



SCIENTIFIC ARTICLE

Effectiveness of magnesium sulfate compared to rocuronium for rapid sequence tracheal intubation in adults: clinical randomized trial[☆]



Fabiano Timbó Barbosa ^{a,*}, Olavo Barbosa de Oliveira Neto^a,
Luciano Timbó Barbosa^b, Raul Ribeiro de Andrade^c, Êurica Adélia Nogueira Ribeiro^a,
Célio Fernando de Sousa Rodrigues^a

^a Universidade Federal de Alagoas, Maceió, AL, Brazil

^b Hospital Geral do Estado Professor Osvaldo Brandão Vilela, Maceió, AL, Brazil

^c Centro Universitário CESMAC, Maceió, AL, Brazil

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KEYWORDS

Orotracheal
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Abstract

Introduction and objectives: Magnesium sulphate has been used in anesthesia because it has relevant clinical features such as: analgesia, autonomic response control and muscle relaxation. Using the agent to establish adequate conditions for tracheal intubation remains controversial. The aim of the study was to compare the effectiveness of magnesium sulfate and rocuronium for rapid sequence tracheal intubation in adults.

Methods: Double blind, randomized, unicentric, prospective study assessed 68 patients, ASA 1 or 2, over 18 years, scheduled for appendectomy under general anesthesia. Patients were divided into two groups. GM patients received 50 mg.kg⁻¹ magnesium sulfate and GR patients, 1 mg.kg⁻¹ rocuronium immediately before anesthesia induction. Arterial Blood Pressure (BP) and Heart Rate (HR) were measured in both groups at five times related to the administration of the drugs studied. The primary variable was the clinical status of tracheal intubation.

Trial Registry: RBR-4xr92k.

Results: GM was associated with no significant hemodynamic parameter change after injection. GM showed 85% (29/34) poor intubation clinical status, 15% (5/34) good, and 0% excellent (< 0.0001).

Conclusion: Magnesium sulfate did not provide adequate clinical status when compared to rocuronium at a dose of 50 mg.kg⁻¹ for rapid sequence intubation in adult patients.

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[☆] Study site: Hospital Geral do Estado Professor Osvaldo Brandão Vilela.

* Corresponding author.

E-mail: fabiano.barbosa@famed.ufal.br (F.T. Barbosa).

PALAVRAS-CHAVE

Intubação orotraqueal;
Anestesia geral;
Ensaio clínico randomizado;
Apendicite

Efetividade do sulfato de magnésio comparado ao rocurônio para intubação em sequência rápida em adultos: ensaio clínico randomizado**Resumo**

Justificativa e objetivos: O sulfato de magnésio vem sendo utilizado em anestesia por apresentar características relevantes à prática da clínica como: analgesia, controle dos reflexos autonômicos e relaxamento muscular. A utilização deste agente para garantir condições adequadas para a intubação traqueal permanece controverso. O objetivo deste trabalho é determinar a efetividade do sulfato de magnésio comparado ao rocurônio para intubação orotraqueal em sequência rápida em pacientes adultos.

Métodos: Este estudo duplamente encoberto, aleatorizado, unicêntrico e prospectivo avaliou 68 pacientes, ASA 1 ou 2, maiores de 18 anos, escalados para cirurgias de apendicectomia sob anestesia geral. Foram alocados em dois grupos, o GM recebeu 50 mg.kg⁻¹ de sulfato de magnésio e o GR, 1 mg.kg⁻¹ de rocurônio imediatamente antes da indução anestésica. Os valores de Pressão Arterial (PA) e Frequência Cardíaca (FC) foram aferidos nos dois grupos em cinco momentos relacionados com a administração dos fármacos do estudo. A variável primária foi condição clínica da intubação.

Registro: RBR-4xr92k.

Resultados: O GM não apresentou alteração significativa dos parâmetros hemodinâmicos após infusão. O GM apresentou 85% (29/34) de condição pobre, 15% (5/34) condição clínica boa e 0% condição clínica excelente < 0,0001.

