Μαγνήσιο περιεγχειρητικά στην παιδιατρική αναισθησία

Το μαγνήσιο είναι ένα βασικό στοιχείο σε όλους τους οργανισμούς, το οποίο συμμετέχει στις περισσότερες κυτταρικές ενζυμικές αντιδράσεις. Από την άλλη μεριά όμως είναι και ένα «υποτιμημένο» μόριο με πολλαπλές βιοχημικές και φυσιολογικές δράσεις.

Τα τελευταία χρόνια η χρήση του στην περιεγχειρητική περίοδο αυξήθηκε σημαντικά, καθώς εμφανίζει αναισθητικές, αναλγητικές και μυοχαλαρωτικές ιδιότητες.

Το μαγνήσιο χρησιμοποιείται για διάφορους λόγους στην παιδιατρική αναισθησία, συνήθως σε δόση 20 – 50 mg/kg. Η επίδραση του στα παιδιά ως επιπρόσθετο στην τοποπεριοχική αναισθησία, για τις αρρυθμίες και για την υπεραντιδραστικότητα των αεραγωγών έχουν αποδειχθεί από πολλαπλές μελέτες. Οι αναλγητικές ιδιότητες που εμφανίζει στις μελέτες στους ενήλικες θα πρέπει να επιβεβαιωθούν και με περισσότερες μελέτες στα παιδιά. Το μαγνήσιο έχει ένα άριστο προφίλ ασφάλειας και πολύ χαμηλό κόστος, και γι’αυτό οι ενθουσιώδεις υποστηρικτές του το ονομάζουν ως το *Super* πρόσθετο.

Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

EDUCATIONAL REVIEW

Magnesium sulfate in pediatric anesthesia: the Super Adjuvant

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Keywords
magnesium; magnesium sulfate; anesthesia; pediatric anesthesia; pediatrics; child

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Section Editor: Mark Thomas

Accepted 24 January 2017

doi:10.1111/pan.13129

Summary

Magnesium is an essential chemical element in all organisms, intervening in most cellular enzymatic reactions; thus, its importance in homeostasis and as a therapeutic tool in highly challenging patients such as pediatrics. The primary purpose of this paper was to review the role of magnesium sulfate as an adjuvant drug in pediatric anesthesia. This compound already has the scientific backing in certain aspects such as analgesia or muscle relaxation, but only theoretical or empirical backing in others such as organ protection or inflammation, where it seems to be promising. The multitude of potential applications in pediatric anesthesia, its high safety, and low cost make magnesium sulfate could be considered a *Super Adjuvant*.

Introduction

Magnesium (Mg) is the fourth most abundant cation in the body and the second most common intracellular one. Also known as 'the forgotten electrolyte', it plays an important role in cellular physiology as a modulator of transmembrane ion transport and energy metabolism (1). In pediatric anesthesia, Mg—as cofactor for over 300 enzymes systems (1)—is a very 'attractive' molecule in the perioperative setting, in both homeostasis (hypomagnesemia is the most common underdiagnosed electrolyte disturbance) and anesthesia (Mg has sedative, analgesic, muscle relaxant, and organ protection properties).

The main objective of this paper was to review the clinical use of magnesium sulfate ($MgSO_4$) as an adjuvant drug in the anesthetic management of pediatric patients. A preliminary commentary on the Mg physiology and homeostasis, as well as the most relevant pharmacological aspects of $MgSO_4$, is also carried out. The literature search for this narrative review was conducted between January 2010 and May 2016, in the following databases and search engines: Google, Pubmed, Embase, and Medline. The search terms were: *magnesium, magnesium sulfate, anesthesia, pediatric anesthesia, pediatrics, newborn, infant,* and *child.*

Magnesium physiology

Magnesium is a divalent cation, with a molecular weight of 24, comprising about 0.03% of total body weight. About 99% of Mg is intracellular (60% bone tissue, 20% muscle tissue, and 19% soft tissue) and 1% is extracellular. Serum Mg accounts for just 0.3% (60% ionized, 30% protein-bound, and 10% complex anions) with a narrow concentration range between 1.7 and 2.4 $mg{\cdot}dl^{-1}$ (0.7–1 $mmol{\cdot}l^{-1}$ or 1.4–2 $mEq{\cdot}l^{-1}$) (1–4).

Mg homeostasis depends on the balance between intestinal absorption and renal excretion. On one hand, 50% of dietary Mg is absorbed by the intestine (mainly in the jejunum and ileum) through an unknown regulatory mechanism; this absorption can fluctuate between 10% and 70%. On the other hand, 80% of total plasma Mg is ultrafiltered in the glomerulus, with 95% of reabsorption (mainly in Henle′s loop) and 5% of excretion. The latter is modulated by plasma concentrations and may vary from 0.5% to nearly 100% (Figure 1) (1,2).

