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ORIGINAL INVESTIGATION

Effects of magnesium sulphate on the onset time of rocuronium at different doses: a randomized clinical trial

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Abstract
Background and aims: Rocuronium may provide excellent onset time, but high doses are required for effective action. Several strategies have managed to shorten rocuronium onset time, including the use of Magnesium Sulphate ($MgSO_4$).
Methods: One hundred and eighty patients were randomized into six groups according to rocuronium dose received (0.3, 0.6 or 1.2 $mg.kg^{-1}$) and the administration of saline or $MgSO^4$ (60 $mg.kg^{-1}$). Correlations between tissue perfusion and rocuronium onset time was determined by variations in perfusion index.
Results: Median (quartiles) rocuronium onset times were 85.5 (74.0–92.0); 76.0 (52.0–87.0) and 50.0 (41.0–59.5) seconds for 0.3, 0.6 $mg.kg^{-1}$ and 1.2 $mg.kg^{-1}$ doses, respectively. $MgSO_4$ decreased rocuronium onset at doses of 0.3 $mg.kg^{-1}$ (60.0 [48.0–74.3] seconds) and 0.6 $mg.kg^{-1}$ (44.0 [39.0–49.0] seconds) but not at 1.2 $mg.kg^{-1}$ (38.0 [33.5–56.3] seconds) ($p < 0.001$). Perfusion index variations in groups that received $MgSO_4$ were greater than in controls. A negative correlation between shorten onset and increased perfusion index was observed in rocuronium doses of 0.3 $mg.kg^{-1}$ ($r = -0.50$; $p < 0.001$) and 0.6 $mg.kg^{-1}$ ($r = -0.424$; $p < 0.001$), but not for 1.2 $mg.kg^{-1}$ dose ($r = -0.25$; $p = 0.07$).

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Conclusion: $MgSO_4$ reduces rocuronium onset time at doses of 0.3 mg.kg^{-1} and 0.6 mg.kg^{-1} being that the latter has a similar effect when compared to the dose of 1.2 mg.kg^{-1}, with or without the use of $MgSO_4$.
Trial registry at: http://www.ensaiosclinicos.gov.br/
Registry Number: RBR-96CY3K

Introduction

Rapid sequence intubation requires the use of rapid-onset neuromuscular blockers to avoid delays in tracheal intubation and the consequent risk of pulmonary aspiration. Succinylcholine has been the choice of neuromuscular blocking agent in this situation, providing intense and short-latency muscle relaxation.[1,2] However, alternatives to this drug are necessary due to its side effects and contraindications.[3] On the other hand, suboptimal neuromuscular blockade can lead to inferior intubation condition,[4] intubation failure,[5] laryngeal lesions and hoarseness.[6]

Higher doses of rocuronium (4 ED95) are required for effective action[7] and may provide very similar onset time to that of succinylcholine. Nonetheless, several strategies have been implemented to reduce onset time of rocuronium, including the use of Magnesium Sulphate ($MgSO_4$).[8–11] However, the use of high doses of rocuronium, especially when associated with magnesium sulfate, may significantly prolong the duration of neuromuscular blockade.[8]

To date, no study has evaluated rocuronium onset time combined with magnesium sulphate using the recommended dose of neuromuscular blockers under rapid sequence intubation conditions (4 ED95) or lower doses of rocuronium (1 ED95). These conditions could decrease drug onset time and improve intubation conditions, allowing more rational application of rocuronium.

The aim of this study was to evaluate the adequate and safe rocuronium dose, in association to magnesium sulfate, that could decrease the action onset time of this neuromuscular blocker drug for rapid sequence intubation.

Methods

This randomized, prospective, double-blinded clinical trial was approved by the Research Ethics Committee of the Federal University of Espirito Santo – UFES (CEP 337287/2013) (Vitoria, Brazil) and was registered at Brazilian Registry of Clinical Trials (REBEC) under the number RBR-96CY3K. Informed consent was obtained from all patients who agreed to participate.

