Lidocaine alone or combined with Magnesium Sulfate stabilizes hemodynamic parameters during General Anesthesia without prolonging the Neuromuscular Blockade: a randomized, double-blind, controlled trial

Waynice N. Paula-Garcia (✉ wgarcia@fmrp.usp.br)
University of Sao Paulo Faculty of Medicine of Ribeirao Preto: Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto
https://orcid.org/0000-0003-0020-5295

Gustavo H Oliveira-Paula
University of Sao Paulo Faculty of Medicine of Ribeirao Preto: Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto

Hans D de Boer
Martini Hospital: Martini Ziekenhuis

Luís Vicente Garcia
University of Sao Paulo Faculty of Medicine of Ribeirao Preto: Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto

Research article

Keywords: lidocaine, magnesium sulfate, neuromuscular blockade, general anesthesia, hemodynamic parameters

DOI: https://doi.org/10.21203/rs.3.rs-69399/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background

Lidocaine and magnesium sulfate have become increasingly utilised in general anaesthesia. The present study evaluated the effects of these drugs, isolated or combined on the hemodynamic parameters as well as on the cisatracurium-induced neuromuscular blockade (NMB).

Methods

At a University hospital, 64 patients, ASA physical status I and II, undergoing elective surgery with similar pain stimulus, were randomly assigned to four groups. Patients received a bolus of lidocaine and magnesium sulfate before the tracheal intubation and a continuous infusion during the operation respectively: 3 mg.kg\(^{-1}\) and 3 mg.kg\(^{-1}\).h\(^{-1}\) (Lidocaine -L group), 40 mg.kg\(^{-1}\) and 20 mg.kg\(^{-1}\).h\(^{-1}\) (Magnesium - M group), equal doses of both drugs (Magnesium plus lidocaine - ML group) and, an equivalent volume of isotonic solution (Control - C group). Haemodynamic parameters and neuromuscular blockade features were continuously monitored until spontaneous recovery of the Train of Four ratio (TOF=0.9).

Results

The Lidocaine group presented a highly significant small hemodynamic fluctuation during the anesthesia induction and maintenance period (p<0.0001) with no change at NMB. The magnesium sulfate infusion alone or combined with lidocaine prolonged all the recovery characteristics (p< 0.0001). The onset time was not influenced by the studied drugs. The percentage of patients who achieved a TOF ratio of 90% without recovering the first Twich (T1-95%) was higher in the M and ML groups.

Conclusion

Intravenous lidocaine plays a significant role in the hemodynamic stability in patients under general anesthesia without exerting any additional impact on the NMB even combined with magnesium sulfate. Aside from prolonging all NMB recovery characteristics without altering the onset speed, magnesium sulfate enhances the TOF recovery rate without T1 recovery. Our findings may aid clinical decisions involving the use of these drugs by encouraging their association in multimodal anesthesia or other therapeutic purposes.

Trial registration

NCT02483611 (registration date: 06-29-2015).

Background

Anesthetic additive drugs like lidocaine and magnesium sulfate have become increasingly utilized, alone or in combination, in general anesthesia to meet various objectives, such as: postoperative pain
reduction, reduced and more balanced anesthetic doses, hemodynamic stabilization, and improvement of surgical conditions.¹⁻⁹ A combination of lidocaine and magnesium sulfate in a multimodal opioid-sparing or even opioid-free anesthesia approach may reduce or eliminate the use of opioids in the perioperative period.¹⁰,¹¹ Opioid-sparing or opioid-free anesthesia is a relatively new strategy that is increasingly being used in daily anesthesia practice. Several studies have demonstrated benefits from this approach, including in cancer patients, elderly and obese patients, or those with obstructive sleep apnea.¹² Drugs like lidocaine and magnesium sulfate are frequently used in combination with neuromuscular blocking drugs of which the latter may contribute to residual neuromuscular blockade, and hemodynamic instability during anesthetic procedures. Drugs like lidocaine and magnesium sulfate are frequently used in combination with neuromuscular blocking drugs, of which the latter may contribute to residual neuromuscular blockade and hemodynamic instability during anesthetic procedures. Approximately 40% of patients admitted to the post-anesthesia care unit have residual neuromuscular blockade¹³, what increases morbidity and mortality, but only 1–3% of patients with residual blockade develop clinically apparent events.¹³,¹⁴

Magnesium sulfate infusion administered before anesthesia has been found to increase the speed of onset of a rocuronium, cisatracurium- or vecuronium-induced neuromuscular blockade (NMB) without necessarily enhancing its duration.¹⁵⁻¹⁷ Furthermore, magnesium sulfate infusion re-establishes a clinically relevant degree of muscle paralysis in patients who had recovered from paralysis and causes a significant, prolonged NMB when induced by a single dose of the neuromuscular blocking drug rocuronium.¹⁸¹⁹ One study showed prolonged rocuronium-induced NMB after pre-treatment of magnesium sulfate, however no change in the speed of onset.²⁰