Mg plays a key role in cellular activity, being its main biochemical functions: Synthesis and degradation of high-energy compounds (ATP binds to Mg [Mg-ATP] to form the biologically active substrate), intervening in the oxidative phosphorylation; Modulation of

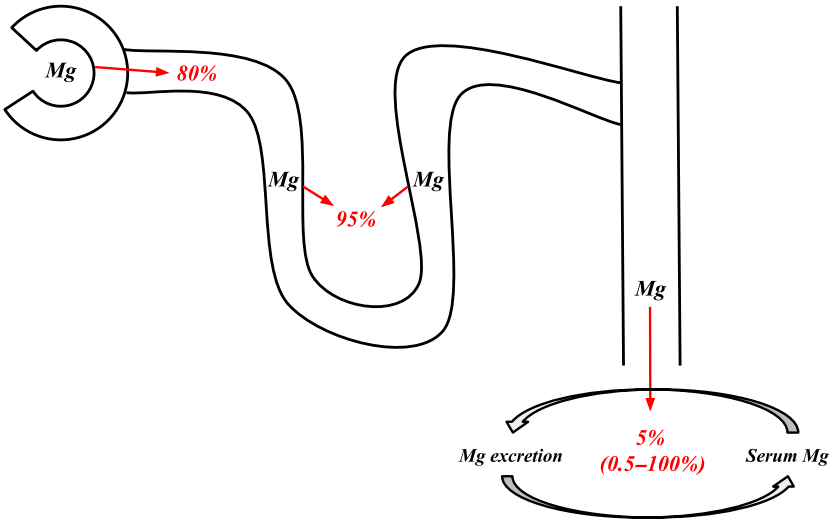

Figure 1 Homeostasis of renal magnesium.

ATP-dependent ion transport (sodium, potassium and calcium); Activation of ATP-dependent enzymes, participating in cellular metabolism of carbohydrates, lipids, and protein (Figure 2) (1,2).

Magnesium sulfate pharmacology

Magnesium sulfate heptahydrate ($MgSO_4 \cdot 7H_2O$) is the pharmaceutical preparation for Mg vials. In Spain, each 10 ml vial contains 1.5 g of $MgSO_4$ and 150 mg of Mg (6 mmol or 12 mEq) (2).

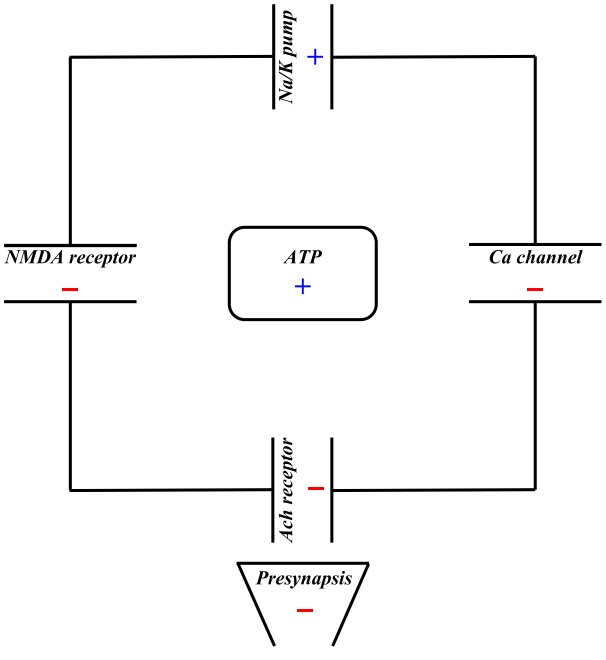

Figure 2 Cellular functions of magnesium (+ Activation – Inhibition).

Concerning pharmacokinetics, intravenous (IV) $MgSO_4$ has an immediate onset of action, with a peak effect in 10 min and duration of action of 30 min (2).

Regarding pharmacodynamics, magnesium's physiological functions includes: Activation of sodium–potassium ATPase pump (inhibition with high serum Mg concentrations); Competitive antagonism of calcium channels and noncompetitive antagonism of *N*-methyl-D-aspartate (NMDA) receptors; Blocking presynaptic acetylcholine release and increasing postsynaptic action potential threshold; Blocking catecholamine release from adrenal glands and adrenergic nerve terminals; Decreasing cytokine release (IL-1, IL-6, TNF-α, and substance P); Sinoatrial and atrioventricular (AV) block, PR prolongation, and QRS widening; Inhibition of platelet aggregation (high serum Mg concentrations) (Figure 2) (1–3). All of the above provides $MgSO_4$ with a number of pharmacological actions (Table 1) (1–3).

