Use Profile of Magnesium Sulfate in Anesthesia in Brazil

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Objectives: The use of magnesium sulfate in the perioperative period has several benefits, including analgesia, inhibition of the release of catecholamines and prevention of vasospasm. The aim of this survey was to provide an overview of the use of magnesium sulfate in anesthesia.

Method: This was a prospective descriptive cross-sectional study. An online questionnaire was sent to 9,869 Brazilian anesthesiologists and trainees. The questionnaire comprised closed questions mainly regarding the frequency, clinical effects, adverse events, and doses of magnesium sulfate used in anesthesia.

Results: Of the 954 doctors who responded to the survey, 337 (35.32%) reported using magnesium sulfate in anesthesia. The most commonly cited clinical effects for the use of magnesium sulfate in anesthesia were (n/%): postoperative analgesia (245/72.70%), reduction of anesthetic consumption (240/71.21%) and prevention and treatment of preeclampsia and seizures in eclampsia (220/65.28%). The most frequently reported adverse events were hypotension (187/55.48%), residual neuromuscular blockade (133/39.46%), hypermagnesemia (30/8.90%), and intravenous injection pain (26/7.71%). The intravenous doses of magnesium sulfate used in most general anesthesia inductions were between 30 and 40 mg.kg⁻¹.

Conclusions: Magnesium sulfate is an important adjuvant drug in the practice of anesthesia, with several clinical effects and a low incidence of adverse events when used at recommended doses.

Keywords: anesthetics (MeSH), analgesics, magnesium sulfate, survey, adverse events

INTRODUCTION

Magnesium is the fourth most common ion in the body, and it participates in several cellular processes, including protein synthesis, neuromuscular function and stability of nucleic acid, as well as regulating other electrolytes such as calcium and sodium. Magnesium acts as a cofactor in protein synthesis, neuromuscular function and stability and the function of nucleic acids. It is a component of adenosine 5-triphosphatases and an endogenous regulator of other electrolytes. It is a calcium antagonist because it is a non-competitive inhibitor of calcium channels with inositol trisphosphate. Magnesium modulates sodium and potassium currents and, as a consequence, interferes with the transmembrane potential. It is a central nervous system depressant, antagonizing N-methyl-D-aspartate (NMDA) and inhibiting the release of catecholamines (Herroeder et al., 2011).
Some studies have shown that the use of magnesium sulfate as an adjunct in anesthesia reduces intraoperative consumption of anesthetics (Koinig et al., 1998; Seyhan et al., 2006; Ryu et al., 2008; Forget and Cata, 2017). It also provides better analgesia and reduces the amount of morphine used in the postoperative period (Mentes et al., 2008; Dabbagh et al., 2009; Hwang et al., 2010). Studies in clinical practice have demonstrated the inhibitory effects of magnesium on the release of catecholamines (Herroeder et al., 2011) through better hemodynamic control during laryngoscopy (Puri et al., 1998; Chin et al., 2011) and pneumoperitoneum insufflation for videolaparoscopy (Mentes et al., 2008). Magnesium sulfate also reduces levels of noradrenaline and vasopressin during anesthesia (Jee et al., 2009).

Other benefits of using intraoperative magnesium have been reported, including hemodynamic control in surgeries for resection of pheochromocytoma (James and Cronjé, 2004), reduced incidence of atrial fibrillation in myocardial revascularization surgeries (Toraman et al., 2001), and prevention of vasospasm (Wong et al., 2006) and neurological protection after subarachnoid hemorrhage (Schmid-Elsaesser et al., 2006). The attenuation of the release of catecholamines by the adrenal glands and antagonism to calcium in smooth muscle cells of arterioles are possible mechanisms of action (Herroeder et al., 2011).

The clinical duration of nondepolarizing neuromuscular blockers is prolonged with the use of magnesium sulfate in anesthesia (Fuchs-Buder et al., 1995; Kussman et al., 1997; Czarnetzki et al., 2010; Rotava et al., 2013). Magnesium interferes with neuromuscular function by reducing the conductance of calcium in presynaptic membranes, decreasing the amount of acetylcholine released by motor neurons (Herroeder et al., 2011). It may also reduce post-synaptic sensitivity to acetylcholine or have a direct effect on the membrane potential of muscle cells (Del Castillo and Engbaek, 1954).