Conclusão: O sulfato de magnésio não propiciou condições clínicas aceitáveis quando comparado ao rocurônio para intubação orotraqueal em sequência rápida em pacientes adultos quando utilizada a dose de 50 mg.kg⁻¹.

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Introduction

Rapid Sequence Intubation (RSI) ensures the establishment of protected airway for patients with risk of lung aspiration. It comprises preoxygenation, administration of anesthesia induction drugs, neuromuscular agents and tracheal intubation that preferentially should occur within one minute. Laryngoscopy stimulates sympathetic response, resulting in increase in heart rate, arterial blood pressure, myocardial oxygen consumption and cardiac arrhythmias.¹

Magnesium Sulfate (MS) has been used in anesthesia due to its relevant anesthetic features, such as analgesia, anesthesia and muscle relaxation.^{2,3} MS has two advantages that can be relevant for tracheal intubation. First, it has anti-adrenergic properties for decreasing suprarenal catecholamine release, leading to protection during laryngoscopy and intubation.³ Second, there is clinical evidence that MS can potentiate effects of neuromuscular blocking agents and provide tracheal intubation conditions without using these agents.^{4,5}

The above listed advantages lead us to the assumption that MS can provide enough muscle relaxation for it not be used in association with a neuromuscular blocking agent. Thus, our aim was to determine the efficacy of MS, compared to rocuronium, for orotracheal RSI in adults.

Methods

Inclusion criteria were: age > 18 years, emergency surgery for acute appendicitis performed exclusively at the research

hospital and American Society of Anesthesiology classification ASA I and II. Exclusion criteria were: pregnancy, neuromuscular disorder, renal failure, body mass index > 30 kg.m⁻², difficult airway anticipated, chronic use of calcium channel blocking drugs, chronic use of Mg-containing medications and allergy to magnesium sulfate. The study was carried out at *Hospital Geral do Estado Professor Osvaldo Brandão Vilela*, in Maceió state of Alagoas, Brazil.

All participants received the same general anesthesia induction technique, except for the medications that described their participation group. The technique consisted of 5 minute pre-oxygenation with 100% oxygen, venous access and initiation of normal saline solution and monitoring with oximetry, continuous ECG and noninvasive arterial blood pressure. All patients received 2.5 mg.kg⁻¹ of propofol and 3 μg.kg⁻¹ of fentanyl intravenously.

Patients were divided into two groups: Group M (GM), receiving a 50 mg.kg⁻¹ dose of magnesium sulfate (MgSO₄), intravenously; and Group R (GR), receiving a 1 mg.kg⁻¹ dose of rocuronium bromate, intravenously. Drugs were prepared with distilled water in a non-labelled 20 mL syringe. The syringe solution was prepared by an individual that did not collaborate in any other phase of the study.

The variables of this trial were divided into three categories: primary variable, which was the clinical condition of tracheal intubation; secondary variables, which were heart rate, systolic blood pressure, diastolic blood pressure and adverse events; and tertiary variables, which were arterial oxygen saturation, age, gender, body mass index, height, weight and physical status according to ASA classification.

Table 1 Clinical conditions of intubation.⁶

Variable assessed	Clinically acceptable		Clinically unacceptable
	Excellent	Good	Poor
Laryngoscopy ^b	Easy	Fair/good	Difficult
Position of vocal cords	Abducted	Intermediate or movement	Closed
Reaction to insertion of tracheal tube and cuff insufflation (Diaphragm movement/cough)	None	Light ^c	Vigorous or sustained ^d

^a Intubation status: Excellent, all qualities are excellent; Good, all qualities are excellent or good; Poor, presence of only one quality listed as "poor"

^b Laryngoscopy: Easy, maxilla relaxed, no resistance to insertion of the blade; Fair, mandible not completely relaxed, light resistance to insertion of the blade; Difficult, mandible poorly relaxed, active resistance of patient to laryngoscopy.

^c Reaction to insertion: One to two weak contractions or movements for less than 5 s.

^d Reaction to insertion: More than two contractions and/or movements for more than 5 s.