Previous studies have shown that local anesthetics, such as lidocaine, interact with neuromuscular blocking drugs.²¹⁻²³ Cardoso et al. noted that the combination of lidocaine and rocuronium increased the time to recovery of T1-25%, T1-75%, and T1-95%, but did not prolong the time to final recovery.²⁴ More recent studies evaluating the clinical effects of lidocaine, in lower dosage, on the neuromuscular blocking drugs cisatracurium and rocuronium have demonstrated no changes in recovery of NMB characteristics or speed of onset.²⁵⁻²⁷

Considering the growing perioperative clinical applications of both lidocaine and magnesium sulfate, the possibility of using these drugs in combination increases. A combination of these drugs may not only be beneficial for surgical patients regarding opioid-sparing effects but may also influence NMB characteristics and promote changes in hemodynamic parameters. Thus, this study's main aim was to evaluate the effects of the lidocaine and magnesium sulfate, isolated or combined, in higher dosage, on the hemodynamic parameters as well as on the cisatracurium-induced neuromuscular blockade (NMB). Considering that studies have shown that lidocaine infusion does not affect NMB, we tested the hypothesis that combined use of lidocaine with magnesium sulfate does not affect cisatracurium-induced NMB compared with magnesium sulfate infusion alone.²⁵⁻²⁷
Methods

In this prospective, randomized, double-blind, controlled trial, sixty-six patients [American Society of Anesthesiologists (ASA) physical status I to II, aged 18 to 60 years] were recruited who were scheduled for surgery (estimated surgical time greater than 90 min, with similar pain stimulus and no need for a neuromuscular block during the surgical procedure). Exclusion criteria were patients with diseases or on medications known to interfere with neuromuscular transmission, hepatic or renal dysfunction, electrolyte abnormalities, allergy to drugs used in the study, body mass index <18 or >29 kg.m$^{-2}$, expected to have difficulties during mask ventilation or intubation, pregnant or breastfeeding.

Using sealed opaque envelopes, numbered sequentially, sixty-four patients were randomly allocated to four parallel treatment groups (figure 1). The seal of the envelope was broken before the induction of general anesthesia by trained study personnel not involved in the data collection. Throughout the perioperative period, care providers, patients, and research team members were blinded to group assignment. The L group received lidocaine 3 mg.kg$^{-1}$ as an IV bolus before the induction of anesthesia and 3 mg.kg$^{-1}$.h$^{-1}$ IV continuous infusion during the operation period; the M group received magnesium sulfate 40 mg.kg$^{-1}$ as an IV bolus before the induction of anesthesia and 20 mg.kg$^{-1}$h$^{-1}$ IV continuous infusion during the operation period. The ML group received equal doses of magnesium sulfate combined with lidocaine at the same conditions during the operation period. The control group received an equivalent volume of isotonic solution.

Patients were monitored using electrocardiography, noninvasive blood pressure measurements, pulse oximetry, capnography (Draeger Medical Systems, Telford, Pennsylvania, USA). Total Intravenous (IV) Anesthesia was standardized for all patients and performed without the use of benzodiazepines, using a propofol target dose (plasma targeting, Injectomat TIVA Agilia, Brazil) of 4 µg.mL$^{-1}$ and a remifentanil infusion of 0.5 mg.kg$^{-1}$.min$^{-1}$. After induction, the propofol infusion target was decreased to 2.5 µg.mL$^{-1}$, and infusion of remifentanil was adjusted to 0.1-0.3 µg.kg$^{-1}$.min$^{-1}$ as needed. If systolic arterial pressure (SAP) or HR increased or decreased by > 30% of baseline for > 60 sec, remifentanil infusion was respectively increased/decreased at 0.05 µg kg$^{-1}$ min$^{-1}$ until achieving the goal value within the range. If necessary, ephedrine bolus (2.5 to 5 mg) was allowed. Hemodynamic parameters were considered stable when BP and HR were within 20% of baseline values.

After induction of anesthesia and loss of consciousness, the neuromuscular function was assessed by monitoring the adductor pollicis muscle via acceleromyography with a TOF-Watch SX device (Organon Ireland Ltd., a subsidiary of Merck & Co., Inc., Swords, Co., Dublin, Ireland) according to the neuromuscular research consensus.\textsuperscript{28}