Indication-specific dosing for $MgSO_4$ is amply described in Magnesium sulfate in pediatric anesthesia and Table 2. Furthermore, we propose a practical rule-of-thumb for IV administration:

$$\text{Bolus dose} + \text{Continuous infusion dose} = x \cdot \text{mg} \cdot \text{kg}^{-1} + \frac{x}{2}\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}.$$

Hemodynamic, respiratory, and neuromuscular (patellar reflex) monitoring is required during $MgSO_4$ intravenous treatment. In case of prolonged therapy, a determination of Mg and creatinine serum levels is recommended (2).

Given its significant physiological effects, $MgSO_4$ can interact with various pharmacological groups (Table 3) (2).

Table 1 Magnesium sulfate pharmacological effects (1–3)

	Pharmacological effect
Central nervous system	Sedation
	Analgesia (cerebral and neuraxial)
	Cerebral vasodilation
	Indirect sympaticolysis
Heart	Antiarrhythmic
	Systemic, pulmonary, and coronary vasodilation
Nonstriated muscle	Arterial vasodilation
	Bronchodilation
	Tocolysis
Striated muscle	Muscle relaxation
Inflammation	Inflammatory response modulation
Metabolism	Membrane stabilization
Platelets	Antiaggregation (very high doses)

Magnesium sulfate's adverse effects are summarized in Table 4 and may occur when serum Mg levels exceed 3 $mg{\cdot}dl^{-1}$ (1.2 $mmol{\cdot}l^{-1}$ or 2.4 $mEq{\cdot}l^{-1}$), being extremely rare in patients with normal renal function (1–4). Overdose toxicity management includes: Supportive care with respiratory and hemodynamic support (if necessary); Magnesium antidote with calcium gluconate (60–100 $mg{\cdot}kg^{-1}$) or calcium chloride (20–30 $mg{\cdot}kg^{-1}$); Magnesium depletion with intensive hydration, furosemide (1–2 $mg{\cdot}kg^{-1}$), and hemodialysis (if necessary) (2,3). In addition, there is currently no evidence of neurotoxicity associated with the use of magnesium sulfate in regional anesthesia, both central (epidural and spinal) and peripheral blocks (5).

Table 3 Magnesium sulfate drug interactions (2,6)

	Interaction
Anesthetic drugs	Mg enhances action of sevoflurane and propofol
Neuromuscular blockers	Mg enhances action of aminosteroids and bencylisoquinolines
	No interaction with depolarizing agents
Calcium	Calcium antagonizes Mg effect
Antiarrhythmic drugs	Mg enhances action of calcium channel blockers
	Mg decreases serum digoxin levels
	Mg increases serum quinidine levels
Antihypertensive drugs	Mg enhances action of calcium channel blockers
Diuretics	Loop diuretics and thiazides increase Mg clearance
Antibiotics	Aminoglycosides and amphotericin B increase Mg clearance
Corticosteroids	Prednisone decreases serum Mg levels

Magnesium sulfate in pediatric anesthesia

Sedation

Magnesium produces an inhibitory effect on the neuron by blocking NMDA glutamate receptors, which is the main excitatory neurotransmitter in the central nervous system. Therefore, it has sedative and anticonvulsant properties (1–3).

$MgSO_4$ (20–50 $mg{\cdot}kg^{-1}$ ± 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$) reduces the need for sedative-hypnotic drugs during general anesthesia: it can decrease the sevoflurane minimum

Table 2 Magnesium sulfate indication-specific dosing

	Indication	Dosing
Sedation	Sedation (IV) (2,6)	20–50 $mg{\cdot}kg^{-1}$ ± 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
	Agitation/Shivering (IV) (7–10)	20–50 $mg{\cdot}kg^{-1}$ ± 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
	Convulsions (IV) (16)	50 $mg{\cdot}kg^{-1}$ + 10–40 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
Analgesia	Analgesia (IV) (17–21)	30–50 $mg{\cdot}kg^{-1}$ ± 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
	Local analgesia (peritonsillar) (14,23)	2–5 $mg{\cdot}kg^{-1}$
	Epidural analgesia (caudal) (5,15,25)	50 mg (total dose)
	Spinal analgesia (intrathecal) (26)	0.5–1 $mg{\cdot}kg^{-1}$
Muscle relaxation	Tracheal intubation (IV) (31)	30 $mg{\cdot}kg^{-1}$
	Laryngospasm (IV) (23,33,34)	15 $mg{\cdot}kg^{-1}$
	Bronchospasm (IV) (36–46)	50–100 $mg{\cdot}kg^{-1}$ + 40–50 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
	Bronchospasm (nebulized) (47–55)	40 $mg{\cdot}kg^{-1}$ or 150 mg (total dose)
Antiadrenergic response	Cardiopulmonary bypass (IV) (57–60)	25–50 $mg{\cdot}kg^{-1}$
	Long QT syndrome (IV) (61)	30–50 $mg{\cdot}kg^{-1}$ + 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
	Neonatal pulmonary hypertension (IV) (63)	200 $mg{\cdot}kg^{-1}$ + 20–150 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
	Pheocromocytoma (IV) (64)	30–50 $mg{\cdot}kg^{-1}$ + 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$
Organ protection	Neuroprotection (IV) (68–72)	250 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$
	Myocardial protection (cardioplegia) (73,74)	40–80 $mg{\cdot}kg^{-1}$
Hypomagnesemia	Perioperative hypomagnesemia (IV) (58,59)	25–50 $mg{\cdot}kg^{-1}$ ± 5–20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$