This study followed standard protocols for neuromuscular blockers.[12] We selected patients of both sex, 18 to 65 years old, with American Society of Anesthesiologists (ASA) physical status I or II, body mass indexes between 18 and 27 kg.m^{-2} who would undergo elective surgeries under general anesthesia. The exclusion criteria were the use of any medication that could influence neuromuscular blockade, the presence of any degree of hepatic or renal dysfunction, any neuromuscular disease, expected difficult mask ventilation or intubation, pregnancy, emergency surgeries, electrolyte disturbances, magnesium supplementation, and cardiac diseases.[12]

We recruited 180 patients who were electronically randomized to determine their dose of rocuronium (0.3, 0.6, or 1.2 mg.kg^{-1}) and whether they would receive $MgSO_4$ (60 mg.kg^{-1}) or not (saline solution). This methodology resulted in six groups of 30 patients:

1) $MgSO_4$, 60 mg.kg^{-1}, plus rocuronium, 0.3 mg.kg^{-1};
2) $MgSO_4$, 60 mg.kg^{-1}, plus rocuronium, 0.6 mg.kg^{-1};
3) $MgSO_4$, 60 mg.kg^{-1}, plus rocuronium, 1.2 mg.kg^{-1};
4) Saline solution, 100 mL, plus rocuronium, 0.3 mg.kg^{-1};
5) Saline solution, 100 mL, plus rocuronium, 0.6 mg.kg^{-1}; and
6) Saline solution, 100 mL, plus rocuronium, 1.2 mg.kg^{-1}.

After randomization, each participant's group information was kept in a sealed opaque envelope. The dose of magnesium sulphate was diluted in saline solution, 100 mL, and all calculated doses of rocuronium were dilute in 20-mL syringes by an anesthesiologist who did not participate in data collection or analysis.

Procedures

Thirty minutes before surgery, an Intravenous line (IV) was set with a 20G or 18G catheter in the antecubital region and midazolam, 0.05 mg.kg^{-1} IV, was administered. Monitoring included a 5-lead electrocardiogram, noninvasive blood pressure, capnography, and a pulse oximeter with a perfusion index monitor (PM100C, New Tech, U.S.A.). Neuromuscular function was assessed via accelerometry of adductor pollicis muscle using a TOF Watch SX (Organon Ltd., Oss, The Netherlands). The monitor was placed on the arm that was not used for blood pressure measurement or venous access and the peripheral temperature sensor in thenar eminence of the superior limb in which neuromuscular function monitor was placed. Surface electrodes were placed on cleaned skin over ulnar nerve on volar side of the wrist. Hypothermia was prevented by warming blanket (Bair Hugger™, 3 M Company, Minnesota, USA).

According to the randomization, the patients received 100 mL of either saline solution or the saline solution with magnesium sulphate, 60 mg.kg^{-1}, using an infusion pump over 15 minutes, preceding anesthetic induction.[8] Any symptoms spontaneously reported by the patients during drug infusion were recorded and analyzed.

After initial solution infusion, anesthetic induction was performed with fentanyl, 5 $\mu g.kg^{-1}$, and a target-controlled infusion of propofol, 3 ± 1 $\mu g.mL^{-1}$.

After loss of consciousness, it was initiated the monitoring of neuromuscular function with automatic calibration of the monitor to calculate the supramaximal stimulation, which was followed by a period of signal stabilization for five minutes with 1-Hz single stimuli. Variations smaller than 5% for one minute were considered to represent stable signals. After stabilization and according to randomization, rocuronium was administered in five seconds.[12]

Outcomes

Primary outcome was the onset time of rocuronium, defined as the period between the end of its injection and the decrease in the motor response to 5% of the initial response. Secondary outcomes were: the conditions for endotracheal intubation (excellent, good, or poor), evaluated by laryngoscopic conditions, i.e., the position of the vocal cords, and the response to tracheal tube insertion,[12] heart rate and blood pressure variations, evaluated before infusion and one minute after tracheal intubation; the perfusion index, used as a surrogate measurement of tissue perfusion, was measured immediately before and after the administration of magnesium sulphate or saline control; serum levels of magnesium were measured by collecting a 3-ml blood sample from each patient before and 10 minutes after the administration of the initial solution.