This survey was conducted to contribute evidence on the use of magnesium sulfate as adjunct of anesthesia due to its potential clinical benefits.

The primary objective of this study was to know the use profile of Magnesium Sulfate in Anesthesia in Brazil.

MATERIALS AND METHODS

The descriptive study was approved by the Research Ethics Committee of the Fluminense Federal University, Niterói, RJ, Brazil (CAAE 35038614.0.0000.5243, opinion 884.839, dated 11/13/2014). The informed consent form was signed electronically.

All the anesthesiologists and trainees members of Brazilian Society of Anesthesiology in 2015 were invited to participate. A self-administered electronic questionnaire was sent via e-mail to 9,869 potential participants of the research using the Survey Monkey software. The invitation was sent by 3 times with the 10-day interval between them.

We did not find in the literature a data collection instrument on the subject of this research. The lead researcher created the electronic questionnaire used in this research, composed of 10 closed questions that addressed the following aspects: duration of practice of anesthesiology, use of magnesium sulfate and other anesthesia adjuvants, indications, complications and doses of magnesium sulfate in anesthesia (Figure 1).

The instrument was pre-tested in two stages. In the first stage, the relevance of the instrument was evaluated and was carried out by the researchers themselves. In the second stage, the questionnaire was evaluated by 8 anesthesiologists and the results were used to create the final version of the questionnaire used in the research.

Data were analyzed using descriptive statistics. The original data can be accessed in the Supplementary Table 1.

RESULTS

Survey responses were received from 945 (9.57%) participants. The length of time of anesthesia practice among the respondents is shown in Table 1.

Of the 945 anesthesiologists who responded to this survey, 331 (35.02%) reported using magnesium sulfate in anesthesia. The frequency of use of adjuvant drugs in anesthesia is described in Table 2.

The number and percentage of clinical effects (n%) for the use of magnesium sulfate in anesthesia were (in descending order, more than one response per participant allowed): postoperative analgesia (242/73,11%), reduction of anesthetic consumption (237/71.60%), prevention and treatment of preeclampsia and seizures in eclampsia (218/65.86%), prevention and treatment of arrhythmias (175/52.87%), reduction of the dose of neuromuscular blockers (168/50.75%), prevention of postoperative chronic pain (167/50.45%), bronchodilation (165/49.84%), prevention of hyperalgesia post remifentanil use (160/48.34%), hypomagnesaemia prevention in large surgeries (128/38.67%), induced systemic arterial hypotension (112/33.83%), brain protection (95/28.70%), sedation (86/25.98%), reduction of surgical bleeding or reduction of perioperative blood replacement (74/22.35%), management of pheochromocytoma (72/21.75%), prevention and treatment of agitation in emergence from general anesthesia (64/19.33%), inhibition of preterm birth (59/17.82%), prevention of myocardial ischemia (54/16.31%), prevention and treatment of shivering (50/15.10%), facilitation of tracheal intubation without the use of neuromuscular blocker agent (44/13.29%), reduction of nausea and vomiting (39/11.78%), prevention and treatment of laryngospasm (38/11.48%), control of fasciculation and myalgia after succinylcholine (31/9.36%), prevention of myoclonus after intravenous injection of etomidate (24/7.25%), treatment of tetanus (20/6.04%), adjuvant in spinal anesthesia (19/5.74%), decrease in platelet aggregation (14/4.23%), attenuation of the sympathetic response to tracheal intubation (1/0.30%) and extension of duration of motor block on subdural anesthesia (1/0.30%).