Table 4 Magnesium sulfate adverse effects (1–4)

	Serum Mg >3–4 mg·dl^{-1}	Serum Mg > 10–12 mg·dl^{-1}
Digestive system	Nausea Vomiting	
Nervous system	Dizziness Headache Lethargy Hyporeflexia	Flaccid palsy Coma
Respiratory system		Respiratory Depression Apnea
Cardiovascular system	Hypotension 1st degree AV block	Complete AV block Asystolia

alveolar concentration by 50% and the induction dose of propofol; it shortens the latency time until a bispectral index value <60 is reached; and it reduces ventilation requirements (tidal volume and respiratory rate) as metabolism decreases (O_2 consumption and CO_2 production) (2,6).

Sevoflurane has certain excitatory effects on the central nervous system, which may be associated with increased seizure activity in children. It seems to be related to emergence agitation and shivering, both of which are common during recovery from pediatric anesthesia (incidence up to 80%) (7,8). In most reviewed studies, IV $MgSO_4$ (20–30 mg·kg^{-1} ± 10 mg·kg^{-1}·h^{-1}) appeared to prevent and reduce the incidence and intensity of both phenomena, mainly in adenotonsillectomy surgery (7–10), while only one paper found no significant difference (11). Moreover, locoregional $MgSO_4$ also showed to decrease the incidence of agitation, both in peritonsillar infiltrations (2–5 mg·kg^{-1}) and in caudal blockades (total dose of 50 mg) (12,13). It supports the 'analgesic theory', which upholds that this effect is due to the analgesic properties of $MgSO_4$, considering pain as a risk factor for emergence agitation (14,15).

In addition, $MgSO_4$ (50 mg·kg^{-1} + 10–40 mg·kg^{-1}·h^{-1}) was successfully used to treat refractory epileptic seizures, so its use may be interesting in the prevention and treatment of perioperative seizures in children with epilepsy (16).

Analgesia

Magnesium may modulate the transmission of nociceptive stimuli and pain perception by blocking NMDA receptors and calcium channels in the central nervous system–brain and spinal cord (1–3). Several studies support the analgesic effect of magnesium in orthopedic, cardiac, abdominal, or otolaryngological surgery.

In adults, perioperative systemic $MgSO_4$ (both as a single dose [30–50 mg·kg^{-1}] and followed by subsequent continuous infusion [5–20 mg·kg^{-1}·h^{-1}]) appears to reduce postoperative pain—more at rest than in motion—and opioid consumption during the first 24 h, and seems to improve postoperative sleep quality (17–21). However, a pediatric clinical trial testing systemic $MgSO_4$ for postoperative analgesia in tonsillectomies, found no significant difference (22).

In children, $MgSO_4$ may be helpful as an analgesic adjuvant in locoregional anesthesia. Peritonsillar infiltration with $MgSO_4$ (2–5 mg·kg^{-1}) combined with local anesthetics reduces perioperative pain in tonsillectomy (12,23). Likewise, topical $MgSO_4$ has also been effective for analgesia in this type of surgery, using gauzes impregnated with $MgSO_4$ (2 mg·kg^{-1}) for 3 min in each tonsillar fossa (24). Moreover, epidural $MgSO_4$ (total dose of 50 mg)—as an adjuvant in caudal blockade—improves and prolongs the analgesic effect of local anesthetics, enhances functional recovery after blockade, and prevents emergence agitation (5,13,25). Additionally, intrathecal $MgSO_4$ (0.5–1 mg·kg^{-1}) reduces perioperative analgesic consumption in open heart surgery and also shortens postoperative extubation time (26).

In adults, preoperative $MgSO_4$ (15–30 min before anesthetic induction) has been effective in reducing postoperative sore throat after endotracheal intubation. The administration can be achieved through gargles ($MgSO_4$ 20 mg·kg^{-1}) and/or nebulization ($MgSO_4$ 225 mg) (27–29). Probably this effect can be extrapolated to children; however, further pediatric studies are required to confirm this hypothesis.

