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EDITORIAL

Magnesium: the underestimated ion

Electrolytes play an important role in homeostasis. Among them, magnesium, considered the ''forgotten electrolyte'', is the fourth most frequent cation in the body, ranking second in the intracellular environment after potassium.[1–3] Magnesium balance in the body depends on intestinal absorption and renal excretion. During glomerular filtration, 80% of plasma magnesium is ultra-filtrated in the glomerulus, 95% of which is reabsorbed, and 5% excreted in urine.[3]

On average, an adult has 24 g of magnesium, 60% of which located in bones, and the remainder in muscle cells and soft tissue.[4] Plasma accounts for only 0.3% of total organic magnesium. Plasma magnesium concentration shows a distinct low-range variation with values between 1.7 and 2.4 $mg.dL^{-1}$, or 0.7 to 1 $mmoL.L^{-1}$, or 1.4 to 2 $mEq.L^{-1}$.[3] Despite magnesium's important physiological role, hypomagnesemia is a frequently underdiagnosed electrolyte imbalance.[3]

Magnesium is an endogenous calcium antagonist and impacts its reabsorption and distribution. It also modulates the transmembrane flow of sodium and potassium, influencing membrane potential. Moreover, it regulates adenylyl cyclase, muscle, cardiac and neuronal activities, in addition to vasomotor tonus. It is a central nervous system depressant, by antagonizing NMDA receptors, and inhibiting catecholamine release.[4] It also takes part in multiple enzyme activities involving energy metabolism and synthesis of nucleic acids.[2,5]

Hypomagnesemia promotes instability of the cell membrane and cytoplasm organelles, decreases intracellular ATP and potassium, and increases intracellular sodium and calcium.[2] The condition is usually symptomatic when plasma concentrations are below 1.21 $mg.dL^{-1}$. Hypomagnesemia occurs due to vomiting or diarrhea, or to the use of laxatives, thiazide diuretics, angiotensin converting enzyme inhibitors, cisplatin, aminoglycosides, or other nephrotoxic drugs. It is also associated with some endocrine disorders (hyperaldosteronism, parathyroid disorders, and diabetes) and chronic alcoholism. Clinical manifestations include several symptoms, including nausea and vomiting, muscular weakness, seizures, tetany, muscle fasciculations, and electrocardiographic changes.[4]

Current diets are increasingly more deficient in essential minerals, and it is estimated that approximately 60% of Americans are not intaking the recommended daily amount of magnesium.[6] Between 7% and 11% of inpatients, and 65% of intensive care patients present hypomagnesemia.[7]

Conversely, hypermagnesemia is rare and occurs in chronic renal patients during administration of the ion, or in patients with eclampsia treated with multiple doses of magnesium sulphate. Hypermagnesemia is associated with cardiac or neuromuscular symptoms, beginning with electrocardiographic abnormalities with a widened QRS complex. When plasma concentrations are above 6 to 7.5 $mmoL.L^{-1}$, patients can present arterial hypotension, respiratory depression, narcosis, and even cardiac arrest. Oral administration of magnesium is usually considered safe.[4]

In the past, magnesium sulphate was proposed as a general anesthetic, but this effect resulted from the cerebral hypoxia caused by cardiac and respiratory depressions.[2,4] It is used as an adjuvant drug in more current anesthetic techniques.

As magnesium decreases the release of acetylcholine mediated by calcium at the neuromuscular junction and attenuates muscle excitability, it has a potentiating effect on neuromuscular blockers.[2,4,8] It also promotes bronchodilation in cases of severe acute asthma, delays cerebral ischemia due to subarachnoid hemorrhage, and can be used in the management of eclampsia seizures and atrial fibrillation after cardiac surgery.[9]

Both the decrease in catecholamine release by the adrenal medulla and adrenergic nervous terminations and the antagonizing of the effect of calcium on vascular smooth muscular cells, may contribute to the effects of magnesium as an adjuvant drug in anesthesia.[2,4] Decreasing catecholamine release is valuable for blunting the

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stress responses to anesthesia stressors, such as tracheal intubation.[10]

