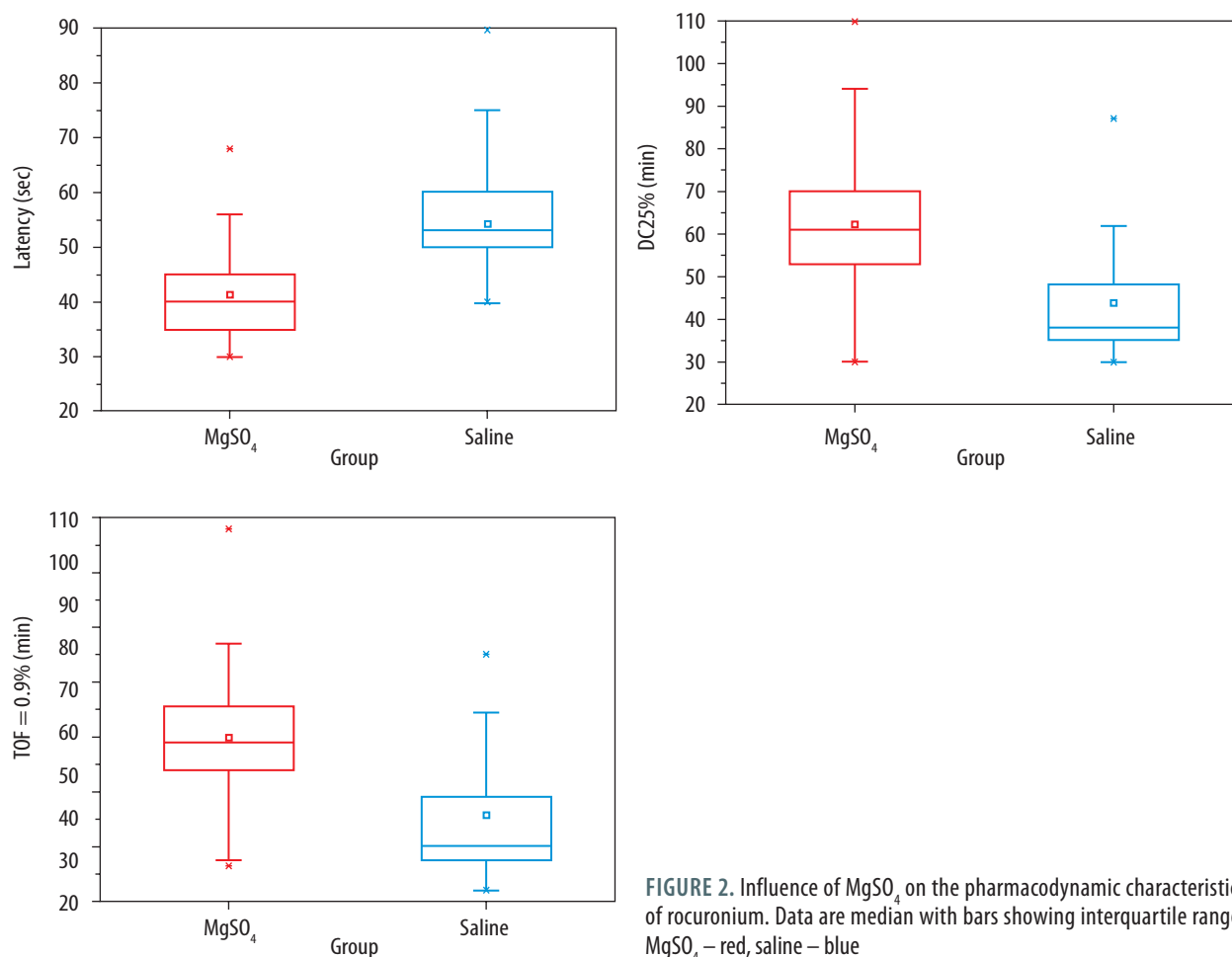
FIGURE 2. Influence of MgSO$_4$ on the pharmacodynamic characteristics of rocuronium. Data are median with bars showing interquartile range. MgSO$_4$ – red, saline – blue

in the time required for its restoration, which may cause residual neuromuscular blockade. Because of this, it is essential to monitor neuromuscular blockade, recommended for all patients undergoing general anesthesia using NMBD [9, 10], especially when MgSO$_4$ is associated with the anesthetic technique. Quantitative monitoring (documentation of TOF ratio ≥ 0.90) is the only method of ensuring that satisfactory neuromuscular function recovery has occurred. Furthermore, adequate monitoring allows for the correct reversal of neuromuscular blockade and the reduction of the inherent risks of residual muscular block, even with the use of sugammadex [11, 12], the direct reversal of rocuronium, since it is of utmost importance to know the degree of neuromuscular block for performing the correct reversal. In 2023, Germano-Filho et al. [13] evidenced that 60 mg kg^{-1} of MgSO$_4$ could decrease the TOF ratio after deep and moderate blocks previously reversed by sugammadex. According to our results, MgSO$_4$ can impair neuromuscular transmission and reduce its safety margin. Sun et al. [14] in a meta-analysis of eleven randomized controlled trials demonstrated that adding MgSO$_4$ as an adjuvant in general anaesthesia altered the pharmacodynamic parameters