$MgSO_4$—systemic and neuraxial—may also be useful in the prevention and treatment of NMDA receptor-mediated central sensitization, among which we find opioid-induced hyperalgesia and chronic postoperative pain (2,4,25).

$MgSO_4$ has also been attributed certain antiemetic properties, which seems to be more related to a reduction of perioperative opioid consumption (4).

Muscle relaxation

Magnesium inhibits presynaptic acetylcholine release and increases postsynaptic depolarization threshold (by blocking calcium channels), providing muscle relaxant and spasmolytic properties (1–3).

$MgSO_4$ reduces onset time, intubating doses and the total requirements of nondepolarizing muscle relaxants (aminosteroids and bencylisoquinolines), while increasing their duration of action. With respect to depolarizing blockers (succinylcholine), $MgSO_4$ does not seem to modify the onset and duration times, although it may

prevent potential fasciculations and hyperkalemia (but not malignant hyperthermia) (2). Likewise, $MgSO_4$ can also decrease the amplitude of motor evoked potentials during scoliosis correction surgery (30).

$MgSO_4$ (30 mg·kg^{-1}) has also shown to improve the conditions for tracheal intubation without neuromuscular blockers (avoiding their adverse effects or contraindications), by combining with propofol and fentanyl during the anesthetic induction (31).

Cerebral palsy can be associated with spasticity due to an excessive release of glutamate (excitatory neurotransmitter) plus a reduction in the release of gamma-aminobutyric acid (inhibitory neurotransmitter). Based on this and the proliferation of extrasynaptic receptors by denervation, these patients may develop resistance to nondepolarizing muscle relaxants. $MgSO_4$ adjuvant (50 mg·kg^{-1} + 15 mg·kg^{-1}·h^{-1}) plays an important role in cerebral palsy, by reducing the requirements of nondepolarizing blockers and preventing the worsening of spasticity by perioperative stress (32).

Laryngospasm is an airway protective reflex, mainly related to stimulation (secretions, blood, or handling) during light anesthesia. The incidence of laryngospasm in pediatric anesthesia is about 2%, increasing to 10% in upper airway infection and even to 25% after extubation in adenotonsillectomy. $MgSO_4$ appears to reduce postextubation laryngospasm in adenotonsillectomy, both in IV administration (15 mg·kg^{-1}) and in peritonsillectomy local infiltration (2–5 mg·kg^{-1}) (23,33,34).

$MgSO_4$ (30 mg·kg^{-1}) also seems to inhibit postextubation cough and opioid-induced cough, both of which may have negative effects in neurosurgical, ophthalmological, and abdominal surgery due to an increase in intracranial, intraocular, and abdominal pressure (33,35).

$MgSO_4$ plays an important role in the prevention and treatment of bronchial hyperresponsiveness and bronchospasm, given its muscle relaxant, spasmolytic, and anti-inflammatory properties (Mg seems to inhibit mast cell degranulation, therefore decreasing histamine and prostaglandin release). Besides, it may prevent hypomagnesemia induced by beta-adrenergic drugs (36). Despite numerous publications supporting the efficacy, safety, and cost-effectiveness of $MgSO_4$ in the management of bronchial hyperresponsiveness, there is no clear consensus in terms of indication, therapy initiation, and dosing regimen (36–41). Intravenous $MgSO_4$ (50–100 mg·kg^{-1} + 40–50 mg·kg^{-1}·h^{-1}) associated with standard treatment—inhaled bronchodilators and systemic corticoids—obtains better results. The best outcomes have been achieved in high severity crisis, early therapy initiation, and with high doses [reducing the needs for ventilatory support, pediatric intensive care unit (PICU) stay, and the costs] (2,36–45). It even appears to be more effective and to have fewer side effects than adjuvant IV therapy with aminophylline and terbutaline (46). The most recent research tries to assess the role of nebulized $MgSO_4$ in the management of bronchial hyperresponsiveness. Although more studies are needed in this line, current results suggest favorable cost-effectiveness; better side effect profile than IV $MgSO_4$; greater response in severe crisis and early treatment; and comparable efficacy to nebulized epinephrine, lower than nebulized beta-2 agonists and IV $MgSO_4$, and higher when it is associated with nebulized beta-2 agonist. The recommended dosing regimen for nebulized $MgSO_4$ is 40 mg·kg^{-1} or a total dose of 150 mg (47–55).

Finally, $MgSO_4$ (adjusted to achieve a target Mg serum level of 3.5–4.5 mg·dl^{-1}) has also been successfully used in the management of tetanus as an adjuvant to treat muscle spasm and contractions, potentially lethal in case of laryngeal muscle involvement (56).