Perfusion index is derived from photoelectric oximetry plethysmographic signal. It is obtained by calculating the light absorption rate of the pulsatile content (pulsatile arterial blood) and non-pulsatile components (venous blood and other tissues). Alterations in peripheral perfusion determine variations in the pulsatile component, without altering the non-pulsatile content, thus varying the perfusion index.[13] The measurement range of the device for the peripheral perfusion index was 0.2% to 20%, with an accuracy of ±0.1% (for measurements between 0.2% and 2%), ±1% (measured between 2% and 10%) and ±2% (between 10% and 20%).

Statistics

Sample size was calculated according to a reduction of the onset time of rocuronium, 0.6 $mg.kg^{-1}$, by an average of 35% (120 to 77 seconds) with the use of magnesium sulphate.[8] Assuming a more conservative difference of 10% between groups with or without magnesium sulphate, i.e., 10 seconds with a standard deviation of 15 seconds, α = 0.05, β = 0.2, a minimum of 25 patients per group were necessary to test the main hypothesis.

Chi-Squared was used test to compare groups' homogeneity (sex, Cormack-Lehane score, Mallampati score, and ASA physical status) and intergroup analysis to compare tracheal intubation conditions. Rocuronium onset time was analyzed by the Kruskal-Wallis test. Correlation between perfusion index and rocuronium onset was evaluated by Spearman's coefficient correlation.

Results

The flow chart for enrolment and allocation is shown in Figure 1. Losses after randomization were due to preoperative hypomagnesemia or hypocalcaemia, surgery suspension, failure in the calibration or signal stabilization of neuromuscular monitor, and errors in rocuronium administration (i.e., incorrect duration or volume losses).

There were no significant differences in sex, age, ASA physical status, Cormack-Lehane score, or Mallampati score among the groups, although there was a predominance of women in all of study groups (Table 1).

All patients were classified as having excellent or good conditions for tracheal intubation. Only three patients from Roc 0.3 group had a mild reaction to intubation. During infusion of magnesium sulphate, 48.75% (39/80) of patients reported warmth feeling, and 8.75% (7/80) referred pain at injection site during injection. All reported symptoms were mild, and it was not necessary to interrupt infusion or any other intervention.

The use of magnesium sulphate reduced rocuronium onset time in doses of 0.3 $mg.kg^{-1}$ and 0.6 $mg.kg^{-1}$ (p = 0.02 and p = 0.03, respectively). However, there was no potentiation when rocuronium was used at 1.2 $mg.kg^{-1}$ (Fig. 2).

There were no significant differences among the Roc 0.6 Mg, Roc 1.2, and Roc 1.2 Mg groups. Perfusion index variations in groups that received magnesium sulphate were higher (before and after infusion) than in control groups (Fig. 3).

Analysis of the scatter plot comparing the perfusion index and rocuronium onset time revealed a negative correlation at doses of 0.3 $mg.kg^{-1}$ (p < 0.001, R = -0.50) and 0.6 $mg.kg^{-1}$ (p < 0.001, R = -0424); in other words, reduced onset time was correlated with increased perfusion index. However, for rocuronium dose of 1.2 $mg.kg^{-1}$, there was no correlation between these two parameters (p = 0.07) (Fig. 4).

The mean plasma concentration obtained after infusion with magnesium sulphate was 4.78 ± 1.46 $mg.dL^{-1}$ (1.96 ± 0.6 $mmoL.L^{-1}$).

A comparison of the period before $MgSO_4$ or saline infusion and one minute after intubation revealed no significant difference in blood pressure between the groups. However, there was a statistically significant increase in the heart rate of patients who received magnesium sulphate (76.9 ± 11.1 bpm) compared to control group (71.5 ± 12.6 bpm).

All patients were extubated after total reversal of neuromuscular blockade, observed by TOF Watch (spontaneously or sugammadex needed). None patient reported muscle weakness in post-anesthesia care unit.

