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SCIENTIFIC ARTICLE

Effects of lidocaine and magnesium sulfate in attenuating hemodynamic response to tracheal intubation: single-center, prospective, double-blind, randomized study

Fabricio Tavares Mendonça*, Lucas Macedo da Graça Medeiros de Queiroz, Cristina Carvalho Rolim Guimarães, Alexandre Cordeiro Duarte Xavier

Centro de Ensino e Treinamento do Hospital de Base do Distrito Federal, Unidade de Anestesiologia e Medicina Perioperatória, Brasília, DF, Brazil

Abstract

Background and objectives: Hemodynamic response to airway stimuli is a common phenomenon and its management is important to reduce the systemic repercussions. The objective of this study is to compare the efficacy of intravenous magnesium sulfate versus lidocaine on this reflex hemodynamics after laryngoscopy and tracheal intubation.

Methods: This single-center, prospective, double-blind, randomized study evaluated 56 patients ASA 1 or 2, aged 18–65 years, scheduled for elective surgeries under general anesthesia with intubation. The patients were allocated into two groups: Group F received 30 mg·kg^{-1} of magnesium sulphate and Group L, 2 mg·kg^{-1} of lidocaine, continuous infusion, immediately before the anesthetic induction. Blood pressure (BP), heart rate (HR), and bispectral index (BIS) were measured in both groups at six different times related to administration of the study drugs.

Results: In both groups there was an increase in HR and BP after laryngoscopy and intubation, compared to baseline. Group M showed statistically significant increase in the values of systolic and diastolic blood pressure after intubation, which was clinically unimportant. There was no difference in the BIS values between groups. Among patients receiving magnesium sulfate, three (12%) had high blood pressure versus only one among those receiving lidocaine (4%), with no statistical difference.

* Corresponding author.
  E-mail: fabricio.tavares@me.com (F.T. Mendonça).

Conclusion: Magnesium sulfate and lidocaine have good efficacy and safety for hemodynamic management in laryngoscopy and intubation.
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Os efeitos da lidocaína e do sulfato de magnésio na atenuação da resposta hemodinâmica à intubação orotraqueal: estudo unicêntrico, prospectivo, duplamente encoberto e aleatorizado

Resumo

Justificativa e objetivos: A resposta hemodinâmica aos estímulos das vias aéreas é um fenômeno comum e seu controle é importante para diminuir as repercussões sistêmicas. O objetivo deste trabalho é comparar os efeitos da administração endovenosa de sulfato de magnésio versus lidocaína na hemodinâmica desse reflexo após a laringoscopia e intubação orotraqueal.
Métodos: Este estudo duplamente encoberto, aleatorizado, unicêntrico e prospectivo avaliou 56 pacientes, ASA 1 ou 2, entre 18 e 65 anos, escalados para cirurgias eletivas sob anestesia geral com intubação orotraqueal. Foram alocados em dois grupos, o M recebeu $30\,mg\cdot kg^{-1}$ de sulfato de magnésio e o L, $2\,mg\cdot kg^{-1}$ de lidocaína, em infusão contínua, imediatamente antes da indução anestésica. Os valores de pressão arterial (PA), frequência cardíaca (FC) e índice biespectral (BIS) foram aferidos nos dois grupos em seis momentos relacionados com a administração dos fármacos do estudo.
Resultados: Em ambos os grupos houve aumento na FC e PA após a laringoscopia e intubação, em relação aos valores basais. No Grupo M observou-se elevação estatisticamente significativa, mas clinicamente pouco importante, nos valores das pressões arteriais sistólica e diastólica após a intubação. Não houve diferença nos valores de BIS entre os grupos. Dos pacientes que receberam o sulfato de magnésio, 3 (12%) apresentaram episódio de hipertensão, ao passo que apenas um dos que receberam lidocaína (4%) apresentou esse sinal, sem diferença estatística.
Conclusão: Sulfato de magnésio e a lidocaína apresentam boa eficácia e segurança no controle hemodinâmico à laringoscopia e intubação.
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Introduction