Antiadrenergic response

Magnesium blocks calcium channels and regulates sodium–potassium transport in the cell membrane, behaving thus as a membrane stabilizer. Besides, it inhibits catecholamine release from adrenal glands and adrenergic nerve terminals. All this gives Mg antiarrhythmic, vasodilator, and spasmolytic properties (1–3).

Pediatric cardiac surgery with cardiopulmonary bypass is associated with hypomagnesemia—caused by hemodilution (cardiopulmonary bypass, fluid therapy, and transfusion therapies), redistribution (beta-adrenergics, calcium, and digoxin) or renal losses (diuretics and hemofiltration)—predisposing to arrhythmias in the postoperative period, which represent a risk factor for late morbidity and mortality. $MgSO_4$—administered during rewarming and weaning from cardiopulmonary bypass (25–50 mg·kg^{-1})—seems to reduce the risk of ectopic junctional tachycardia by more than 50% (the most common arrhythmia, with an incidence of 10–20%). The higher the dose (50 over 30 mg·kg^{-1}) and the more the complexity of the surgical procedure, the greater the effect. Likewise, the incidence of hypomagnesemia related to this surgery can be reduced by 30% (57–60).

Long QT syndrome consists of an alteration of repolarization which can predispose to the torsade de pointes—polymorphic ventricular tachycardia, potentially lethal—during adrenergic stimulation (anxiety, pain, light anesthesia) and when using certain medication (halogenated agents, ondansetron, and droperidol). $MgSO_4$ can be used as a first-choice drug in torsade de pointes treatment, and as preventive therapy for this

arrhythmia in the anesthetic management of long QT syndrome (30–50 $mg \cdot kg^{-1}$ + 5–20 $mg \cdot kg^{-1} \cdot h^{-1}$) (2,61).

Regarding digoxin-induced ventricular arrhythmias, $MgSO_4$ may be used as a first-line drug (25 $mg \cdot kg^{-1}$)—especially if hypomagnesemia and hypokalemia are present—until the anti-digoxin antibody is available (2).

$MgSO_4$ (40 $mg \cdot kg^{-1}$) has also been applied successfully in the prevention and control of bronchial hyperresponsiveness-associated tachycardia (triggered by hypoxemia, hypercarbia, or beta-adrenergic drugs), reducing thereby O_2 consumption in a situation of decreased O_2 supply (62).

Neonatal persistent pulmonary hypertension is a syndrome associated with various cardiopulmonary diseases in neonates (perinatal asphyxia, pulmonary hypoplasia, hyaline membrane disease, congenital heart disease, etc.). It consists of a marked increase in pulmonary artery pressure and pulmonary vasoreactivity, which results in a right-to-left shunt with subsequent refractory hypoxemia. $MgSO_4$ appears to provide certain benefits in the management of neonatal persistent pulmonary hypertension, when it is refractory to mechanical hyperventilation and to nitric oxide, as it behaves as a pulmonary arterial vasodilator (also systemic vasodilator). The main treatment limitations that may arise are the onset time (the oxygenation enhancement begins after 1 h of treatment and is significant after 6 h) and systemic hypotension (vasopressor drugs can be necessary). The initiation of $MgSO_4$ therapy includes a loading dose of 200 $mg \cdot kg^{-1}$ followed by an infusion of 20–150 $mg \cdot kg^{-1} \cdot h^{-1}$ (serum levels >10 $mg \cdot dl^{-1}$) (3,63).

Pheochromocytoma is a catecholamine-producing adrenal tumor, whose diagnosis in the pediatric age reaches up to 20%. The hemodynamic management in the course of surgical resection involves a real challenge for the anesthesiologist. $MgSO_4$ therapy may be beneficial through different mechanisms: inhibition of catecholamine release from the adrenal medulla and adrenergic nerve terminals; direct blockade of adrenergic receptors; arterial vasodilation (mixed vasodilators, such as nitroglycerin and nitroprusside, can be deleterious due to venous vasodilation, especially if hypovolemia coexists); and antiarrhythmic effect (calcium antagonism) (1–3). As an adjuvant drug in the perioperative period, $MgSO_4$ reduces the needs for administration of alpha–beta blockers and other vasodilators. The proposed dosing regimen consists of a loading dose of 30–50 $mg \cdot kg^{-1} \cdot h^{-1}$ (which can be increased) followed by a continuous infusion of 15–30 $mg \cdot kg^{-1} \cdot h^{-1}$, with additional boluses of 5 $mg \cdot kg^{-1}$ during peak blood pressure and heart rate (2,3,64).