The monitoring system was positioned on the side opposite to the blood pressure cuff and IV line. Pediatric surface electrodes (Red Dot$^{®}$, 3M Health Care, Neuss, Germany) were placed on cleaned skin over the ulnar nerve on the volar side of the wrist. The transducer’s position was secured by placing the thumb in a hand adapter and fixed a temperature sensor at the distal end of the forearm. TOF tracing was
stabilized by administering 1 min of TOF repetitive stimulation, followed by 5 s of 50-Hz tetanus
stimulation, and then another period of repetitive TOF stimulation for 3-4 min. CAL 2 mode determined
the supramaximal threshold and to calibrate the transducer of the accelerometer. After calibrating the
device and stabilization, the mean of three TOF's values was recorded in each patient and used as a
reference. Then, the TOF recovery value was considered the measured equivalent of 90% of this
predefined value. The same procedure was performed for the T1 measurements. Then, bolus doses of
solutions were administered to assigned groups over 5 min. Subsequently, a total of 0.15 mg.kg\(^{-1}\)
cisatracurium over 5 seconds (time point zero) was administered, which was followed by tracheal
intubation when the TOF ratio reached zero. Patients were monitored until they achieved spontaneous
recovery from NMB (TOF ratio=0.9). Values of T1, T2, T3, T4, and TOF ratio, as well as skin temperature,
were recorded. No additional cisatracurium injections were permitted. After measuring onset time,
stimulation mode was changed to TOF (2 Hz, stimulus duration of 200 µs, square wave, 15 s intervals).
Finally, adequate normalization of the TOF recovery results according to the baseline values was
provided to detect residual paralysis reliably.

All neuromuscular monitoring data were transferred in real-time and stored on a laptop using the TOF-
Watch SX monitor computer program (version 2.5.INT; Organon Ltd., Dublin, Ireland).

The following variables were measured:

1. Speed of onset – time in seconds required to reduce T1 response to 5% of initial contraction force.
2. Clinical duration (Dur25%) – elapsed time in minutes for T1 response to recover 25% of its initial
   value.
3. Recovery index – elapsed time in minutes between the recovery of the T1 response from 25% of its
   initial value (Dur25%) to 75% of its initial value (Dur75%).
4. Pharmacological duration – elapsed time in minutes for the T1 response to recover 95% of its initial
   value (Dur95%).
5. Spontaneous recovery – time in minutes to the recovery of T4/T1 to 90% of its initial value.

Body temperature, respiratory (end-tidal CO2) and hemodynamic parameters (systolic, diastolic, mean
blood pressure and heart rate) were recorded and annotated at various times: M1- when the patient
arrived in the operating room; M2- immediately before induction of anesthesia; M3- before the infusion of
the tested solutions (saline, magnesium sulfate or magnesium sulfate associated with lidocaine); M4-
five minutes after M3 (end of the infusion loading dose of test solutions); M5 immediately before
intubation; M6- one minute after tracheal intubation and M7 every fifteen minutes until the end of the
study. Heating elements were used to maintain their skin and central temperatures above 32 and 36 °C,
respectively. All unexpected events that occurred during the study were recorded as adverse effects.

The Shapiro-Wilk test was used to assess normality. The clinical and demographic characteristics are
expressed as the means ± SD or medians (IQR [range]) and were compared by analysis of variance, the
Kruskal-Wallis test, or the chi-square test, where appropriate. Given that studies have suggested that the
area under the curve (AUC) can provide a more accurate analysis of the hemodynamic data\textsuperscript{29,30}, this approach was used to compare the hemodynamic responses among the study groups. The pharmacodynamic variables (i.e., speed of onset, clinical duration, recovery rate, and total duration) were represented as box-and-whisker plots showing the range, quartiles, and median. The AUCs of the changes in mean arterial pressure (MAP) and HR were expressed as mean ± SD (normally distributed data). The pharmacodynamic variables were compared among the groups via the Kruskal-Wallis test, followed by Dunn's multiple comparison test. The AUCs of the changes in mean arterial pressure (MAP) and HR were compared among the groups by the one-way ANOVA followed by Tukey multiple comparison test. Both multiple comparison tests were used to control the type I error at 5%. The percentage of patients who achieved a TOF ratio of 90\% without reaching 95\% recovery of the first twitch (T1) response was compared among the groups by the chi-square test. A p-value <0.05 was considered statistically significant for all outcome variables.

For the sample size calculation, we considered a previous study showing that magnesium sulfate prolongs rocuronium-induced NMB\textsuperscript{16}. Having chosen a significance level of 5\% and a power of 80\%, we used the spontaneous recovery means of that previous study (73.2 ± 22 min with MgSO\textsubscript{4} and 57.8 ± 14.2 min with saline) to calculate the number of participants required to detect a similar effect\textsuperscript{31}. The calculation revealed that N=14 patients were needed per group. As we included N=15-16 per group, we had 85\% power to detect the same differences as planned a priori.

**Results**

Between 2015 and 2018, 64 patients were recruited and randomized in this study. Patient characteristics are shown in Table 1. Most patients were ASA1, who underwent rhinoplasty and reductive mastopexy. There was no significant difference in the baseline variables between the groups. After data collection, one patient was excluded from the control group because her surgical procedure was completed in less than 90 min (figure 1).