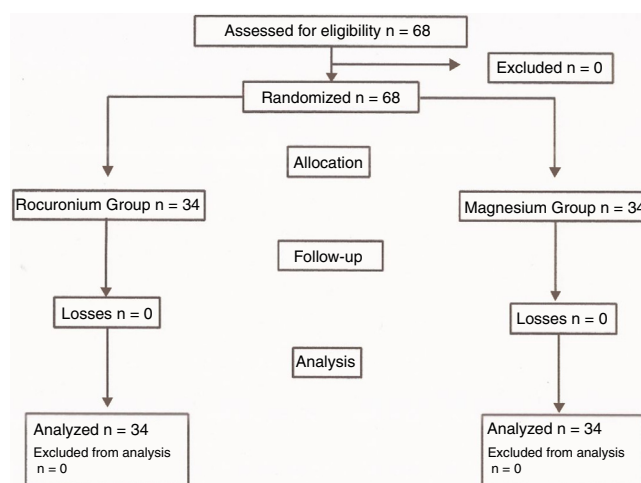
Clinical status upon intubation was defined as the status of airways present at the time of orotracheal intubation.⁶ Assessment considered laryngoscopy, vocal cord positioning and reactions patients presented at the time of orotracheal tube insertion in airways. Assessment used the Good Clinical Research Practice Guidelines intubation score system, as shown in Table 1.⁶ Clinical status was classified as acceptable or unacceptable. Unacceptable clinical status was considered when laryngoscopy was considered difficult, vocal cords were closed or when there was muscle reaction when the tube passed through vocal cords. Assessment was performed by visual inspection at the moment of tracheal intubation.

Heart rate, systolic blood pressure and diastolic blood pressure were registered at four times: before magnesium sulfate or rocuronium administration, after drug administration; and at 1, 3 and 5 minutes after tracheal intubation.

Randomization was performed by throwing six-side dice with three odd and three even faces. When the upper face was even, the participant was allocated into the intervention group (GM), conversely the odd face allocated the participant to the comparison group (GR). Participant allocation was performed after signing the informed consent form and immediately before performing the general anesthesia to enable blind allocation.

Confidentiality of allocation of drugs was assured when medication was prepared and disposed in syringes of the same size, colorless content, with no label or any indication regarding the group the participant was allocated to. Only the individual responsible for preparing syringes knew which group the participant belonged to and that information was unconcealed only after data analysis. The individual responsible for data analysis and participants were blind to group allocation.

Categorical variables were analyzed by Chi-Square or Fisher tests whenever indicated. Shapiro-Wilk test was used to assess symmetric distribution of continuous data. Student's *t*-test was used to compare continuous variables presenting symmetrical distribution, and the Mann-Whitney U-test when asymmetry in the distribution was found. Two-way analysis of variance (ANOVA) for repeated measures was

**Figure 1** Randomization flow chart.

used for comparisons between groups (GM e GR) and among the data collection moments (before administration, immediately after administration and at 1, 3 and 5 minutes after administration). Bonferroni's post hoc test for multiple comparisons was employed to identify differences in variables in which F values were higher than the adopted statistical significance. Level of significance was 5%. Data were presented as percentages, absolute values and means with standard deviation. Analysis was performed using Biostat 5.0 and GraphPad Prism 5 applications (GraphPad Software Inc., San Diego, CA, USA).

Results

Sixty-eight patients took part in the study and were randomly assigned to two groups (Fig.1). Participants were assessed according to their allocation group. There was no participant loss or exclusion. Data were collected from July 2017 to July 2018.

The demographic features of participant's – age, gender, body mass index, height, weight and physical status

Table 2 Demographic characteristics.

Characteristics of patients	Group R	Group M	Value of <i>p</i>
Age (years)	34.3 ± 11.96	26.4 ± 9.85	0.10 ^a
Weight (kg)	68 ± 11.16	70.4 ± 17.38	0.76 ^a
Height (m)	1.61 ± 0.04	1.67 ± 0.08	0.05 ^b
BMI (kg. m ²)	26.33 ± 4.15	24.74 ± 3.84	0.33 ^a
ASA I/II	24/10	25/9	0.9 ^c
Sex (m/f)	14/20	18/16	0.68 ^c

Values expressed as mean ± standard deviation.