Sickle-cell disease is the most common structural hemoglobinopathy, where (rigid and nondeformable) hemoglobin S does not cross the microcirculation; hence, it becomes hemolyzed and produces microthrombi. The main clinical features are hemolysis and vaso-occlusive crisis; the latter can cause organ damage (brain, kidney, spleen, liver, and lung) and are usually related to stress (anxiety, pain, and surgery), dehydration, acidosis, hypoxemia, hypercarbia, and hypothermia. In the course of their disease, these patients may need surgical treatments (such as splenectomy, cholecystectomy, or hip arthroplasty), whose anesthetic management requires a meticulous prevention and an aggressive treatment of the potential complications. $MgSO_4$ can play a beneficial role, given its vasodilator, analgesic, and anti-inflammatory effect. Although there is no specific research on $MgSO_4$ applied to the anesthetic management of this pathology, recent clinical trials have assessed hospital stay and its analgesic use in children hospitalized for vaso-occlusive crisis and treated with $MgSO_4$ (40–100 $mg \cdot kg^{-1}$ every 8 h). Current results make no significant difference to the standard treatment, being necessary further studies in the clinical setting, especially in the perioperative (65–67).

Organ protection

Cell ischemia consists of the reduction of oxygen/nutrient input and catabolite removal, causing cell injury in which the following pathophysiological mechanisms are involved: Inhibition of the oxidative phosphorylation with intracellular reduction of O_2 partial pressure and ATP levels; Inhibition of active ion transport (by ATP-powered pumps) with intracellular accumulation of calcium and sodium, which draws H_2O into the cell causing cellular swelling; Production of free radicals (during reperfusion) by reacting O_2 with anaerobic catabolites; Expression of cytokines (IL-1, IL-6, TNF-α, and substance P) with the subsequent inflammatory response and immune cell invasion; Excitotoxicity, consisting of an excessive release of glutamate in the central nervous system, which overactivates NMDA receptors and enhances the intracellular influx of calcium and sodium (1–3,68,69).

The significant role of Mg in organ protection is due to its physiological effects, performed at the cellular level: Maintaining levels of intracellular ATP (ATP-Mg complex) for energy production and cell function; Inhibiting the influx and accumulation of intracellular calcium (blockade of calcium channels and NMDA receptors), preventing cell swelling or edema; Attenuating the production of free radicals and inflammatory

mediators, with the subsequent reduction of oxidative cell damage (1–3).

Regarding neuroprotection, both serum Mg in upper limits (2.4 $mg \cdot dl^{-1}$) and $MgSO_4$ therapy have shown to be effective and safe in hypoxic-ischemic encephalopathy, both in prevention (antenatal maternal administration in preterm birth) and treatment (postnatal newborn administration). A number of clinical trials have reported an improvement, with no significant side effects, in short-term neurological outcomes (lethargy, hypotonia/hyporreflexia, and seizures). They found no difference in long-term neurological outcomes (cerebral palsy). Postnatal $MgSO_4$ administration consists of a single daily dose during 3 days (after birth): the most frequently used regimen is three doses of 250 $mg \cdot kg^{-1}$; an alternative regimen is one dose of 250 $mg \cdot kg^{-1}$ + two doses of 125 $mg \cdot kg^{-1}$. Nevertheless, further studies are needed to strengthen the initial evidence in short-term outcomes, and to provide it (if exists) in long-term ones (68–72).

Concerning myocardial protection after cardiopulmonary bypass, $MgSO_4$ supplementation in cardioplegic solutions—especially in normocalcemic ones—preserves myocardial function and vascular oxidative stress caused by ischemia–reperfusion, counteracting thus the deleterious effects of intracellular hypercalcemia (cellular edema and negative lusitropy) and hyperkalemia (arrhythmias). 'Traditional' calcium channel blockers have a reduced and prolonged effect in children, which can lead to myocardial depression in the postoperative period. The optimal $MgSO_4$ concentration in cardioprotective cardioplegia is 2–4 $g \cdot l^{-1}$ (2–4 $mg \cdot ml^{-1}$), starting with a bolus dose of 20 $ml \cdot kg^{-1}$, equivalent to 40–80 $mg \cdot kg^{-1}$ of $MgSO_4$ (73,74).

In relation to the modulation of systemic inflammatory response, serum levels of proinflammatory mediators in neonates are related to organ damage. Cytokine release is increased in hypomagnesemia, so that $MgSO_4$ adjuvant therapy may have beneficial effects on immunomodulation (75).

Almost all the reviewed studies of this section focused on neonatal neuroprotection and myocardial protection in cardiac surgery. However, it seems reasonable to infer the benefit of $MgSO_4$ therapy for perioperative organ protection—cerebral, myocardial, renal, or splanchnic—in other surgeries (neurosurgery, cardiothoracic, and transplant surgery) and clinical situations (severe systemic inflammatory response syndrome and circulatory shock) with high hypoxic-ischemic-inflammatory risk. Future studies in this research field may provide valuable insight into the proven cellular protective effect of Mg and its high therapeutic index.