Hemodynamic parameters among study groups, evaluated by the AUCs for changes in MAP and HR at the six times points during anesthesia induction, are shown in figure 2 (A-D). The lidocaine group presented a significant small fluctuation on MAP and HR measures during anesthesia induction (Total AUC ± SE: L Group- 18.11 ± 12.17 and 6.49 ± 7.01 respectively; compared to the other groups: C group- 59.34 ± 11.87 and 20.56 ± 20.34 respectively; M group-53.41 ± 9.85 and 25.79 ± 11.92; ML Group-52.88 ± 8.97 and 16.49 ± 14.05; p<0.0001. During the maintenance phase of anesthesia, the study groups presented similar behavior: Total AUC ± SE: L Group- 932.6 ± 307.6 and 144.3 ± 106.3 respectively; compared to the other groups: C group-1609 ± 281.5 and 548.50 ± 296.1 respectively; M group- 1375 ± 248.7.85 and 387.7 ± 195.0; ML Group-1453 ± 268.4 and 295 ± 192; p<0.0001.

Concerning to the NMB characteristics, lidocaine infusion did not exert any effect. However, an infusion of magnesium sulfate, associated, but not lidocaine, prolonged all NMB recovery features (p<0.0001,
Without changing the speed of onset of cisatracurium (C group: 147.8±29.75; L group: 134.9±29.62; M group: 146.9±45.27; ML group: 142.8±42.80, p=0.7624, figure 3).

Interestingly, the percentage of patients who achieved a TOF ratio of 90% without reaching T1-95% was higher in the M and ML groups than in the C and L groups (50.0%, 56.2% and 20.0%, 25.0% respectively). There were no adverse events reported in this study.

**Discussion**

This prospective, randomized, double-blind, controlled study evaluated the effects of intravenous lidocaine combined with magnesium sulfate (bolus and continuous infusions) in general anesthesia. The main findings of the study showed that: (a) Intravenous lidocaine plays a significant role for the hemodynamic stability in patients under general anesthesia, without exerting any additional impact on the NMB even combined with magnesium sulfate; (b) Magnesium sulfate prolonged the time of recovery in all pharmacodynamic parameters studied (i.e., clinical duration, recovery index, total duration, and spontaneous recovery); (c) There were no differences in the speed of onset among groups; (d) Patients in the magnesium sulfate groups had higher rates of TOF recovery without T1 recovery than those in the control and L group.

The concept of multimodal general anesthesia has recently extended the idea of balanced anesthesia, including some other additional drugs like lidocaine, magnesium sulfate, β-blockers, and α2-agonists that target different neuroanatomical circuits and multiple neurophysiologic mechanisms. The pharmacologic explanation of the multimodal general anesthesia approach is based on the firmly established observation that when anesthetic drugs of different mechanisms are combined, they typically interact synergistically. Lidocaine and magnesium sulfate indirectly block sympathetic effects and are well established in opioid-sparing multimodal analgesic strategies. Interaction between parenteral magnesium and nondepolarizing neuromuscular blocking drugs has been previously described. Facilitating a neuromuscular blockade with magnesium involves the following mechanisms: decreased pre-junctional release of acetylcholine via inhibition of voltage-dependent calcium channels; reduced sensitivity of endplate to acetylcholine; and attenuating the direct excitability of muscle fibers, presumably by altering electrical threshold of muscle membrane. Typically, magnesium sulfate is administered as a bolus dose of 30–50 mg.kg⁻¹, followed by a maintenance dose of 6–20 mg.kg⁻¹.h⁻¹. Previous studies have shown similar results as described in this study concerning the prolongation of NMB by magnesium using a similar dosage.

Contradictory findings have been reported concerning whether the NMB latency period (speed of onset) is reduced or not by magnesium sulfate pre-treatment. Preadministration of magnesium sulfate (30–50 mg kg⁻¹) infused over 10 minutes has been shown to prolong recovery and reduce the onset time of rocuronium and vecuronium. However, a short period of infusion before administering a neuromuscular blocking drug left onset time unchanged. Also, pre-treatment with magnesium sulfate...
(60 mg kg\(^{-1}\)) infused over 1-minute prolonged recovery but did not reduce the onset time of rocuronium- and pancuronium-induced neuromuscular blockade. These findings possibly reflect differences in neuromuscular blocking drugs' pharmacodynamic properties, and the prolonged infusion time before administering the neuromuscular blocking drug seemed to improve the drug's action.