All anesthesiologists reported using the intravenous route (331/100.00%) to administer magnesium sulfate. Other routes were used less frequently: muscular (16/4.83%), nerve plexus...
Questionnaire - Use of Magnesium Sulphate in Anesthesia in Brazil

1. Duration as anesthesiologist:
   ( ) 1 to 5 years  ( ) 6 to 10 years  ( ) 11 to 15 years  ( ) 6 to 20 years  ( ) more than 20 years

2. Do you use magnesium sulfate in anesthesia?
   ( ) yes  ( ) not

3. Except for magnesium sulfate, which of the adjuvants do you use in anesthesia? (More than one answer is possible)
   ( ) clonidine  ( ) dexmedetomidine  ( ) ketamine  ( ) lidocaine  ( ) other  ( ) I do not use anesthesia adjuvants

If you use magnesium sulfate, please answer the following questions:

4. What is the clinical effect(s) for the use of magnesium sulphate during anesthesia? (More than one answer is possible)
   ( ) prevention of myocardial ischemia
   ( ) brain protection
   ( ) reduction of the dose of neuromuscular blocker
   ( ) attenuation of sympathetic response to tracheal intubation
   ( ) postoperative analgesia
   ( ) decreased anesthetic consumption
   ( ) inhibition of preterm birth
   ( ) prevention and treatment of preeclampsia and seizures in eclampsia
   ( ) bronchodilation
   ( ) adjuvant in spinal anesthesia
   ( ) prevention / treatment of cardiac arrhythmias
   ( ) handling of pheochromocytoma
   ( ) prevention of hypomagnesemia in large surgeries
   ( ) decreased platelet aggregation
   ( ) prevention / treatment of laryngospasm
   ( ) prevention of myoclonus after venous injection of etomidate
   ( ) prevention of chronic postoperative pain
   ( ) facilitation of tracheal intubation without the use of neuromuscular blocker
   ( ) control of fasciculation and myalgia after succinylcholine
   ( ) prevention of hyperalgesia after use of remifentanil
   ( ) prevention / treatment of shivering
   ( ) reduction of surgical bleeding
   ( ) reduction of perioperative blood replacement
   ( ) tetanus treatment
   ( ) reduction of nausea and vomiting
   ( ) induced hypotension
   ( ) sedation
   ( ) prevention / agitation treatment on awakening from anesthesia
   ( ) prevention / treatment of chronic pain
   ( ) other

5. Which route(s) do you use to administer magnesium sulfate? (More than one answer is possible)
   ( ) intravenous  ( ) intramuscular  ( ) spinal  ( ) nerve plexus  ( ) intravenous regional  ( ) surgical wound infiltration

6. Which of the adverse events of using magnesium sulfate in anesthesia have you witnessed? (More than one answer is possible)
   ( ) residual neuromuscular blockade  ( ) intravenous injection pain  ( ) respiratory depression  ( ) systemic arterial hypotension
   ( ) hypermagnesemia  ( ) other

7. In the case of observed adverse events, how do you classify them in terms of severity? (More than one answer is possible)
   ( ) mild  ( ) moderate  ( ) severe  ( ) death

8. What is the intravenous dose you often use in inducing general anesthesia? (only one answer)
   ( ) <30 mg.kg⁻¹  ( ) 30 to 40 mg.kg⁻¹  ( ) 40 to 50 mg.kg⁻¹  ( ) 50 to 60 mg.kg⁻¹  ( ) >60mg.kg⁻¹  ( ) I do not use inducing doses

9. What venous dose do you often use to maintain general anesthesia? (only one answer)
   ( ) <30 mg.kg⁻¹  ( ) 30 to 40 mg.kg⁻¹  ( ) 40 to 50 mg.kg⁻¹  ( ) 50 to 60 mg.kg⁻¹  ( ) >60mg.kg⁻¹  ( ) I do not use maintenance doses

10. Doses used for sedation?
    ( ) <30 mg.kg⁻¹  ( ) 30 to 40 mg.kg⁻¹  ( ) 40 to 50 mg.kg⁻¹  ( ) 50 to 60 mg.kg⁻¹  ( ) >60mg.kg⁻¹  ( ) I do not use magnesium sulfate for sedation

FIGURE 1 | Electronic questionnaire used in research “Use of Magnesium Sulfate in Anesthesia in Brazil.” Brazil, 2015.
TABLE 1 | Distribution of anesthesiologists that answered the questionnaire (n = 945) by the duration of anesthesia practice (n, %).

| Time of practice of anesthesia | n  | %   |
|--------------------------------|----|-----|
| Trainee                        | 135| 14.29|
| 1–5 years                      | 240| 25.40|
| 6–10 years                     | 116| 12.27|
| 11–15 years                    | 83 | 8.78 |
| 16–20 years                    | 82 | 8.67 |
| 21 years or more               | 289| 30.59|

Brazil, 2015.