The hemodynamic response to stimuli evoked by laryngoscopy and intubation is a common phenomenon, resulting from the release of endogenous catecholamines reflexively to the upper airway afferents when stimulated.[1] This inappropriate response may increase perioperative morbidity and mortality, especially in patients with coexisting disease, particularly patients with cardiovascular disease. The management of this defensive reflex is essential because it prevents adverse events, such as tachycardia, systemic hypertension, pulmonary hypertension, and arrhythmias, which may result in stroke or myocardial infarction resulting from hemodynamic instability produced by laryngoscopy and intubation. Many drugs are the subject of studies, including those with good results, such as magnesium sulfate[1-3] and lidocaine.[4-6]

The magnesium sulfate mechanism of action for hemodynamic response attenuation appears to result from the inhibition of catecholamine release from the adrenal medulla, maintains the plasma concentration of epinephrine practically unchanged, and also reduces the increased circulating norepinephrine when compared to that of a control group.[2] It also has a systemic and coronary vasodilation effect by antagonizing calcium ion in vascular smooth muscle.[7] As for lidocaine, when used systemically, it has an antagonistic action on sodium channels and NMDA receptors, reduces the release of substance P, has glycinergic action, which decreases the airway reactivity.[8,9]

The aim of this study was to compare the effects of intravenous magnesium sulfate with lidocaine on hemodynamics during intubation.

Material and methods

This prospective, randomized, double blind, single-center study was approved by the Research Ethics Committee — FEPECS/SES-DF — under the opinion number 799,112 on September 22, 2014, and is identified in the *Plataforma Brasil* (http://aplicacao.saude.gov.br/plataformabrasil) as CAAE No 33365114.7.0000.5553 and registered in ClinicalTrials (NCT02359370). After written informed consent was given, 56 patients, ASA 1 or 2, aged between 18–65 years, scheduled for elective surgery with orotracheal intubation (OTI) were assessed for eligibility, between September and November 2014 at the *Hospital de Base do Distrito Federal* (Fig. 1).

Patients with contraindications or history of hypersensitivity to the study drugs, those with coronary ischemic
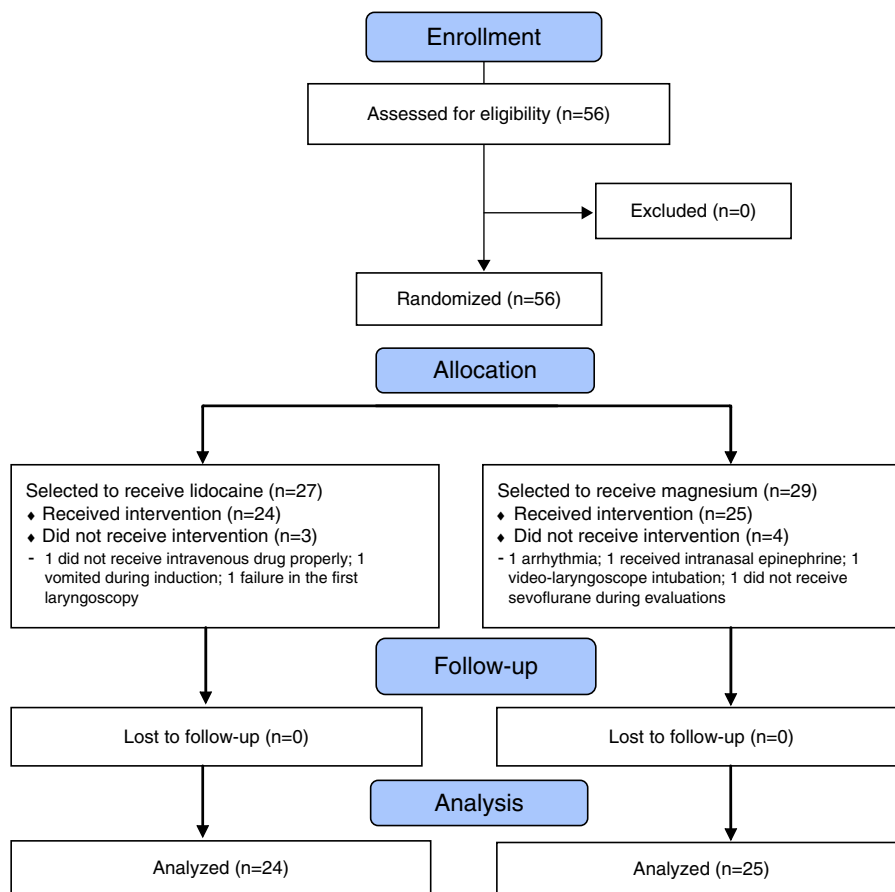
Figure 1 Flowchart of randomization.