Our findings corroborate those of Kussman and James.\(^20,40\) Analogous to Kussman's suggestion about rocuronium's pharmacodynamics, one possible explanation for the constant speed of cisatracurium onset observed in our study is that we used a short time's period for magnesium sulfate infusion. Indeed, a 5-min infusion period immediately before muscle relaxant administration provides insufficient time for the magnesium sulfate to reach terminal motor nerves at a high enough concentration to interfere with cisatracurium initiation. Some reports have even shown no enhancement of NMB by magnesium sulfate, using magnesium sulfate only as a pre-treatment dosage.\(^{15,17}\)

Interestingly, many patients in magnesium sulfate infusion groups reached 90% of their initial TOF response without T1 recovering to 95% of its original value. According to Kopman et al.\(^41\), after spontaneous recovery of the TOF ratio to 80% or higher, the T1 response often returns to 150% or higher relative to control value. In contrast, Staals et al.\(^42\) reported findings that were similar to ours. After they achieved the reversal of rocuronium-induced NMB with sugammadex, the authors observed that a full recovery of the TOF ratio was reached while T1 remained depressed. The real meaning of this finding is unknown and probably does not have significant clinical repercussions. Although these authors suggested that using TOF value as a single measure may not be enough to prevent a residual blockade under those particular conditions, other studies observed that magnesium sulfate did not significantly affect the time of reversal of rocuronium-induced neuromuscular blockade by sugammadex.\(^43\)

In our study, the prevalence of individuals in groups M and ML, who recovered their TOF ratio to 90% without recovering of T1, suggests magnesium sulfate's interference. However, further studies are needed to confirm and better understand this effect.

Perioperative IV administration of lidocaine varies among studies based on the dose of lidocaine bolus (100 mg or 1–5 mg kg\(^{-1}\)), infusion during maintenance (1–6 mg kg\(^{-1}\) h\(^{-1}\) or 2–4 mg min\(^{-1}\)) and duration of infusion.\(^{44,45}\) However, the use of doses and lidocaine as high as 5 mg.kg.h\(^{-1}\) infused for 6 hours is reported without adverse effects.\(^46\) Typically, lidocaine dose used in studies assessing its impact on NMB\(^25–27\) has been between 1.5 and 2 mg.kg\(^{-1}\) (bolus) and 2 mg.kg\(^{-1}\).h\(^{-1}\) (maintenance) and results similar to ours were obtained in these studies. Although lidocaine is widely used and is especially useful as an adjuvant during general anesthesia for its analgesic and opioid-sparing effects, few studies have systematically assessed the incidence of adverse effects or optimal dose.\(^44\) We have considered using high doses to evaluate possible hemodynamic changes. Some studies have shown some interactions between local anesthetics and neuromuscular blocking drugs.\(^{21–24}\) However, more recently, studies evaluating the clinical effects of lidocaine on neuromuscular blocking actions of cisatracurium and rocuronium have demonstrated no changes in NMB recovery characteristics or speed of onset periods.\(^{25–}\)
Corroborating these observations, in the present study, lidocaine infusion, even in higher doses, did not result in any additional effects of magnesium sulfate alone on NMB and effectively prevented MAP and HR fluctuations during anesthesia induction and maintenance. Importantly, this hemodynamic stability is particularly relevant in specific conditions, such as in intracranial aneurysm management.\textsuperscript{45}

Surgical patients need to be fully awake at the recovery ward postoperative, with acceptable pain, without respiratory depression, especially for morbid obesity or obstructive sleep apnea.\textsuperscript{12} It is also known that opioids present side effects including postoperative nausea and vomiting, shivering, ileus, and urine retention\textsuperscript{47} and can achieve both short-lasting analgesia and long-lasting hyperalgesia due to their upregulation of compensatory pronociceptive pathways.\textsuperscript{48} In addition, opioids may have detrimental immunological effects and may affect surgical outcomes or a variety of disease processes, including bacterial and viral infections and cancer.\textsuperscript{49, 50} The impact of opioid-mediated immune effects can be particularly dangerous in certain vulnerable populations, such as elderly or immunocompromised patients.

Choosing drugs without hyperalgesia or damaging immune effects may be an essential consideration in anesthesia. Therefore, opioid-free or opioid-reduced anesthesia procedures are justified and have gained popularity.\textsuperscript{51, 52} Given these new situational demands for anesthesia and pain control protocols, evidence that the lidocaine can provide hemodynamic stability during anesthesia and its addition to magnesium sulfate does not add any side effect is valuable. These findings may encourage the lidocaine infusion alone or combined with magnesium sulfate in clinical practice for various therapeutic purposes, including opioid-free/ sparing anesthesia with or without neuromuscular blockers. The mechanisms and the precise dosage regimen for the hemodynamic stability provided by lidocaine warrants further research.

Our study has some limitations. The actual plasma concentrations of cisatracurium were not measured. However, we choose this nondepolarizing neuromuscular blocking agent because its duration of action has low inter-individual variability.\textsuperscript{53} Moreover, its clearance from plasma results from a nonenzymatic degradation whose rate is primarily affected by pH and temperature.\textsuperscript{54} The arterial blood gases were not measured, but we excluded surgical procedures potentially resulting in metabolic acidosis and, also, the mean nasopharyngeal temperatures and end-tidal CO\textsubscript{2} partial pressures were in the normal range and, did not differ between groups.