TABLE 2 | Frequency of use of adjuvant drugs in anesthesia (n, %).

| Adjuvant drug          | n   | %    |
|------------------------|-----|------|
| Clonidine              | 805 | 85.19|
| Ketamine               | 689 | 72.91|
| Lidocaine              | 614 | 64.97|
| Dexmedetomidine        | 417 | 44.12|
| Magnesium sulfate      | 331 | 35.02|
| No use of adjuvant     | 39  | 4.13 |

More than one response per participant was possible (n = 945). Brazil, 2015.

TABLE 3 | Frequency of adverse events during use of magnesium sulfate witnessed at least once by the anesthesiologist.

| Adverse events                              | n   | %    |
|---------------------------------------------|-----|------|
| Systemic arterial hypotension               | 184 | 55.59|
| Residual neuromuscular blockade             | 131 | 39.57|
| Hypermagnesemia                             | 28  | 8.45 |
| Intravenous injection pain                  | 22  | 6.64 |
| Respiratory depression                       | 22  | 6.64 |
| Heat sensation                              | 4   | 1.20 |
| Bradycardia                                 | 4   | 1.20 |
| Facial/cervical flushing                    | 2   | 0.60 |
| Tachycardia                                 | 2   | 0.60 |
| Intense sedation                            | 2   | 0.60 |
| Cardiac arrhythmia                          | 1   | 0.30 |
| Prolonged emergence from anesthesia          | 1   | 0.30 |
| Myocardial depression                       | 1   | 0.3  |
| None                                        | 40  | 12.08|

More than one response per participant was possible (n = 331). Brazil, 2015.

some adverse events were reported as severe, i.e., respiratory depression (4), hypotension (4), residual curarisation (4), hypermagnesemia (2) and bradycardia (1).

Table 5 shows the dosages of intravenous magnesium sulfate commonly used for induction of general anesthesia and sedation.

TABLE 4 | Rate of intensity level of adverse events witnessed by anesthesiologists using magnesium sulfate anesthesia (n = 305).

| Adverse events | n   | %    |
|----------------|-----|------|
| Mild           | 225 | 73.78|
| Moderate       | 71  | 23.27|
| Severe         | 9   | 2.95 |

Brazil, 2015.

TABLE 5 | Magnesium sulfate intravenous doses most commonly used in the induction of general anesthesia and sedation (n = 331).

| Doses            | n  | %    |
|------------------|----|------|
| Induction of general anesthesia | <30 mg.kg\(^{-1}\) | 55  | 16.61 |
|                   | 30–40 mg.kg\(^{-1}\) | 114 | 34.45|
|                   | 40–50 mg.kg\(^{-1}\) | 47  | 14.20|
|                   | 50–60 mg.kg\(^{-1}\) | 9   | 2.71 |
|                   | No use for induction of general anesthesia | 106 | 32.03 |
| Sedation         | <30 mg.kg\(^{-1}\) | 58  | 17.52|
|                   | 30–40 mg.kg\(^{-1}\) | 28  | 8.46 |
|                   | 40–50 mg.kg\(^{-1}\) | 10  | 3.02 |
|                   | 50–60 mg.kg\(^{-1}\) | 1   | 0.30 |
|                   | No use for sedation | 234 | 70.70|

Brazil, 2015.

DISCUSSION

Little or no scientific literature exists that reports on surveys on the use of magnesium sulfate in anesthesia. Approximately 10% of those who received the invitation to participate completed the survey, specifically, 945 anesthesiologists. Several medical polls have reported similar response rates (Naguib et al., 2010; Locks et al., 2015). Low adherence of participants can be explained by the electronic method used for data collection.