Hypomagnesemia

It is the most common underdiagnosed electrolyte disturbance (serum Mg <1.5 $mg \cdot dl^{-1}$ or 0.62 $mmol \cdot l^{-1}$). Its incidence in hospitalized children is 15% and can increase up to 50% in cancer patients. In PICU, it rises above 20% and may reach 70% after certain surgical procedures (cardiac, major orthopedic, and oncologic surgery) (58,59,76,77). Hypomagnesemia may increase mortality of children admitted to PICU up to 25%. It also increases morbidity and is associated with hypokalemia, hypocalcemia, hypoalbuminemia, metabolic alkalosis, need for ventilatory support, and longer stay in PICU (2,3,77).

The causes of perioperative hypomagnesemia can be classified into two broad categories (1,2):

Losses: Renal losses are the most common ones, especially promoted by diuretic treatment (except potassium-sparing ones) and antibiotics (aminoglycoside and amphotericin B). Digestive losses are related to mechanical bowel preparation prior to colorectal surgery and to perioperative vomiting. Finally, the effect of intraoperative blood losses on Mg plasma levels must be taken into account.

Redistribution: Aggressive fluid replacement, transfusion therapy, cardiopulmonary bypass and hemofiltration may provoke a dilutional hypomagnesemia. Parenteral nutrition, insulin, citrate, and adrenergic agonists facilitate the intracellular transport of Mg.

Clinical characteristics of hypomagnesemia are caused by increased cellular excitability in different tissues: weakness, cramps, or tetany (muscle); tremors, hyperreflexia, seizures, or confusion (nervous system); tachycardia, arrhythmia, or hypertension (cardiovascular system) (1,2).

The treatment is based on Mg repletion with $MgSO_4$ administration, starting with a loading dose (25–50 $mg \cdot kg^{-1}$) followed by a continuous infusion (5–20 $mg \cdot kg^{-1} \cdot h^{-1}$). Hemodynamic, respiratory, and neuromuscular (patellar reflex) monitoring is required, and Mg and creatinine determination in plasma is recommended (58,59).

Therapeutic index and cost-effectiveness

Regardless of the positive results in terms of effectiveness, most of the reviewed studies support the safety of $MgSO_4$. Only bradycardia and hypotension were reported as consistent adverse effects, with no clinical consequences and with no need for treatment withdrawal. There were no cases of 'clinical hypermagnesemia' related to treatment overdosing (almost exclusively in patients with renal dysfunction). Therefore, $MgSO_4$ appears to present an optimal safety profile (2,5,17–20,31,36–46,48,49,59,68–72).

According to the Spanish Agency for Medicines and Medical Devices (www.aemps.gob.es), the price of $MgSO_4$ vial is 0.8–0.9€ ($0.9–1). Most $MgSO_4$ regimens for pediatric anesthesia require two vials: one for bolus and another for infusion (diluted in saline solution 100 ml). The cost of $MgSO_4$ treatment would be <2 Euros/Dollars.

Therefore, $MgSO_4$ therapy applied to pediatric anesthesia seems to have a high therapeutic index and a favorable cost-effectiveness.

Summary

Magnesium is an 'undervalued' molecule with multiple biochemical and physiological functions, making its use very attractive in a challenging field such as pediatric anesthesia. Some applications of $MgSO_4$ to pediatric anesthesia (like locoregional analgesia, arrhythmias, or bronchial hyperresponsiveness) have the endorsement of multiple research studies, while others (like systemic analgesia, organ protection, pheochromocytoma, or epilepsy), already demonstrated in adults or empirically supported, need more pediatric studies to be undertaken. $MgSO_4$ therapy in children offers a simple pattern of preparation and administration (preventing medication error), an excellent safety profile and a very low cost. All this gives $MgSO_4$ a high therapeutic index and an optimal cost-effectiveness.

For the aforementioned reasons, we could consider $MgSO_4$ a *Super Adjuvant* in pediatric anesthesia. Nevertheless, future studies providing new evidence in certain aspects and applications are required.

Reflective questions

- What three major biochemical actions at intracellular and membrane level determine the important role of magnesium physiologically and as a 'multi-tool' in pediatric anesthesia?
- Why is magnesium sulfate therapy very safe and overdose toxicity very unlikely in patients with renal normofunction?
- In which clinical settings magnesium sulfate may have a modulatory role—given its cellular protective effect—to be studied in future research?

Ethics approval

Ethics approval not required.

Funding

The study received no external funding.

Conflict of interest

The authors report no conflict of interest.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Audio S1 Summary of the key points and answers to reflective questions.

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