disease, atrioventricular block of any degree, known cardiac arrhythmias, heart failure, renal failure of any kind, on beta blockers or calcium channel blockers, expected difficult intubation, and BMI $\geq 35\,kg \cdot m^{-2}$ were excluded. Patients who had undergone neuraxial block before the anesthetic induction, who refused to participate after informed consent presentation, required two or more attempts at laryngoscopy for orotracheal tube placement, as well as those with any other condition that, in the researchers' opinion, could pose risks to the patient or interfere with the study objectives were also excluded.

Of the 56 patients selected for the study according to the inclusion criteria, seven were excluded during assessments (Fig. 1) for patients' safety reasons or issues not covered by the Protocol. Four patients from Group M (magnesium sulfate) were excluded due to frequent ventricular extrasystoles, introduction of nasal swab of adrenaline before the end of the assessments, intubation with video-laryngoscope and lack of sevoflurane in the vaporizer not checked during the evaluations. Three patients from Group L (lidocaine) were excluded due to leakage of drugs (loose fixation of venous access), another due to vomiting with consequent aspiration under mask ventilation, and another for intubation failure in the first laryngoscopy.

Patients who met the inclusion criteria were selected and received an identification number, according to the order of inclusion in the study. The investigators responsible for assessing the study period were blind to group allocation.

Patients were randomized using a list of numbers generated in random order. An investigator not involved with data assessment randomly assigned the patients to one of two groups using sealed envelopes containing a numeric sequence generated in random order, recorded their data in medical charts, prepared the infusion pump and delivered it in the operating room, so the investigators were unaware of which drug is used.

In the operating room, the patient was first identified, followed by standard monitoring with electrocardiogram (ECG), saturation of peripheral oxygen (SpO_2), noninvasive blood pressure (NIBP), and bispectral index (BIS). Venipuncture was performed at the discretion of the anesthesiologist, in accordance with the surgery/anesthesia scheduled (admission time). Subsequently, midazolam $0.05\,mg \cdot kg^{-1}$ was used as premedication. After two minutes (time 2 post-MDZ), infusion with the study drug was started with 2% lidocaine ($2\,mg \cdot kg^{-1}$) without vasoconstrictor (Xylestesin, Cristália®) or magnesium sulphate ($30\,mg \cdot kg^{-1}$), both diluted in 15 mL of solution and infused in 10 min by continuous infusion pump (CIP). At the end of infusion (CIP end time), pre-oxygenation and anesthetic induction with intravenous fentanyl $2\,mcg\,kg^{-1}$ were performed, followed by propofol $2\,mg \cdot kg^{-1}$ and rocuronium $0.6\,mg \cdot kg^{-1}$ (post-induction time). Laryngoscopy was performed three minutes after the end of the rocuronium injection and if the BIS value was equal to or less than 50 (post-OTI time). If the BIS value was not reached, a venous increment of propofol ($1\,mg \cdot kg^{-1}$) was

administered. After orotracheal intubation, anesthesia was maintained with 2% inhaled sevoflurane, and new measurements were taken three and six minutes after intubation (3′ post-OTI and 6′ post-OTI). Hypertension was considered when the BP values were 20% above baseline values or SBP >140 mmHg. Hypotension was considered when BP values were lower than 20% of baseline or SBP < 90 mmHg. Tachycardia was considered when HR was higher than 20% of baseline or HR > 100 bpm. Bradycardia was considered when HR values were lower than 50 bpm.