The potential analgesic effect of magnesium sulphate is very important to anesthesiologists. Magnesium acts as an analgesic in neuropathic pain, potentiates opioid effect and attenuates opioid tolerance.[11] Its analgesic effect is due to antagonism of the NMDA receptor and to the modulation of intracellular inflow of calcium. By inhibiting NMDA receptors located on the posterior horn of the spinal cord, magnesium can also decrease the risk of chronic pain by mitigating or preventing central sensitization that follows peripheral tissue inflammation or injury.[4,11]

In pre-eclampsia, and eclampsia, magnesium sulphate improves general and cerebral symptoms, and improves uterine vasodilation. Moreover, it prevents progression to eclampsia, and it is recommended as the treatment of choice for seizures.[4,12] Doses used in this scenario increase the risk of hypermagnesemia, and consequently muscle relaxant interaction is more likely, especially in this population who is already more sensitive to these drugs.[12] During clinical practice, this drug interaction has not been valued enough in scenarios requiring rapid sequence intubation (obstetrics, e.g.) or even involving emergency patients, such as COVID-19.

The present edition of BJAN is publishing three randomized clinical trials focusing on the analgesic and hemodynamic effects of magnesium sulphate, in addition to the effect on the dose of rocuronium.

The study by Almeida et al. included 180 patients and aimed to assess three different doses of rocuronium (1 ED95, 2 ED95 and 4 ED95) on patients submitted to general anesthesia. Patients received 60 mg.kg^{-1} of magnesium sulphate or saline. Onset of action latency of muscular relaxant in the magnesium group, assessed with TOF monitoring, was significantly shorter for 1 ED95 and 2 ED95 doses when compared to the control group. The authors suggested that one of the factors associated with rapid onset of muscular relaxant action was due to change in the peripheral blood perfusion index, which is increased in groups receiving magnesium.[13]

Silva Filho et al. studied the effectiveness of magnesium sulphate as the main analgesic agent during anesthesia, comparing it to remifentanil, during total venous anesthesia. The secondary outcomes were propofol consumption and intraoperative hemodynamic stability, and postoperative analgesia.[14] The study randomized 50 patients submitted to post-bariatric abdominoplasty, divided into two groups: remifentanil and magnesium sulphate. Fentanyl (1 mcg.kg^{-1}) was available as rescue analgesia. Among magnesium sulphate group subjects, only 36% required supplementary analgesia, while none of the individuals in the remifentanil group required fentanyl. Bispectral index-guided propofol consumption was 36.6% higher among patients in the magnesium group, with less requirement of ephedrine in the intraoperative. However, there were no differences in postoperative pain scores between the two groups.[14]

The study by Farouk et al. included 60 patients submitted to bilateral inguinal herniorrhaphy under subarachnoid anesthesia with a 15 mg dose of hyperbaric 0.5% bupivacaine. Study subjects were allocated into three groups with continuous infusion of magnesium sulphate, dexmedetomidine or saline. The primary outcome was total duration of analgesia and, the secondary outcomes were onset and duration of motor and sensitive blocks, perioperative hemodynamic status (blood pressure, heart rate, cardiac output, and systolic volume), and postoperative morphine consumption during the first 24 hours.[15] Duration of sensitive and motor blocks, and of analgesia was longer for the groups receiving magnesium sulphate or dexmedetomidine, when compared to the group receiving saline. No differences were observed for the groups that received active treatments. Postoperative morphine consumption was higher in the saline group, with no differences among the remaining groups. No differences were found in hemodynamic variables for the groups studied.[15]

Magnesium plasma concentration disorders should not be neglected, because both hypo and hypermagnesemia have deleterious effects. However, as an adjuvant in anesthesiology, magnesium sulphate is an efficacious analgesic and hemodynamically safe. Magnesium properties favor its use in intra and postoperative opioid sparing scenarios.

The studies published in this edition of BJAN support clinical use of magnesium sulphate in anesthesiology. However, clinicians should be prudent to avoid adverse effects associated with plasma concentration disorders, mainly hypermagnesemia. Still, we recommend more randomized clinical trials, including diversified populations and larger samples, to be performed for all potential therapeutic effects to be corroborated.

Conflicts of interest

NSPM declares no conflicts. GAMB is a researcher and has given lectures on behalf of Laboratório Cristália.

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