**Conclusions**

Intravenous lidocaine plays a significant role in the hemodynamic stability in adults patients under general anesthesia without exerting any additional impact on the NMB even combined with magnesium sulfate. Aside from prolonging all NMB recovery characteristics without altering the onset speed, magnesium sulfate enhances the TOF recovery rate without T1 recovery. Our findings may aid clinical decisions involving the use of these drugs by encouraging their association in multimodal anesthesia or other therapeutic purposes.
Abbreviations

ASA American Society of Anesthesiology
AUC Area under curve
CI Confidence interval
CO₂ Carbon dioxide
HR Heart Rate
IQR Interquartile range
IV Intravenous
MAP Mean Arterial Pressure
NMB Neuromuscular blockade
SD Standard deviation
SE Standard error
TOF Train of Four
T₁ first twitch
T₂ second twitch
T₃ third twitch
T₄ fourth twitch

Declarations

Competing interest

Hans D. de Boer has received research grants from Merck and is treasurer of the ERAS Society. The authors declare that they have no other competing interests.

Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available as permission from participants to publicity share the dataset has not been obtained.

**Ethics approval and consent to participate**

This study has been approved by the Institutional Ethics Committee of the Hospital das Clínicas of the Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Brazil (protocol number: 5362/2013). The protocol adhered to the applicable Equator guidelines and was published by ClinicalTrials.gov ID (number NCT02483611)-registration date: 06-29- 2015. https://clinicaltrials.gov/ct2/show/NCT02483611. Written informed consent was obtained from each participant prior to data collection or study intervention.

**Consent for publication**

Not Applicable

**Funding**

Not Applicable

**Authors' contributions**

WNPaula-Garcia and LVGarcia designed and conducted the study, analyzed the data, and wrote the manuscript. GHOliveira-Paula and HDdeBoer analyzed the data and wrote the manuscript. All authors have read and approved the manuscript.

**Acknowledgments:**

We thank the Clinical Hospital of Ribeirao Preto and the postgraduation program that made the development of this work possible. No external funding source was used.

**References**

1. Altermatt FR, Bugedo DA, Delfino AE, Solari S, Guerra I, Munoz HR, et al. Evaluation of the effect of intravenous lidocaine on propofol requirements during total intravenous anaesthesia as measured by bispectral index. Br J Anaesth. 2012;108(6):979–83.
2. Govindarajan R, Shah A, Reddy VS, Parithivel V, Ravikumar S, Livingstone D. Improving the functionality of intra-operative nerve monitoring during thyroid surgery: is lidocaine an option? J Clin Med Res. 2015;7(4):282–5.
3. James MF. Magnesium: an emerging drug in anaesthesia. Br J Anaesth. 2009;103(4):465–7.
4. Kim MH, Oh AY, Han SH, Kim JH, Hwang JW, Jeon YT. The effect of magnesium sulphate on intubating condition for rapid-sequence intubation: a randomized controlled trial. J Clin Anesth. 2015;27(7):595–601.

5. Ryu JH, Koo BW, Kim BG, Oh AY, Kim HH, Park DJ, et al. Prospective, randomized and controlled trial on magnesium sulfate administration during laparoscopic gastrectomy: effects on surgical space conditions and recovery profiles. Surg Endosc. 2016;30(11):4976–84.

6. Shahrami A, Assarzadegan F, Hatamabadi HR, Asgarzadeh M, Sarehbandi B, Asgarzadeh S. Comparison of therapeutic effects of magnesium sulfate vs. dexamethasone/metoclopramide on alleviating acute migraine headache. J Emerg Med. 2015;48(1):69–76.

7. Sun J, Zhou R, Lin W, Zhou J, Wang W. Magnesium Sulfate Plus Lidocaine Reduces Propofol Injection Pain: A Double-blind, Randomized Study. Clin Ther. 2016;38(1):31–8.

8. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M, Steegers MA, et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2016;20(5):655–74.

9. Ventham NT, Kennedy ED, Brady RR, Paterson HM, Speake D, Foo I, et al. Efficacy of Intravenous Lidocaine for Postoperative Analgesia Following Laparoscopic Surgery: A Meta-Analysis. World J Surg. 2015;39(9):2220–34.

10. Bafuma PJ, Nandi A, Weisberg M. Opiate refractory pain from an intestinal obstruction responsive to an intravenous lidocaine infusion. Am J Emerg Med. 2015;33(10):1544 e3–4.

11. Sousa AM, Rosado GM, Neto Jde S, Guimaraes GM, Ashmawi HA. Magnesium sulfate improves postoperative analgesia in laparoscopic gynecologic surgeries: a double-blind randomized controlled trial. J Clin Anesth. 2016;34:379–84.

12. Isono S. Obesity and obstructive sleep apnoea: mechanisms for increased collapsibility of the passive pharyngeal airway. Respirology. 2012;17(1):32–42.

13. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology. 2003;98(5):1042–8.

14. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg. 2010;111(1):120–8.

15. Kim MH, Oh AY, Jeon YT, Hwang JW, Do SH. A randomised controlled trial comparing rocuronium priming, magnesium pre-treatment and a combination of the two methods. Anaesthesia. 2012;67(7):748–54.