The primary endpoint was to determine the effects of lidocaine and magnesium sulfate (Group L vs. Group M) on SBP immediately after intubation (post-OTI). The secondary endpoints were the assessment of changes in SBP, DBP, HR, and BIS before and after the administration of study drugs, its changes within six minutes after intubation, as well the identification of adverse events with the use of both techniques.

Considering the primary outcome of SBP immediately after intubation (post-OTI PAS), a 24% variance with 20% effect difference, two-tailed alpha error of 5% and power of 80%, the calculated sample size would be 25 patients in each group.

Statistical analysis was performed with the XLSTAT software for Excel. Shapiro–Wilks test was used to determine the normal distribution of continuous variables. All continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as number of patients or percentage (%). Quantitative variables with normal distribution were assessed using the Student's t-test for independent samples; variables without normal distribution were assessed using the Mann–Whitney nonparametric U test; and categorical variables using the chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered significant. Data were expressed as mean ± SD (mean, standard deviation) or absolute numbers.

Results

There was no statistical difference in both groups regarding age, sex, weight, height, and BMI, as well as physical status classification by ASA. The drugs taken as antihypertensive agents by the study patients were diuretics, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitors, with no statistical difference in the number of hypertensive patients or users of drugs from each medication class (Table 1).

There was no statistical difference between groups in HR, SBP, DBP and BIS values at admission; after midazolam, infusion pump, and induction times. There was an increase in HR, SBP and DBP in both groups after laryngoscopy compared to baseline. Group M had a statistically significant increase in SBP (p = 0.018) and DBP (p = 0.0467) post-OTI (Fig. 2), but of little clinical importance. There were higher pressure values in the 3rd and 6th minutes post-OTI in Group M, but without statistical significance. After this period, both groups showed a gradual reduction in blood pressure values. There was a trend to higher HR values in the continuous infusion post-pump time (CIP end) in Group M, also with no statistical difference. There was no statistical difference in HR values at time points (Fig. 3). There was an increase in heart rate after laryngoscopy in both groups, followed by gradual decline. Regarding BIS values, both groups showed a similar gradual decrease trend up to the induction, followed by an increase after intubation, without statistical difference (Fig. 4).

There was a tendency to hypotension in Group L, defined as a decrease over 20% of the baseline SBP or SBP < 90 mmHg, but without statistical significance (p = 0.062). No patient received atropine or ephedrine. In Group M, three patients (12%) had episodes of hypertension (increase in SBP >20% of baseline) compared to one patient (4%) in Group L, with no statistical difference between groups. In Group M, seven patients (28%) had tachycardia compared to three patients

Table 1 Demographic and clinical data of patients.

	Group L	Group M	p
Age (years)	48.54 ± 12.28	43.32 ± 13.63	0.1651
Weight (kg)	71.30 ± 14.48	71.08 ± 13.29	0.95
Height (cm)	164 ± 10	168 ± 9	0.1328
BMI (kg m^{-2})	26.47 ± 3.6	25.22 ± 3.69	0.2372
Sex (n)			0.879
Male	13	13	
Female	11	12	
Physical state (n)			0.32
ASA I	11	15	
ASA II	13	10	
SAH (n)	7	3	0.098
Drugs used (n)			
Diuretics (n)	4	1	0.143
ARA	4	3	0.641
ACE	3	0	0.068