Duration of Anesthesia Practice of the Survey Participants

In the present survey, anesthesiologists with more than 20 years of anesthesia practice (30.59%) reported using magnesium sulfate in anesthesia and sedation most frequently; this group was followed by those with between 1 and 5 years of clinical practice (25.40%). The frequent use of magnesium sulfate among the more experienced anesthesiologists may stem from common use in certain specialties, particularly obstetrics. The high frequency of use of magnesium sulfate among the younger group of anesthesiologists may be result of the recent attention being paid...
to this drug, as well as the introduction of multimodal analgesic and anesthesia techniques (Czarnetzki et al., 2010; Herroeder et al., 2011; Shin et al., 2011; Rotava et al., 2013).

**Adjuvant Drugs in Anesthesia**

Anesthesia adjuvants are agents that are administered in association with anesthetics to increase effectiveness, improve delivery, or decrease required dosage. The survey showed that the drug most commonly used in Brazil as an anesthesia adjuvant is clonidine (85.18%); magnesium sulfate (35.02%) ranks fifth among the medicines included as possible survey responses.

Giovannitti et al. (2015) postulated that agonists of the α-2 adrenergic receptors, including clonidine and dexmedetomidine, are important tools in the arsenal of modern anesthesia because of their ability to induce calm without causing respiratory depression. They also promote cardiovascular stability and reduce anesthetic requirements.

The drug reported as the second most frequently used adjuvant was ketamine. Bakan et al. (2014) conducted a randomized clinical trial and showed that ketamine, when associated with remifentanil in total intravenous anesthesia in children, is well suited to rigid bronchoscopic procedures.

Although this survey found that lidocaine ranked third on the list of most used drugs, Kranke et al. (2015), in a systematic review, reported that there is only little or moderate evidence that a continuous infusion of lidocaine has an impact on pain intensity, especially in the early postoperative period, or on postoperative nausea. There is limited evidence that it has consequences in other clinical outcomes, such as gastrointestinal recovery, length of hospital stay and opioid use (Kranke et al., 2015).

Gupta et al. (2006) demonstrated that magnesium sulfate has anesthetic, analgesic and muscle relaxing effects and significantly reduces the need for anesthetic drugs and neuromuscular blockers.

**Clinical Effects of Magnesium Sulfate in Anesthesia**

As noted in this survey, there is a wide range of clinical effects for the use of magnesium sulfate in anesthesia. The great variety of clinical effects could be explained by the substantial involvement of magnesium in the physiology of various organs and systems.

Magnesium participates in over 325 cellular enzyme systems and is the second most abundant intracellular cation after potassium. Magnesium participates in numerous physiological and homeostatic functions, such as binding of hormone receptors, the transmembrane flow of ions, regulation of adenylate cyclase, calcium release, muscle contraction, cardiac excitability, neuronal activity, control of vasomotor tone and release of neurotransmitters, blood pressure and peripheral blood flow. Mg$^{2+}$ modulates and controls the input of cell Ca$^{2+}$ and Ca$^{2+}$ release from the sarcoplasmic reticulum (Altura, 1994).

Magnesium is essential in the transfer, storage and utilization of energy in cells. The intracellular level of free Mg$^{2+}$ ([Mg$^{2+}$]$^i$) regulates intermediate metabolism, synthesis and structure of DNA and RNA, cell growth, reproduction and membrane structure (Altura and Altura, 1996).

**Adverse Events of Magnesium Sulfate Use and Classification of Intensity**

Herroeder et al. (2011) reported that the vasodilator effect of magnesium is the likely cause of burning or heat sensations in the body. Prolonged PR and QT intervals as well as atrioventricular blockage may occur. Toxicity occurs with the administration of venous doses greater than 30 g or with plasma concentrations above 14.4 mg/dl (Herroeder et al., 2011). Hypermagnesemia is manifested by abolition of tendon reflex; treatment consists of calcium gluconate, furosemide furosemide and hemodialysis (Herroeder et al., 2011).

In this survey, 2.95% of respondents reported severe complications from the use of magnesium sulfate. It is worth mentioning that the occurrence of severe adverse events is of fundamental importance, demonstrating that the administration of magnesium sulfate is not risk free. As in the present research, Herroeder et al. (2011) related as severe adverse events from the use of magnesium sulfate: arterial hypotension, bradycardia, muscle weakness, and respiratory depression. The results of our survey demonstrated similar results. Despite the occurrence of reports of serious AEs, the use of magnesium sulfate can be safe in recommended doses with close monitoring of patients (Kutlesic et al., 2017).
Marret and Ancel (2016) used magnesium sulfate in obstetric patients at an initial venous dose of 4 g followed by 1 g/h, without exceeding the cumulative total dose of 50 g. In their analysis of short and medium-term outcomes, they found no serious maternal adverse effects nor adverse effects on the newborns.