Discussion

Magnesium enhances neuromuscular blockade by inhibiting calcium-mediated release of acetylcholine from presynaptic terminals[14,15] via reduction of post-synaptic sensitivity to acetylcholine and a direct effect on the membrane potential of myocytes.[9,16] In addition to its actions on cellular level, magnesium may help reduce neuromuscular blockers onset time by improving haemodynamics, allowing a greater amount of rocuronium to reach the motor end-plate. Studies have demonstrated that magnesium has vasodilatory

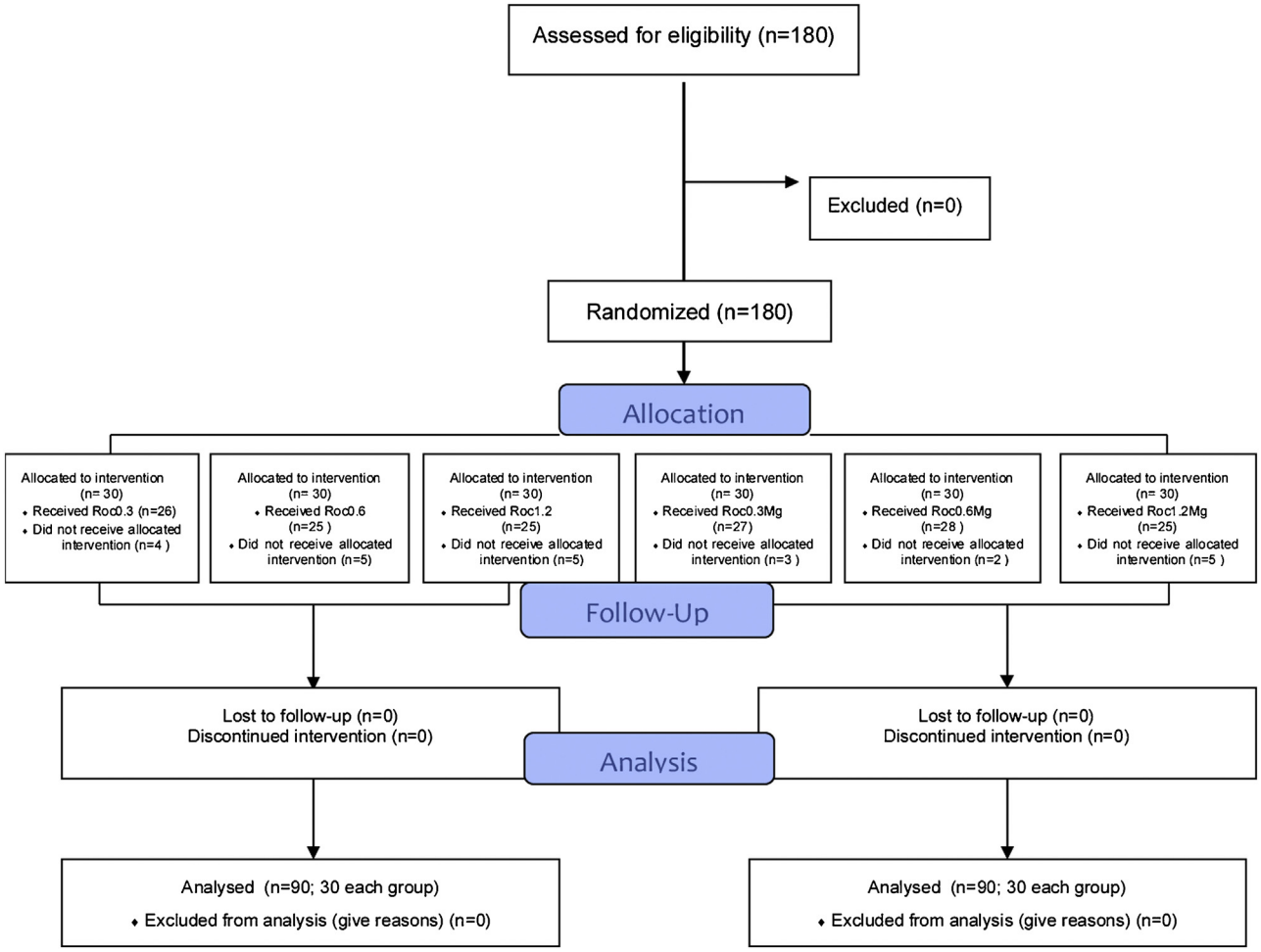

Figure 1 Flow chart for enrolment and allocation.

Table 1 Characteristics of the patients in each study group.