Values are expressed as mean ± DP and numbers; there was no statistical difference between groups. BMI, body mass index; SAH, systemic arterial hypertension; ARA, angiotensin receptor antagonist; ACE, angiotensin converting enzyme inhibitor.
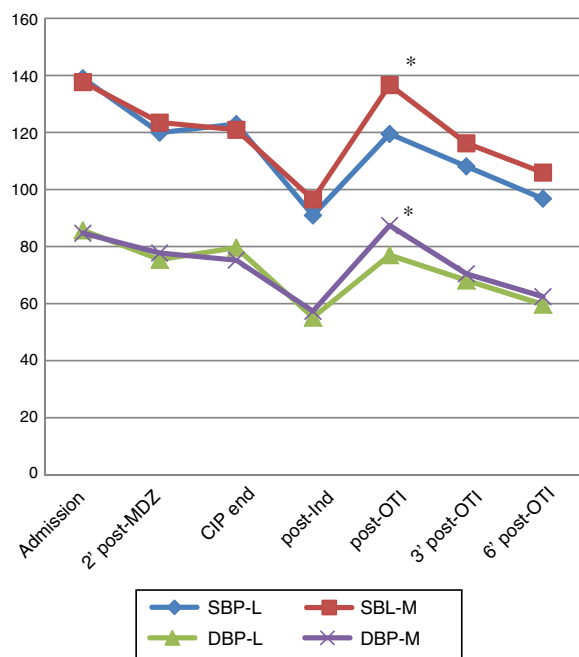
Figure 2 Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. There was statistical difference in the post-OTI time (*$p = 0.0180$ for SBP, and *$p = 0.0467$ to DBP). MDZ, midazolam; CIP, continuous infusion pump; Ind, anesthetic induction; OTI, orotracheal intubation.
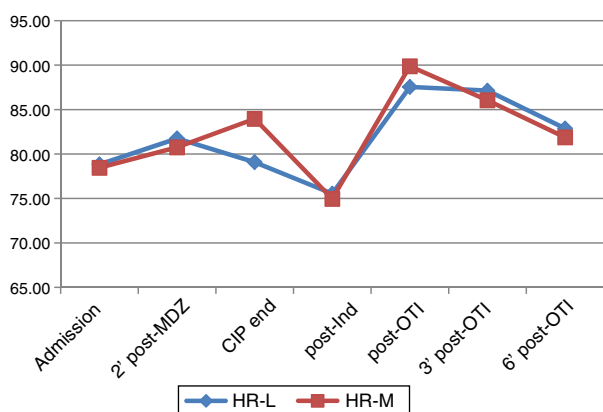

Figure 3 Mean heart rate values. There were no statistical differences. HR, heart rate; MDZ, midazolam; CIP, continuous infusion pump; Ind, anesthetic induction; OTI, orotracheal intubation.

(12%) in Group L, also with no statistical difference. There were no episodes of bradycardia in both groups (Table 2).

Discussion

Similar to the results reported by Ramires et al.[10] and Nooarei et al.[7], we observed a tendency to increased heart rate in Group M at the end of magnesium sulfate infusion, which can be physiologically explained by the direct vasodilator effect of this drug.[2,7,10,11] Despite its vasodilator properties, there was a greater tendency to hypotension in
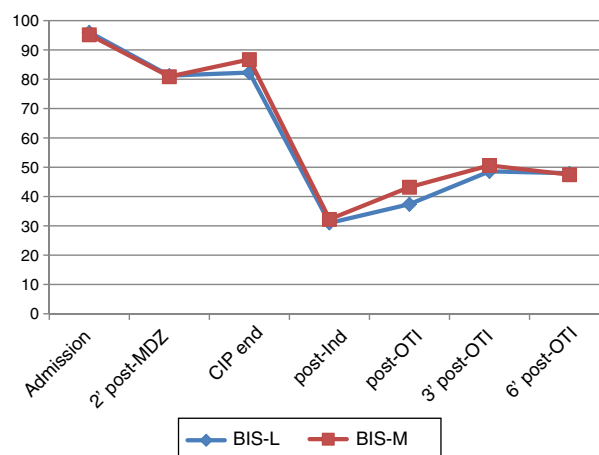

Figure 4 Mean bispectral index (BIS) values; there was no statistical difference. MDZ, midazolam; CIP, continuous infusion pump; Ind, anesthetic induction; OTI, orotracheal intubation.

Table 2 Intraoperative data.

	Group L (n = 24)	Group M (n = 25)	p
Ephedrine (n)	0	0	1.0
Atropine (n)	0	0	1.0
Hypotension (n)	13	7	0.062
Hypertension (n)	1	3	0.317
Tachycardia (n)	3	7	0.178
Bradycardia (n)	0	0	1.0

Data are expressed as number of patients. Group G, lidocaine; Group M, magnesium sulfate. There was no statistical difference between groups.