R, Rocuronium; M, Magnesium; m, male; f, female.

^a Student *t* test.

^b Mann-Whitney U test.

^c Chi-Square.

Table 3 Conditions of intubation.

Groups	Clinically acceptable (excellent/good)	Clinically unacceptable (poor)	Value of <i>p</i>
R (n)	24/10	0	< 0.0001 ^a
M (n)	0/5	29	

R, Rocuronium group; M, Magnesium group; n, number of participants.

^a Chi-square.

Table 4 Changes in heart rate.

Times	Group R	Group M	Value of <i>p</i>
FCa	92.5 ± 18.86	96.6 ± 17.09	0.074 ^a
FCap	92.8 ± 19.01	103.3 ± 14.43	
FC1	102.9 ± 14.54	100.13 ± 13.55	
FC3	108.8 ± 11.50	100.73 ± 15.01	
FC5	95.2 ± 16.53	95 ± 16.85	

Values expressed as mean ± standard deviation.

R, rocuronium; M, magnesium; FCa, heart rate before; FCap, heart rate after; FC1, heart rate 1 minute after; FC3, heart rate 3 minutes after; FC5, heart rate 5 minutes after.

^a ANOVA two factors.

Table 5 Changes in systolic blood pressure.

Times	Group R	Group M	Value of <i>p</i>
PSa	138.1 ± 9.17	129.73 ± 14.74	0.114 ^a
PSap	125.6 ± 13.72	106 ± 13.27	
PS1	127.5 ± 20.16	122.3 ± 18.53	
PS3	123.9 ± 15.58	114.3 ± 18.38	
PS5	114.4 ± 14.89	114.2 ± 19.61	

Values expressed as mean ± standard deviation.

R, Rocuronium; M, Magnesium; PSa, Blood Pressure before; PSap, Blood Pressure after; PS1, Blood Pressure 1 minute after; PS3, Blood Pressure 3 minutes after; PS5, Blood Pressure 5 minutes after.

^a Two-factor ANOVA.

classification – did not show statistical difference as seen on [Table 2](#). Arterial blood oxygen saturation did not differ between groups, and was not below 99% during any of the analysis moments.

The primary variable or clinical status of tracheal intubation revealed unfavorable results for magnesium use when compared to rocuronium. GM registered 85% (29/34) of patients with poor status, 15% (5/34) with good clinical status and 0% (0/34) with excellent clinical status, as shown in [Table 3](#). There were no tracheal intubation failures.

Assessment of hemodynamic parameters showed that heart rate did not differ between groups ([Table 4](#)); however, there was interaction between factors (interaction, $p=0.042$; time, $p=0.043$; group, $p=0.074$); systolic blood pressure showed no statistical difference between groups ([Table 5](#)) (interaction, $p=0.284$; time, $p=0.0005$; group, $p=0.114$); and diastolic blood pressure did not differ between groups ([Table 6](#)), however, there was interaction between factors (interaction, $p=0.019$; time, $p=0.0001$; group, $p=0.683$). There was statistically significant differ-

Table 6 Changes in diastolic blood pressure.

Times	Group R	Group M	Value of <i>p</i>
PDa	75.9 ± 8.24	78.7 ± 11.35	0.683 ^a
PDap	72 ± 10.11	54.3 ± 9.35	
PD1	74.7 ± 15.60	80.3 ± 20.88	
PD3	69.2 ± 13.57	66.7 ± 13.77	
PD5	62.5 ± 13.50	64.1 ± 13.92	

Values expressed as mean ± standard deviation.

R, Rocuronium; M, Magnesium; PDa, Blood Pressure before; PDap, Blood Pressure after; PD1, Blood Pressure 1 minute after; PD3, Blood Pressure 3 minutes after; PD5, Blood Pressure 5 minutes after.