	Age (mean ± SD)	Sex (%)		ASA (%)		Cormack-Lehane score (%)			Mallampati score (%)		
Group		Women	Men	I	II	I	II	III	I	II	III
Roc 0.3	39 (12.4)	76.9	23.1	69.2	30.8	69.2	30.8	0	57.7	42.3	0
Roc 0.3 Mg	41 (12.26)	77.8	22.2	74.1	25.9	70.4	25.9	3.7	51.9	33.3	14.8
Roc 0.6	39 (10.84)	68.0	32.0	76.0	24.0	76.0	24.0	0	52.0	48.0	0
Roc 0.6 Mg	40 (11.1)	78.6	21.4	82.1	17.9	60.7	39.3	0	57.1	39.3	3.6
Roc 1.2	40.64 (10.51)	68.0	32.0	72.0	28.0	76.0	24.0	0	64.0	36.0	0
Roc 1.2 Mg	40.76 (14.02)	16	9	72	28	72	28	0	64.0	36.0	0

actions and increases cardiac output.[17,18] Other studies have attempted to reduce the onset time of neuromuscular blockers by including drugs that reduce neuromuscular blocker's circulation time in the bloodstream, such as ephedrine.[19,20]

Combinations of magnesium sulphate with neuromuscular blockers have been widely adopted due to their synergistic action.[8,11] One advantage of such combinations is a reduction in neuromuscular blocker onset of action. However, studies conducted to date have been limited to the dose of rocuronium used in elective intubations (2 ED95). Low-potency blockers, including rocuronium, have lower onset time, especially when used in higher doses (4 ED95) once they provide larger number of molecules for diffusion from the central compartment to the muscles.[21]

Our results combining magnesium sulphate and rocuronium at a dose of 0.6 $mg.kg^{-1}$ are consistent with those of most studies using the same methodology. The onset time we observed (44 seconds) was lower than that found by Czarnetzki and colleagues[8] (77 seconds) and Kim and colleagues[11] (94 seconds). Another study reported the absence of potentiation when magnesium was administered in bolus before using rocuronium, and these authors postulated that there was insufficient time for magnesium action in the motor endplate.[9] Shorter onsets time observed in this study, even in

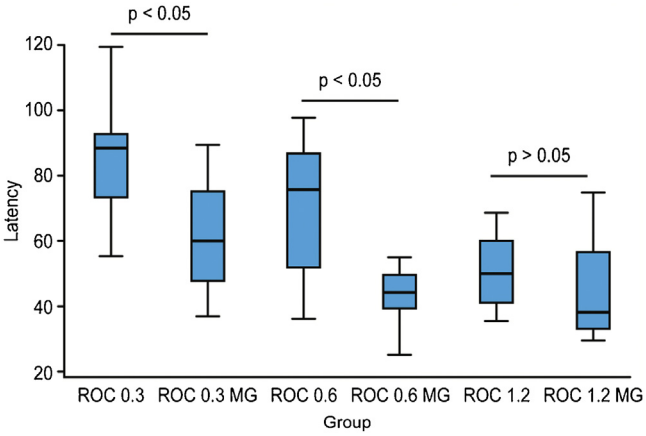

Figure 2 Rocuronium latency in the studied groups. Figure shows the median values (horizontal bar), first and third quartiles (rectangle height), and upper and lower limits (vertical lines).

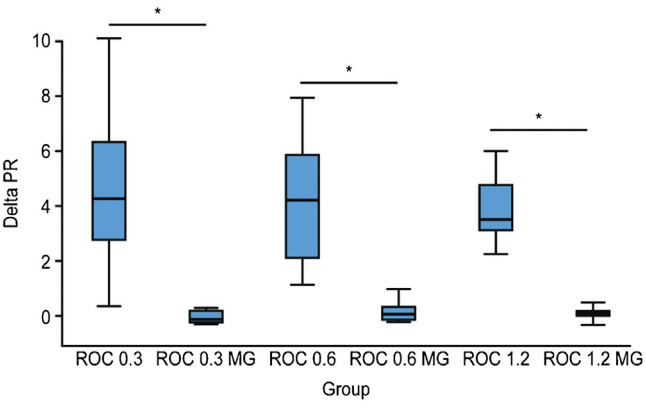

Figure 3 Changes in perfusion rate (delta PR). Figure shows the median values (horizontal bar), first and third quartiles (rectangle height), and upper and lower limits (vertical lines).

the control groups, could have been due to the characteristics of the groups (e.g., the preponderance of females) and demographic changes, as described in other studies.[22,23]

Although there was onset time reduction in the groups that received rocuronium dose of 1.2 mg.kg^{-1} (12 seconds), this difference was not statistically significant. This result could have been due to multiple factors, including reaching the potentiation threshold, either through the transport of higher neuromuscular blocker levels to the motor endplate, limit in blood flow, or high availability of rocuronium molecules when used in high doses.[21] These possibilities are reinforced by the lack of a statistical correlation between increased perfusion index and the reduced onset time for this dose of rocuronium.