TABLE 3. Intra-operative and postoperative data in patients receiving MgSO$_4$ or saline. Values are median (IQR [range]). Mann-Whitney test

Factor	MgSO$_4$ ($n = 35$)	Saline ($n = 35$)	P-value
Intra-operative propofol consumption (mg kg^{-1} min^{-1})	0.10 (0.09−0.11 [0.04−0.36])	0.10 (0.08−0.11 [0.03−0.14])	0.30
Intra-operative remifentanil (µg kg^{-1} min^{-1})	0.08 (0.06−0.12 [0.01−0.36])	0.10 (0.08−0.12 [0.03−0.18])	0.07
Duration of anaesthesia (min)	155.00 (135−190 [109−290])	150.00 (130−165 [50−269])	0.19
Duration of surgery (min)	118.00 (90−150 [70−252])	113.00 (85−130 [25−250])	0.30
Awake time (min)	15.00 (10−21 [5−35])	13.00 (9−15 [1−45])	0.01
PACU − LOS (min)	155.00 (120−186 [95−420])	130.00 (101−200 [60−317])	0.12
Morphine (equivalents) consumption in PACU	0.00(0−0.66 [0−1.33])	0.33 (0−1.00 [0−1.33])	0.03

PACU — post-anesthetic care unit, LOS — length of stay

of rocuronium. It significantly shortened the onset time and prolonged the clinical duration, as well as the recovery time of neuromuscular blockade. Various mechanisms by which $MgSO_4$ can interfere with neuromuscular blockade have been described. Magnesium lowers acetylcholine release due to the inhibition of calcium-dependent channels, reduces the sensitivity to acetylcholine in the motor plate, and directly attenuates muscle fiber excitability [5].

Furthermore, the analysis of hemodynamic repercussions revealed an equivalence between the groups studied, indicating that the use of 30 mg kg^{-1} of $MgSO_4$ did not cause abrupt effects on cardiovascular parameters during the perioperative period, as already stated by other studies [1]. Conditions during laryngoscopy and tracheal intubation were comparable in both groups, with a predominance of satisfactory conditions in the $MgSO_4$ group, reinforcing the safety and effectiveness of using $MgSO_4$ in this context [3, 14].

A relevant finding was the statistically significant result that awakening time was prolonged in the group that received $MgSO_4$ compared to the control group. This result suggests a direct influence of $MgSO_4$ on anesthetic depth with possible synergism with hypnotic drugs and opioids, as mentioned by previous authors [1, 15–18]. Our results showed a difference of 2 min (median) between groups. It is important to highlight that awakening time was a secondary outcome and probably does not have enough power to confirm this evidence; likewise, we need to think about the clinical relevance of the 2-minute (median) difference between groups. Nevertheless, intra-operative consumption of propofol and remifentanil was not significantly different between groups, in contrast to the evidence published by other authors [1, 18].

Moreover, in the PACU, the consumption of opioids was even lower in the $MgSO_4$ group, whereas many authors have stated that there is no clinical evidence of the influence of $MgSO_4$ on opioid activity to treat difficult types of pain, for instance, neuropathic and inflammatory [15]. Although $MgSO_4$ reduced opioid consumption, it did not shorten the duration of the PACU stay, demonstrating that the use of $MgSO_4$ neither shortened nor prolonged the recovery phase of patients, in agreement with other studies [1].

Limitations of the study

We did not measure the intra-operative serum concentration of $MgSO_4$. As the groups were homogeneous, we assumed that the absence of this measure was not a major problem for comparative results. Also, our goal was to study the clinical and

usual dosage of $MgSO_4$ (30 mg kg^{-1}), not lower or higher doses, since we wanted to correlate it with the current clinical practice. Another possible limitation is the lack of external validity for other types of surgery. Since we studied only open hysterectomies, the results may not be generalizable to other kinds of surgery.

Despite the evidence of synergistic interaction of $MgSO_4$ and rocuronium, the residual neuromuscular block is still an unresolved concern for anesthesiologists [19]. A change of mindset is still needed to break the barriers of the lack of NMBD monitorization.

CONCLUSIONS

The conclusive results of this research offer a solid basis for considering $MgSO_4$ as a promising and safe option as an anesthetic adjuvant, but always with the presence of quantitative neuromuscular blockade monitoring. Additional studies are needed to improve the effects of $MgSO_4$ in different clinical contexts.