^a Two-factor ANOVA.

ence for adverse events, as they occurred in 20% (7/34) of participants in the magnesium sulfate group and 0% (0/34) in the rocuronium group ($p=0.0237$; Fischer's test). The adverse event identified in the study was sweating.

Discussion

The study did not show effectiveness of magnesium sulfate as a single agent to promote muscle relaxation for oro-tracheal intubation. Clinical status of tracheal intubation was assessed by an international protocol showing results consistent with inadequate status for tracheal intubation. The hypothesis tested arose from the reported magnesium sulfate action inhibiting acetylcholine release at neuromuscular junction and MS potentiating action of neuromuscular blocking agents.³

Study limitations were absence of previous assessment of difficult tracheal intubation, time of magnesium sulfate infusion, and absence of magnesium serum level measurements. Absence of previous assessment of difficult tracheal intubation did not compromise our results, since no patients presented any challenge during oro-tracheal intubation and all participant vocal cords were observed by laryngoscopy, indicating that no participant had a level higher than two in the Cormack Lehane classification.⁷ Participants of both groups received the drugs used in syringes and in no longer than one minute, which may indicate that the time for drug action could have been insufficient. However, other researchers used this same administration protocol without affecting results. Magnesium blood level was not measured, but two aspects need to be taken into account. First, patients had no known predisposing conditions that would lead to changes in magnesium levels, such as hospital bedridden status, diabetes mellitus, alcoholism, medication use or chronic kidney disease.³ Second, the objective of a clinical trial is to assess its research protocol under conditions similar to those encountered in daily clinical practice, and preoperative verification of magnesium blood levels is not routine workout.

Clinical status for tracheal intubation in the magnesium sulfate group was considered poor in 85% of patients and clinically unacceptable. The result of this study differs from other clinical trials, but the benefit found in other studies can be explained by the use of magnesium sulfate in combination with a neuromuscular blocker.^{8,9} Magnesium sulfate not associated with neuromuscular blocker has already been assessed in another study with positive results, however, there are clinical and design study differences that may explain result disparity in relation to our study, such as: comparison with saline, geriatric age group, use of magnesium infusion and sample size based on low statistical power.¹⁰ We attributed the negative result found in our study to the dose of magnesium sulfate used, which may have been insufficient for the age range and associated surgical disorders. The optimal dose for magnesium sulfate as an agent not associated with a neuromuscular blocker drug has not been established, and there is no consensus to date.

Assessment of hemodynamic parameters showed that systolic blood pressure did not decrease significantly after magnesium sulfate use. The present study cannot reach a definitive conclusion regarding heart rate and systolic blood pressure. A clinical trial assessed the effect of several doses of magnesium sulfate on cardiovascular response to laryngoscopy and intubation, showing a decrease in hemodynamic parameters after MS administration.⁸ The dose used in our study has not been shown to be harmful to patients at oro-tracheal intubation, since adverse events, other than profuse sweating, after drug infusion were not observed. The effect of blunting the hemodynamic response during tracheal intubation with magnesium sulfate has been shown in other clinical trials.⁹⁻¹¹

The clinical implication from our results is that the 50 mg.kg⁻¹ dose of MS, in absence of a neuromuscular blocker, is insufficient to ensure acceptable clinical conditions for tracheal intubation. The dose, however, does not lead to hemodynamic instability and may be used to decrease the hemodynamic response to stress in rapid sequence oro-tracheal intubation. Neuromuscular blockers are recommended to ensure adequate clinical conditions for tracheal intubation.

The main implication for future research is that higher doses need to be assessed to identify if magnesium sulfate can be used unassociated with a neuromuscular blocker. Clinical settings other than those analyzed here, such as patients in another age group, intubation status in elective surgery, and different doses of hypnotics that have potential use for muscle relaxation such as propofol associated with magnesium sulfate for successful tracheal intubation, may also be assessed.

In summary, a 50 mg.kg⁻¹ dose of magnesium sulfate did not provide acceptable clinical conditions for rapid sequence tracheal intubation in adults when compared with rocuronium.

Conflicts of interest

The authors declare no conflicts of interest.

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