Griffiths and Kew (2016) observed few adverse effects when intravenous magnesium sulfate was used for treatment of asthma in children in the emergency department.

Wilson et al. (2014) realized a retrospective cohort study to evaluated the tolerability and safety of high doses of intravenous magnesium sulfate for tocolysis in preterm labor. The frequency of severe adverse events was 5.3% while in our survey it was 2.95%. This difference can be explained because all patients in the study received high doses of magnesium sulfate. They concluded that side effects occurred in 9 out of 10 patients and were considered severe for 1 out of every 20 pregnant women.

**Intravenous Dose of Magnesium Sulfate Most Frequently Used in Induction of General Anesthesia and Sedation**

Germano Filho et al. (2015), in a randomized controlled study, demonstrated a significant increase in magnesium plasma concentrations after infusions of 40 mg.kg\(^{-1}\) solution containing magnesium sulfate among ASA 1 or 2 patients. This confirmed that this dose is capable of increasing magnesium serum levels.

The magnesium sulfate doses reported in this survey are in accordance with those found in other publications. There are reports of magnesium sulfate induction doses in general anesthesia from 15 mg.kg\(^{-1}\) to 75 mg.kg\(^{-1}\) (Beşogul et al., 2009; Gozdemir et al., 2010; Rotava et al., 2013; Kahraman and Eroglu, 2014; Rodrigo et al., 2014; Honarmand et al., 2015; Rower et al., 2017) and doses up to 50 mg.kg\(^{-1}\) in sedation (Lecuyer et al., 2017).

We observed that the Brazilian anesthesiologist uses magnesium sulfate rationally. Clinical effects, doses and routes of administration are found in the literature.

This survey describes the wide range of purposes magnesium sulfate is used for in anesthesia in Brazil. Although anesthesiologists have free access to the use of magnesium sulfate, research data have shown that the drug has been used primarily in those indications approved by the Health Authorities and/or supported by critical evaluation of systematic reviews and meta-analyses. The frequency of its use is related to the amount and strength of evidence of its effects reported in the literature.

This survey has some limitations. Only Brazilian anesthesiologists participated in the study. Further, the participation of the anesthesiologists was voluntary; those who agreed to participate are likely those most interested in the use of magnesium sulfate in anesthesia. This may have created bias that could interfere with the generalization of the responses to the full population of anesthesia specialists. Only 10% effectively responded to the survey, that the results may thus be biased. The questionnaire was not validated.

We conclude that magnesium sulfate is among the five most commonly used adjuvants in anesthesia, along with clonidine, ketamine, lidocaine and dexmedetomidine. Several clinical effects for magnesium sulfate were reported, especially postoperative analgesia, reduction of anesthetic consumption and the prevention and treatment of preeclampsia and eclampsia seizures. Hypotension, residual neuromuscular blockade, hypermagnesemia and pain on intravenous injection were the most frequent adverse events and, in general, were considered mild. Magnesium sulfate intravenous doses used in most general anesthesia induction were between 30 and 40 mg.kg\(^{-1}\).

**ETHICS STATEMENT**

This study was carried out in accordance with the recommendations of Brazilian National Health Council (Resolution number 466, from December 12, 2012) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Research Ethics Committee of the Fluminense Federal University, Niterói, RJ, Brazil (CAAE 35038614.0.0000.5243, opinion 884.839, dated 11/13/2014).

**AUTHOR CONTRIBUTIONS**

IC, FL, and MS designed the study and performed the experiments, IC, RCF, EB, and NV analyzed the data and wrote the manuscript.

**FUNDING**

The study was supported by the Fluminense Federal University, Niterói, Brazil and Brazilian Society of Anesthesiology, Rio de Janeiro, Brazil. There was no funding source for this study.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2019.00429/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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