

also be reviewed by the authors, *effectiveness* is the term suggested;

- Finally, I leave as a recommendation the observation to the authors that there are larger doses, equally safe and equally effective, that could have been tested in this clinical trial and increased the degree of information related to the topic.³

I congratulate the authors for the brilliant initiative, while celebrating at the same time the possibility of creating this line of research in anesthesia in Brazil. Thank you for the opportunity to contribute to this topic.

Conflicts of interest

The author declares no conflicts of interest.

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Reply to the letter to the Editor[☆]



Resposta à carta ao Editor

Dear Editor,

We thank Barbosa's¹ letter in which he appreciates our work and praises the study "Effects of lidocaine and magnesium sulfate in attenuating hemodynamic response to orotracheal intubation: a single-center, prospective, double-blind, randomized study" carried out in our service.² For us, author and author's guest to write this replay, it is only fair that we respond with attention to all questions, within our limitations:

- Question: The authors refer to a discrete statistical difference, which does not allow the reader to draw his own conclusions: "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." The values should be demonstrated in text because, as it is in Figure 2, it is not possible to capture the magnitude of them, so that the lack of clinical importance does not represent absence of biological relevance.

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[☆] Author's reply to the Letter to the Editor: Effects of lidocaine and magnesium sulfate in attenuating hemodynamic response to orotracheal intubation: a single-center, prospective, double-blind, randomized study.

Regarding Item 1, it was really flawed, but not intentional, on our part to omit these data. The missing data are on Table 1.

- Question: Data were, in part or in whole, analyzed over time and patients also received anesthetics, in addition to the medications tested, which may be additional or not. It is known that magnesium sulfate has a prolonged clinical effect after venous use, whereas lidocaine has a

Table 1 Comparison of the mean \pm standard deviation of blood pressure in mmHg at the different times of the study.

SBP	Group L	Group M	p-Value
Admission	139 \pm 19.1	137.7 \pm 17.7	0.8072
Post-MDZ	119.9 \pm 15.5	123.5 \pm 14.3	0.4055
CIP end	122.9 \pm 17.7	120.9 \pm 16.6	0.6657
Post-IND	90.9 \pm 16.1	96.5 \pm 16.3	0.1912
Post-OTI	119.5 \pm 24.6	134 \pm 24.6	0.0180 ^a
3' Post-OTI	108.1 \pm 22.3	116.2 \pm 16.2	0.1482
6' Post-OTI	96.8 \pm 17.3	105.9 \pm 16.2	0.0520
DBP	Group L	Group M	p-Value
Admission	85.7 \pm 12.6	84.6 \pm 11.5	0.7680
Post-MDZ	75.4 \pm 10.7	77.7 \pm 10.2	0.4473
CIP end	79.6 \pm 11.8	75.2 \pm 15.1	0.2646
Post-IND	55.1 \pm 11	57.3 \pm 11.3	0.4956
Post-OTI	77 \pm 19.9	87.4 \pm 15.2	0.0467 ^a
3' Post-OTI	68.1 \pm 18.3	70.4 \pm 12.8	0.6189
6' Post-OTI	59.6 \pm 14.9	62.1 \pm 11.6	0.5192

SBP, systolic blood pressure; MDZ, midazolam; CIP, continuous infusion pump; IND, induction (of anesthesia); OTI, orotracheal intubation; DBP, diastolic blood pressure.

^a Statistically significant.

short protective effect against magnesium. Thus, there are two factors that must be considered in this statistical analysis: time and treatment. The best statistical test to be performed in this situation is two-way ANOVA. The results analyzed as they are in the text may be erroneously positive, and the possibility of a type I error in this study is clearly perceived.

Regarding Item 2, we disagree with the statement. Two-way ANOVA is applicable when there are a numerical dependent variable and two categorical independent variables.^{3,4} Time is a numerical variable, and this data collection design is known as repeated measures. ANOVA with repeated measures or a non-parametric option (such as mixed effects models) is indicated in these situations, not two-way ANOVA.^{3,5} Consider the following: there is no independence between measures in relation to time (historical dependence), which violates an important assumption of two-way ANOVA.^{3,4} And, contrary to what has been stated, repeatedly using hypothesis tests at each time-pair increases the number of tests and also the incidence of false-positive, one of the main reasons for repeated measures ANOVA.⁵ On the other hand, several factors prevent us from using repeated measures ANOVA in this sample because we would violate assumptions, such as sphericity and normality (note that time between measurements is not regular). Mixed effects models could be applied; however, due to its low sensitivity, they require very large samples, being of little use in this sample. Furthermore, considering that the main objective of the study is the one used to calculate the sample size, that is, the systolic blood pressure simple variation after orotracheal intubation (OTI), performing repeated measures analysis that were not predicted would be characterized as data mining, which would be inappropriate.

- (3) Question: If the authors consider correct the use of the Student's *t*-test, or more appropriately in some cases the Mann-Whitney *U* test, according to the text, they should have corrected the *p*-value with the procedure for multiple hypothesis correction test, instead of considering only 5% as the level of significance in all analysis. The possibility that the result was positive in the statistical analysis and occurred at random is 5%. Correcting the *p*-value would decrease the probability of the statistical result random occurrence. Thus, the possibility of type I error in this study is clear.

Regarding Item 3, we partially agree. Many authors recommend that the exact *p*-values should be published,⁶ since there is no consensus regarding the best method for correction using multiple tests, and the critical *p*-value correction being considered for significance rather than correcting the *p*-value of each hypothesis test performed as a well-recommended alternative.⁷ In this study, using the correction method proposed by Bonferroni, for example, the critical *p*-value would be $5\%/16=0.003125\%$. Bonferroni's correction is the most conservative, but there are those who discuss whether it applies to the sole test of the study main outcome or only to all other additional hypothesis tests, or even whether it should be used.^{8,9}

- (4) Question: The authors' objective was "to compare the efficacy of intravenous magnesium sulfate versus

lidocaine on this reflex hemodynamics after laryngoscopy and tracheal intubation". The authors' conclusion was "magnesium sulfate and lidocaine have good efficacy and safety for hemodynamic management in laryngoscopy and intubation", which does not fit the proposed objective. It is necessary that the authors relate which were the efficacy variables and the safety variables so that the conclusion is better understood. It should be noted that the term efficacy should generally be used in studies whose execution conditions are ideal, as with laboratory studies. The authors should also review this term, a suggestion is to use the term effectiveness.

Regarding Item 4, there was really a problem in drafting conclusions. The most accurate conclusion would be: our study was not able to detect a statistically significant difference in post-OTI systolic blood pressure (SBP) among the groups that received magnesium sulfate or lidocaine. Because it is a study of superiority (it is not written, but as we do not use margin of inferiority in calculating the sample size, only this option is compatible), the study may not conclude, besides, everything else is discussion. We reinforce for other readers that if no difference is found in a study of superiority, it does not mean that there is equality or non-inferiority.

- (5) Question: Finally, I leave as a recommendation the authors' observation that there are larger doses, equally safe and equally effective, that could have been tested in this clinical trial and increased the degree of information related to the topic.

Regarding Item 5, we appreciate the suggestion and will consider it in future studies.

Conflicts of interest

The authors declare no conflicts of interest.

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