Group L, but without statistical significance. There was no use of vasopressor in patients, as hypotension was observed immediately before laryngoscopy, a time known to increase vasomotor tone.

Airway management during laryngoscopy and intubation cause physiological changes that can be harmful to a number of patients.[12] Pharynx, larynx, trachea, and carina are highly innervated by sympathetic and parasympathetic fibers. Defensive reflex responses to airway manipulation include tachycardia, bronchospasm, increased blood pressure and intracranial pressure. Studies have shown that laryngoscopy causes 20 mmHg increase in systolic blood pressure[12–17] and a simple tracheal suction causes at least a 5 mmHg increase in intracranial pressure.[12,18,19]

Lidocaine and magnesium sulfate are widely used in order to decrease the hemodynamic response to airway management, with proven effectiveness.[1,3,7,10] Magnesium sulfate blocks the release of catecholamines from adrenergic nerve terminals and adrenal gland,[1,7,10] has cardioprotective and antiarrhythmic action,[10,20] and induces coronary and systemic vasodilation by antagonizing calcium ion in vascular smooth muscle.[1,7,10,21] Lidocaine has an antagonistic action on sodium channels, NMDA receptors, reduces the release of substance P, and has glycinergic action,[8,9] resulting in decreased airway reactivity.[4]

In a similar study performed by Nooraei et al., the authors compared the effect of lidocaine and magnesium sulfate on the hemodynamic variables of laryngoscopy and found better control of blood pressure values with magnesium sulfate, although with increased HR.[7]

Puri et al.[1] also compared the effects of magnesium sulfate and lidocaine on cardiovascular response to intubation in coronary artery disease patients undergoing CABG and found better attenuation of the hemodynamic variables with magnesium sulfate. The hemodynamic results were higher cardiac index, minimum increase in HR, and significant reduction in systemic vascular resistance. In this study, the authors observed that three patients in Group L showed ST segment depression, while this finding was not observed in Group M.

The above results diverge from the present study probably due to the difference in used doses of the drugs studied. Noorei et al.[7] used magnesium sulfate (60 mg·kg^{-1}) and lidocaine (1.5 mg·kg^{-1}) and Puri et al.[1] used magnesium sulfate (50 mg·kg^{-1}) and lidocaine (1 mg·kg^{-1}). We used magnesium sulfate (30 mg·kg^{-1}) because, according to Panda et al.,[3] it is the optimal drug dose to attenuate the hemodynamic response to intubation in hypertensive patients. In this study doses were compared at 30, 40, and 50 mg·kg^{-1} of magnesium sulfate and 1.5 mg·kg^{-1} of lidocaine and it was concluded that magnesium sulfate maintains better stability compared to the pretreatment with lidocaine and that the use of doses at 40 and 50 mg·kg^{-1} led to more episodes of hypotension requiring intervention.[3] Therefore, our choice was to use magnesium sulfate 30 mg·kg^{-1}, in order to avoid complications during the procedure. The dose of lidocaine was chosen based on the work by Vivancos et al.[4]

Our study was performed with healthy patients scheduled for elective surgeries. Our technique of anesthesia induction caused some degree of hypotension, which was well tolerated in this population. Therefore, our results may not extend to emergency surgery or elderly patients or patients ASA 3–4 in which the hemodynamic tolerance may be poor. Magnesium may cause a dose-dependent potentiation of neuromuscular blockers (NB), which was not monitored in our study. So one should be cautious when using MgSO4 with a non-depolarizing NB,[22] such as rocuronium, for short surgeries or in special situations, when a difficult mask ventilation or intubation is expected.

Conclusion

Our study showed that lower magnesium sulfate doses are sufficient to attenuate the hemodynamic response to tracheal intubation, with results similar to lidocaine. We conclude that the used doses of magnesium sulfate and lidocaine have good efficacy and safety for hemodynamic control during laryngoscopy and intubation, presenting as an option to mitigate the stimulation of upper airway in patients undergoing general anesthesia.

Conflicts of interest

The authors declare no conflicts of interest.

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