Combination of magnesium sulphate with 1 ED95 rocuronium (0.3 mg.kg^{-1}) produced a significant decrease in onset time, from 88.5 to 60.0 seconds. This onset value was statistically similar to that obtained using a single dose of rocuronium for tracheal intubation in common situations (2 ED95).

Changes in peripheral perfusion index determine changes in pulsatile component without altering the non-pulsatile component, resulting in perfusion index variations.[13] The

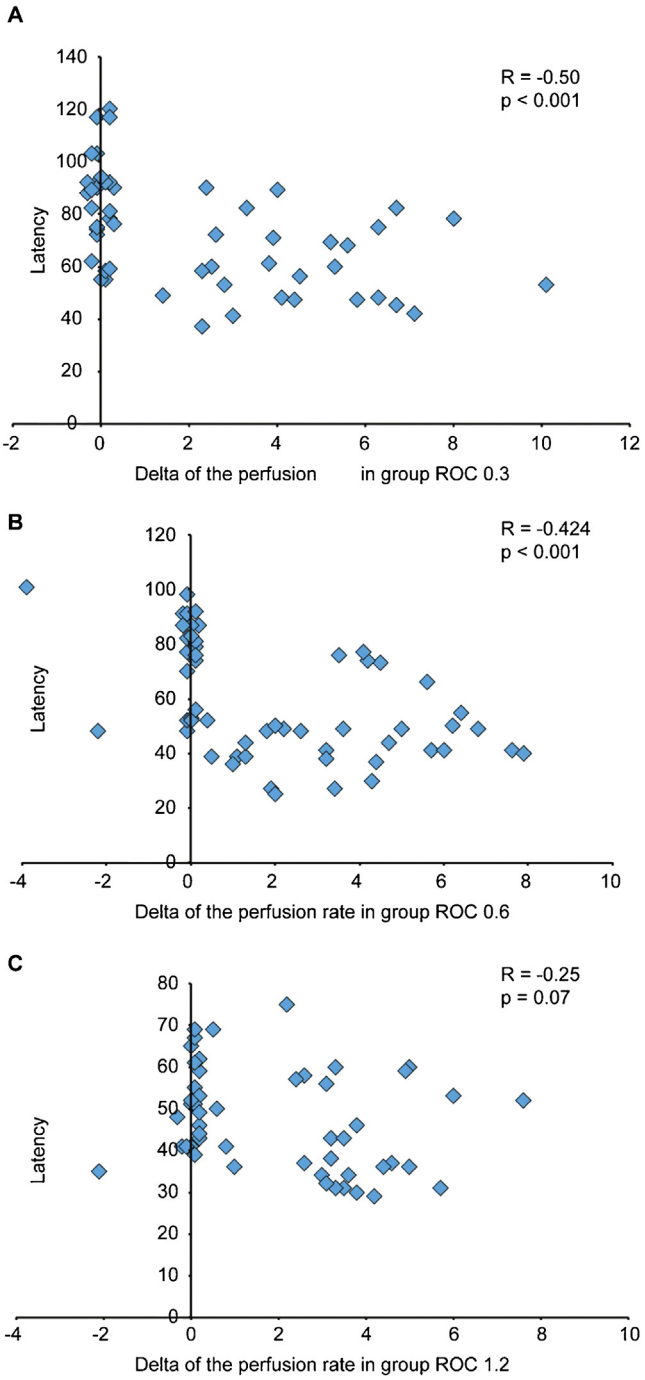

Figure 4 Scatter plots showing rocuronium latency (in seconds) and variations in the infusion rate. A, he Roc 0.3 and Roc 0.3 Mg groups; B, the Roc 0.6 and Roc 0.6 Mg groups; C, the Roc 1.2 and Roc 1.2 Mg.

perfusion index has been widely used to quantify vascular tone.[24,25]

Perfusion index values show wide variation in population. Therefore, we used the difference between the values measured before and after the infusion of the investigated solution. The short time (15 minutes) and maintenance of body temperature by active warm-up ensured that perfusion index oscillations were due to magnesium sulfate action.