REFERENCES

1. Silva Filho SE, Sandes CS, Vieira JE, Cavalcanti IL. Analgesic effect of magnesium sulfate during total intravenous anesthesia: randomized clinical study. Braz J Anesthesiol 2021; 71: 550-557. DOI: 10.1016/j.bjane.2021.02.008.
2. Srebro D, Vuckovic S, Milovanovic A, Kosutic J, Vujovic KS, Prostran M. Magnesium in pain research: state of the art. Curr Med Chem 2017; 24: 424-434. DOI: 10.2174/0929867323666161213101744.
3. Almeida CED, Carvalho LR, Andrade CVC, Nascimento PD Jr, Barros GAM, Modolo NSP. Effects of magnesium sulphate on the onset time of rocuronium at different doses: a randomized clinical trial. Braz J Anesthesiol 2021; 71: 482-488. DOI: 10.1016/j.bjane.2021.07.023.
4. Weber V, Abbott TEF, Ackland GL. Reducing the dose of neuromuscular blocking agents with adjuncts: a systematic review and meta-analysis. Br J Anaesth 2021; 126: 608-621. DOI: 10.1016/j.bja.2020.09.048.
5. Queiroz Rangel Micuci AJ, Verçosa N, Filho PAG, de Boer HD, Barbosa DD, Cavalcanti IL. Effect of pretreatment with magnesium sulphate on the duration of intense and deep neuromuscular blockade with rocuronium: a randomised controlled trial. Eur J Anaesthesiol 2019; 36: 502-508. DOI: 10.1097/EJA.0000000000001003.
6. Czarnetzki C, Lysakowski C, Elia N, Tramèr MR. Time course of rocuronium-induced neuromuscular block after pre-treatment with magnesium sulphate: a randomised study. Acta Anaesthesiol Scand 2010; 54: 299-306. DOI: 10.1111/j.1399-6576.2009.02160.x.
7. Helbo-Hansen S, Ravlo O, Trap-Andersen S. The influence of alfentanil on the intubating conditions after priming with vecuronium. Acta Anaesthesiol Scand 1988; 32: 41-44. DOI: 10.1111/j.1399-6576.1988.tb02685.x.
8. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J; 8th International Neuromuscular Meeting. Good clinical research practice in pharmacodynamic studies of neuromus-

cular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007; 51: 789-808. DOI: 10.1111/j.1399-6576.2007.01352.x.

9. Naguib M, Brull SJ, Kopman AF, Hunter JM, Fülesdi B, Arkes HR, et al. Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg 2018; 127: 71-80. DOI: 10.1213/ANE. 0000000000002670.

10. Thilen SR, Weigel WA, Todd MM, Dutton RP, Lien CA, Grant SA, et al. 2023 American Society of Anesthesiologists practice guidelines for monitoring and antagonism of neuromuscular blockade: a report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade. Anesthesiology 2023; 138: 13-41. DOI: 10.1097/ ALN.0000000000004379.

11. Germano Filho PA, Cavalcanti IL, Barrucand L, Verçosa N. Effect of magnesium sulphate on sugammadex reversal time for neuromuscular blockade: a randomised controlled study. Anaesthesia 2015; 70: 956-961. DOI: 10.1111/anae.12987.

12. Vieira Carlos R, Luis Abramides Torres M, de Boer HD. Train-of-four recovery precedes twitch recovery during reversal with sugammadex in pediatric patients: a retrospective analysis. Paediatr Anaesth 2018; 28: 342-346. DOI: 10.1111/pan.13343.

13. Germano-Filho PA, Cavalcanti IL, Micuci AJQR, Velarde LGC, de Boer HD, Verçosa N. Recurarization with magnesium sulfate administered after two minutes sugammadex reversal: a randomized, double-blind, controlled trial. J Clin Anesth 2023; 89: 111186. DOI: 10.1016/j.jclinane.2023.111186.

14. Sun H, Jin T, Wu X, Yang L, Zuo Y, Liao R. Efficacy of magnesium sulfate as an adjuvant to rocuronium in general anaesthesia: a meta-analysis. J Int Med Res 2021; 49: 3000605211027736. DOI: 10.1177/03000605211027736.

15. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: theory and practice. Anesth Analg 2018; 127: 1246-1258. DOI: 10.1213/ANE.0000000000003668.

16. Bujalska-Zadrożny M, Tatarkiewicz J, Kulik K, Filip M, Naruszewicz M. Magnesium enhances opioid-induced analgesia – what we have learnt in the past decades? Eur J Pharm Sci 2017; 99: 113-127. DOI: 10.1016/j.ejps.2016.11.020.

17. Seyhan TO, Tugrul M, Sungur MO, Kayacan S, Telci L, Pembeci K, Akpir K. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. Br J Anaesth 2006; 96: 247-252. DOI: 10.1093/bja/aei291.

18. Telci L, Esen F, Akcora D, Erden T, Canbolat AT, Akpir K. Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements. Br J Anaesth 2002; 89: 594-598. DOI: 10.1093/ bja/aef238. PMID: 12393361.

19. Blum FE, Locke AR, Nathan N, Katz J, Bissing D, Minhaj M, Greenberg SB. Residual neuromuscular block remains a safety concern for perioperative healthcare professionals: a comprehensive review. J Clin Med 2024; 13: 861. DOI: 10.3390/jcm13030861.