16. Czarnetzki C, Lysakowski C, Elia N, Tramer MR. Time course of rocuronium-induced neuromuscular block after pre-treatment with magnesium sulphate: a randomised study. Acta Anaesthesiol Scand. 2010;54(3):299–306.

17. Kim SH, So KY, Jung KT. Effect of magnesium sulfate pretreatment on onset and recovery characteristics of cisatracurium. Korean J Anesthesiol. 2012;62(6):518–23.
18. Hans GA, Bosenge B, Bonhomme VL, Brichant JF, Venneman IM, Hans PC. Intravenous magnesium re-establishes neuromuscular block after spontaneous recovery from an intubating dose of rocuronium: a randomised controlled trial. Eur J Anaesthesiol. 2012;29(2):95–9.

19. Habe K, Kawasaki T, Sata T. [A case of prolongation of rocuronium neuromuscular blockade in a pregnant patient receiving magnesium]. Masui. 2014;63(7):817–9.

20. Kussman B, Shorten G, Uppington J, Comunale ME. Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block. Br J Anaesth. 1997;79(1):122–4.

21. Toft P, Kirkegaard Nielsen H, Severinsen I, Helbo-Hansen HS. Effect of epidurally administered bupivacaine on atracurium-induced neuromuscular blockade. Acta Anaesthesiol Scand. 1990;34(8):649–52.

22. Matsuo S, Rao DB, Chaudry I, Foldes FF. Interaction of muscle relaxants and local anesthetics at the neuromuscular junction. Anesth Analg. 1978;57(5):580–7.

23. Katz RL, Gissen AJ. Effects of intravenous and intra-arterial procaine and lidocaine on neuromuscular transmission in man. Acta Anaesthesiol Scand Suppl. 1969;36:103–13.

24. Cardoso LS, Martins CR, Tardelli MA. Effects of intravenous lidocaine on the pharmacodynamics of rocuronium. Rev Bras Anestesiol. 2005;55(4):371–80.

25. Hans GA, Defresne A, Ki B, Bonhomme V, Kaba A, Legrain C, et al. Effect of an intravenous infusion of lidocaine on cisatracurium-induced neuromuscular block duration: a randomized-controlled trial. Acta Anaesthesiol Scand. 2010;54(10):1192–6.

26. Vivancos GG, Klamt JG, Garcia LV. Effects of 2 mg.kg(-)(1) of intravenous lidocaine on the latency of two different doses of rocuronium and on the hemodynamic response to orotracheal intubation. Rev Bras Anestesiol. 2011;61(1):1–12.

27. Czarnetzki C, Lysakowski C, Elia N, Tramer MR. Intravenous lidocaine has no impact on rocuronium-induced neuromuscular block. Randomised study. Acta Anaesthesiol Scand. 2012;56(4):474–81.

28. Fuchs-Buder T, Claudia C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand. 2007;51(7):789–808.

29. Liu NT, Holcomb JB, Wade CE, Darrah MI, Salinas J. Utility of vital signs, heart rate variability and complexity, and machine learning for identifying the need for lifesaving interventions in trauma patients. Shock. 2014;42(2):108–14.

30. Nobre F, Mion D Jr. Is the area under blood pressure curve the best parameter to evaluate 24-h ambulatory blood pressure monitoring data? Blood Press Monit. 2005;10(5):263–70.

31. Singer J. A simple procedure to compute the sample size needed to compare two independent groups when the population variances are unequal. Stat Med. 2001;20(7):1089–95.

32. Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. Anesth Analg. 2018;127(5):1246–58.
33. Hendrickx JF, Eger El 2nd, Sonner JM, Shafer SL. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anest Analg. 2008;107(2):494–506.

34. Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. Anesthesiology. 2017;126(4):729–37.

35. Dube L, Granry JC. The therapeutic use of magnesium in anesthesia, intensive care and emergency medicine: a review. Can J Anaesth. 2003;50(7):732–46.

36. Do SH. Magnesium: a versatile drug for anesthesiologists. Korean J Anesthesiol. 2013;65(1):4–8.

37. Fuchs-Buder T, Wilder-Smith OH, Borgeat A, Tassonyi E. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. Br J Anaesth. 1995;74(4):405–9.

38. Pinard AM, Donati F, Martineau R, Denault AY, Taillefer J, Carrier M. Magnesium potentiates neuromuscular blockade with cisatracurium during cardiac surgery. Can J Anaesth. 2003;50(2):172–8.

39. Rotava P, Cavalcanti IL, Barrucand L, Vane LA, Vercosa N. Effects of magnesium sulphate on the pharmacodynamics of rocuronium in patients aged 60 years and older: A randomised trial. Eur J Anaesthesiol. 2013;30(10):599–604.