Our results indicate that magnesium increased the perfusion index in all groups that received it. These variations in perfusion index showed vasodilation caused by magnesium sulphate. The negative correlation coefficient found in the scatter plots at rocuronium doses of 0.3 and 0.6 $mg.kg^{-1}$ showed a relation between onset time reduction and perfusion index increase, proving the importance of hemodynamic effects of magnesium sulphate in rocuronium onset of action.

Plasma levels achieved through the administration of 60 $mg.kg^{-1}$ (4.78 $mg.dL^{-1}$; 1.9 $mmoL.L^{-1}$) of magnesium sulphate were safe, and the primary side effect was the sensation of warmness. Despite the frequency of this side effect (48%), patients described this symptom as being of low intensity, and no interventions or interruptions of drug administration were necessary. We opted to use the same dose described by Czarnetzki and colleagues[8] to optimize the potentiation of the neuromuscular blocker. Plasma levels obtained were similar to those obtained with the use of magnesium sulphate in the treatment of eclampsia.[26] Other studies using lower doses of magnesium sulphate also succeeded at reducing rocuronium onset time.[10,11] Maintenance dose of magnesium sulfate was not used in this study due to the purpose of the clinical trial, that was to determine rocuronium onset time. For this reason, magnesium plasma concentration was analyzed when rocuronium latency was measured by accelerometry of adductor pollicis muscle.

Some studies have demonstrated the effectiveness of magnesium sulphate in improving intubation conditions,[27] even in the absence of neuromuscular blockers.[28] Furthermore, all patients evaluated in our study had good or excellent intubation conditions. The use of motor response of adductor pollicis muscle as an end point may have affected our results once onset time of neuromuscular blocker action is faster in muscles that are involved in the intubation procedure (laryngeal adductors, diaphragms, and masseter) compared to evaluated muscle.[29]

In addition to improving intubation clinical conditions, magnesium sulphate may help attenuate the adrenergic response to tracheal intubation.[30] In our study, there was no significant difference in blood pressure among the groups. This result may have been due to the fentanyl dose (5 $\mu g.kg^{-1}$) used during anaesthesia, which could have provided haemodynamic stability in control groups. The increase in the heart rate of patients receiving magnesium sulphate compared with patients in control groups may have been due to its cardiovascular effects, such as vasodilatation and reflex tachycardia.[17]

High doses of rocuronium may significantly prolong the duration of neuromuscular blockade. However, clinical trials have demonstrated the efficacy of sugammadex in reversing rocuronium-induced neuromuscular block even after prior administration of magnesium sulfate. Reversal was complete and effective even in deep and moderate neuromuscular blocks.[31] These findings confirm the possibility of using high doses of rocuronium associated with magnesium sulfate with the objective of reducing neuromuscular blocker latency.

Limitations of this study included the predominance of women in the study groups and the fact that the duration of neuromuscular blockade using this drug combination was not measured. Moreover, the randomization of patients in pre-anaesthesia consultations led to a greater number of losses than expected. However, these losses did not reduce statistical analysis power. Therefore, future studies should evaluate different populations, determine neuromuscular blockade duration, and use other doses of magnesium sulphate.

Rocuronium and magnesium sulphate combinations used in this study reached their potentiation limit at rocuronium dose of 2 ED95. Patients receiving magnesium therapy who have plasma levels of magnesium similar to those described here (e.g., those with eclampsia) or patients for which magnesium is used as an anaesthetic adjuvant can have their induction dose in RSI reduced to 2 ED95. Overall, this knowledge of the pharmacokinetic profile of rocuronium combined with magnesium sulphate allows for the rational administration of rocuronium.

Conflicts of interest

No external funding and no competing interests declared. This manuscript is part of results from thesis of CEDA (first author), available at https://repositorio.unesp.br/handle/11449/149730.

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