40. James MF, Schenk PA, van der Veen BW. Priming of pancuronium with magnesium. Br J Anaesth. 1991;66(2):247–9.

41. Kopman AF, Kumar S, Klewickett MM, Neuman GG. The staircase phenomenon: implications for monitoring of neuromuscular transmission. Anesthesiology. 2001;95(2):403–7.

42. Staals LM, Driessen JJ, Van Egmond J, De Boer HD, Klimek M, Flockton EA, et al. Train-of-four ratio recovery often precedes twitch recovery when neuromuscular block is reversed by sugammadex. Acta Anaesthesiol Scand. 2011;55(6):700–7.

43. Germano Filho PA, Cavalcanti IL, Barrucand L, Vercosa N. Effect of magnesium sulphate on sugammadex reversal time for neuromuscular blockade: a randomised controlled study. Anaesthesia. 2015;70(8):956–61.

44. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth. 2016;116(6):770–83.

45. Khan ZH, Samadi S, Ameli S, Emir Alavi C. Lidocaine as an Induction Agent for Intracranial Aneurysm Surgery: A Case Series. Anesth Pain Med. 2016;6(1):e33250.

46. Tremont-Lukats IW, Hutson PR, Backonja MM. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. Clin J Pain. 2006;22(3):266–71.

47. de Boer HD, Detriece O, Forget P. Opioid-related side effects: Postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature. Best Pract Res Clin Anaesthesiol. 2017;31(4):499–504.
48. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology. 2006;104(3):570–87.

49. Wybran J, Appelboom T, Famaey JP, Govaerts A. Suggestive evidence for receptors for morphine and methionine-enkephalin on normal human blood T lymphocytes. J Immunol. 1979;123(3):1068–70.

50. Sacerdote P, Franchi S, Panerai AE. Non-analgesic effects of opioids: mechanisms and potential clinical relevance of opioid-induced immunodepression. Curr Pharm Des. 2012;18(37):6034–42.

51. Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg. 1998;87(1):206–10.

52. Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Braz J Anesthesiol. 2015;65(3):191–9.

53. Hans P, Welter P, Dewandre PY, Brichant JF, Bonhomme V. Recovery from neuromuscular block after an intubation dose of cisatracurium and rocuronium in lumbar disc surgery. Acta Anaesthesiol Belg. 2004;55(2):129–33.

54. Sparr HJ, Beaufort TM, Fuchs-Buder T. Newer neuromuscular blocking agents: how do they compare with established agents? Drugs. 2001;61(7):919–42.

**Tables**

**Table 1:** Clinical and demographic characteristics of the patients.

|          | C       | L        | M       | ML      | \( p \) value |
|----------|---------|----------|---------|---------|--------------|
| n        | 15      | 16       | 16      | 16      |              |
| Age (years) | 36±11.84 | 34.6±9.45 | 34.8±11.95 | 32.8±9.06 | NS           |
| Gender (F/M) | 7/8     | 8/8      | 8/8     | 8/8     | NS           |
| ASA PS I/II | 14/1    | 14/2     | 14/2    | 13/3    | NS           |
| BMI (Kg/m²) | 24.07±3.79 | 24.95±3.44 | 25.74±3.46 | 23.24±2.63 | NS           |

**ASA PS:** American Society of Anesthesiologists physical status; **BMI:** body mass index; **C:** control group; **L:** lidocaine group; **M:** magnesium sulfate group; **ML:** magnesium sulfate plus lidocaina group. Values are the mean ± S.D. **NS:** not significant

**Table 2:** Neuromuscular Blockage Recovery characteristics
Figures

Figure 1

CONSORT flow diagram of participants allocation. C: control group; M: magnesium sulfate group; ML: magnesium sulfate combined with lidocaine group.
Figure 2

Area under the curve (AUC) of hemodynamic parameters. (A) AUC of the mean arterial pressure (MAP) in the induction period. (B) AUC of the MAP during the maintenance period. (C) AUC of heart rate (HR) in the induction period. (D) AUC of HR during the maintenance period. C: control group; M: magnesium sulfate group; ML: magnesium sulfate combined with lidocaine group. The box-and-whisker plots show the range and quartiles. The boxes extend from the 25th percentile to the 75th percentile, with a line at the median. The whiskers show the highest and lowest values; * p=0.0033 versus the C and M groups.
Figure 3

Speed of onset. C: control group; M: magnesium sulfate group; ML: magnesium sulfate combined with lidocaine group. The box-and-whisker plots show the range and quartiles. The boxes extend from the 25th percentile to the 75th percentile, with a line at the median. The whiskers show the highest and lowest values; p>0.05 versus the M and ML groups.
Recovery characteristics. (A) Clinical duration. (B) Recovery index. (C) Total duration. (D) Spontaneous recovery. C: control group; M: magnesium sulfate group; ML: magnesium sulfate combined with lidocaine group. The box-and-whisker plots show the range and quartiles. The boxes extend from the 25th percentile to the 75th percentile, with a line at the median. The whiskers show the highest and lowest values; * p<0.0001 versus the M and ML groups.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc