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Magnesium sulphate in the Emergency Department: an old, new friend

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Abstract. With our study, we searched the medical literature to find magnesium (Mg) correlation with Emergency situations or its use in Emergency Medicine. Our aim is to fill the gap that we find in our daily routine between Mg studies on its role in Emergency and the real conception that doctors have of it in medical practice. We searched the literature for terms as magnesium or magnesium sulphate, magnesium in emergency, eclampsia, arrhythmias, acute asthma exacerbation, magnesium, and pediatric population. After a thorough research, we divided our discoveries into chapters to sort out a large amount often discordant articles.

Key Words
Magnesium sulphate, Emergency Department, Eclampsia, Atrial and ventricular arrhythmias, Acute asthma exacerbation, Migraine, Fetal neuroprotection.

Introduction

Magnesium (Mg) is one of the most common cations in the human body and its role is well known in human biology. Many researches in the last decades focused on studying its role as an aid or even a therapy for different conditions, some of which are life-threatening. However, solid large prospective studies are lacking.

Up to now the use of Mg in the Emergency Department (ED) has entered the daily routine in the treatment of many conditions. However, this is often due to personal experiences and not to codified international guidelines, and in any case, this is done in the absence of solid scientific basis. Furthermore, there is an important lack of clinical studies which waits to be filled.

With our research, we tried to take stock of the situation to start filling the gap in the medical emergency literature.

The discovery of magnesium sulphate ($MgSO_4$) as a drug happened in the late 19th century, as it was used for treating eclamptic fits by intrathecal injections in 1906[1].

Magnesium is an abundant mineral in the body, present in the bone, the heart, and the central nervous system. Of all the cations in the human body, Mg is the fourth most common one, or the second if you consider only the intracellular level[2]. It has an extremely important role in the ATP cycle, in DNA, RNA and protein metabolism and is a cofactor for more than 300 enzymatic reactions[3]. It plays a part in regulating muscle relaxation, blood pressure, electrical excitability in the heart cells, insulin metabolism, vasomotor tone, neuromuscular conduction, and nerve transmission.

It affects smooth muscle relaxation by:

- Regulating ion passage through calcium channels and inside the cell through competitive action;
- Reducing the depolarizing effect of acetylcholine on the neuromuscular endplate;
- Reducing the effect of calcium on the release of neurotransmitters at motor-nerve terminals;
- Stimulating the smooth muscle relaxing effect of prostaglandins;
- Acting as a crucial part in the activation of adenylate cyclase through the interaction of the beta-agonist receptor complex, G protein, and GTP[4].

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It helps regulate the activation of cardiac muscle by:

– Affecting myocardiocyte depolarization by modulating the calcium channel activity;
– Affecting the resting membrane potential of myocardiocytes by influencing inward rectifier potassium channels. Because of this, it is crucial for the ATPase pump function and its action helps stabilize membranes in any excitable tissue. It has anti-inflammatory properties because of the reduction of super-oxide creation it causes (*in vitro*), and the free-radical scavenging. The normal serum concentration of Mg is 1.5-2.5 mEq/L (1.8-3.0 mg/dL).

Mg is bound to plasmatic proteins in a percentage that varies from 30% to 50%[5]. Markedly, the only biologically active part is the ionized one[6]. One vial of $MgSO_4$ heptahydrate contains 1 g/10 ml, which corresponds to 8.1 mEq. This is the most frequently used dosage, although vials of 2 g/10 ml, 2.5 g/10 ml, and 2 mEq/mL exist. There is no oral-use Mg-based drug with an equivalent dosage. Saline solution (0.9%) and glucose solution (5%) are used to dilute it. The solution's pH is between 5.5-7.0, with an osmolarity of 811 mOSm/L. The right way to store it is at room temperature. The drug precipitates if mixed with solutions containing high-concentration alcohol, heavy metals, carbonates and bicarbonates, sodium hydrocortisone, succinates, phosphates, polymyxin B sulphate, procaine hydrochloride, calcium salicylate, clindamycin phosphate, and tartrates. Extra precautions are needed if the patient is taking some drugs[7], as shown in Table I. A Mg bolus leads to a significant but short-lived increase of Mg serum concentration, due to renal excretion and distribution, as well shown by Biesenbach et al[8].

Side effects of Mg administration are rare, thanks to its wide therapeutic index. If they occur, they usually consist of facial flushing or transient hypotension if the infusion is too fast. In renal failure, the dose of $MgSO_4$ must be adjusted and the serum levels must be frequently monitored[9].

Hypomagnesemia is present in various chronic diseases, like Alzheimer's disease, hypertension, insulin resistance, type-2 diabetes mellitus, cardiovascular diseases, migraines, ADHD, and chronic kidney failure[10]. It can cause platelet dysfunction, neurological and cardiovascular alterations, immune system depression, changes in insulin response, and electrolyte imbalances. The most frequent cause of low Mg levels is the chronic use of PPIs (proton pump inhibitors), especially when associated with diuretics, as is often done in chronic kidney failure. Other causes of chronic hypomagnesemia are low intake (starvation), high requirement (pregnancy, early childhood or lactation) or excessive loss (malabsorption from the GI tract, the kidneys, or both, e.g. in alcoholism). Possible acute causes are epinephrine administration, exposure to extreme cold, extensive surgery or acute injury. Hypomagnesemia can be asymptomatic. If it is not, it can manifest itself with: myoclonus, ataxia, seizures, psychiatric symptoms (apathy, delirium), Chvostek sign, Trousseau sign (rare), nystagmus, dysphagia, spontaneous carpopedal spasm (rare), cardiac arrhythmias (which can cause unexpected death), hypocalcemia (sensitive only to Mg infusion), tremor, and hypokalemia (almost only sensitive to Mg infusion). The standard dose for correcting hypomagnesemia is 1 mEq/kg on the first day, followed by 0.3 to 0.5 mEq/day for 3 to 5 days[11]. In emergencies (seizures, and dangerous cardiac arrhythmias) a bolus injection of 1 g (8.1 mEq) can be used.

Table I. Drugs for which caution is required in the administration of magnesium.

Depressors of the central nervous system (barbiturates, narcotics, hypnotics, general anesthetics)	In this case the dosage of $MgSO_4$ has to be reduced
Cardiac glycosides.	In case of Mg overdose these drugs worsen the effects on cardiac conduction.
Eltrombopag (oral agonist of trombopoietin receptors).	$MgSO_4$ reduces its effect
Rocuronium	Together the two drugs amplify the neuromuscular blockage and risk causing an important respiratory depression
Labetalol	Mixing the two can cause bradycardia, reduction of the cardiac output and syncope
Calcium antagonists	Together they can cause severe hypotension
Neuromuscular blockers (like aminoglycoside antibiotics)	$MgSO_4$ can amplify their effect
Nifedipine	It has an additive effect

Table II. Relation between Mg plasma concentration and side effects.

$MgSO_4$ plasma concentration	Side effect expected
From 3.5 to 5 mmol/L	Loss of the patellar reflex
From 5 to 6.5 mmol/L	Respiratory paralysis
>7.5 mmol/L	Cardiac conduction alterations
>12.5 mmol/L.	Cardiac arrest

Hypermagnesemia is not often seen and is almost always iatrogenic. If 12 mg/dL of Mg serum levels are reached, the side effects are abnormal cardiac conduction, and respiratory depression due to muscle insufficiency and absence of reflexes (Table II[12]). In more severe cases, coma and cardiac arrest are possible. This is why a repeated evaluation of the patellar tendon reflex proves to be an efficient method of assessing the presence of toxicity. Older patients are more at risk for hypermagnesemia due to the prevalence of kidney failure that compromises renal clearance. It is common to miss hypermagnesemia due to the fact that it is not a part of standard bloodworks. When diagnosed, it can be treated with calcium gluconate. There is a possible connection between high Mg levels at admission in the emergency department and early in-hospital death[13].

Magnesium in Eclampsia

$MgSO_4$ has been the first and gold standard treatment for preeclampsia and eclampsia for more than 50 years[14]. Its routine use started about 100 years ago, although at the beginning of the twentieth century it was administered intrathecally, for fear of respiratory paralysis secondary to intravenous infusion[15]. However, the best plasma concentration range to be used to obtain the strongest results and avoid side effects is not yet known[16]. Compared to the use of Mg in other conditions, the plasmatic levels of Mg obtained in preeclampsia and eclampsia are significantly elevated. The plasma concentration necessary to prevent or treat preeclampsia or eclampsia is between 3.5-7 mEq/L (4.2-8.4 mg/dL)[17]. To obtain these ranges, there are two worldwide used protocols for treatment: intravenous Zuspan[18] or the intramuscular Pritchard[19]. The intravenous protocol is given as a 4 g dose, followed by a maintenance infusion of 1 to 2 g/h by controlled infusion pump. The intramuscular regimen is most commonly a 4 g intravenous loading dose, immediately followed by 10 g intramuscularly and then by 5 g intramuscularly every 4 h. Evidently, the doses vary greatly between the two protocols. Due to the strong differences between the normal and the therapeutic range, the focus of many researches has been on finding the lowest effective dose, to avoid toxic effects. In 2016, Okusanya et al[20] produced the biggest meta-analysis on the subject to study the efficacy of different intravenous and intramuscular regimens, but no clear target serum level was found. The authors conclude the meta-analysis by suggesting that the effective serum Mg levels are lower than those normally accepted and obtained with the standard regimens. Therefore, they suggest the creation of clinical trials designed to identify serum reference levels. The pathway of $MgSO_4$ is not completely clear but it is well known that its action against eclampsia and preeclampsia is not caused by a single effect. Many possible roles of Mg were suggested by various authors. Some believe Mg is effective because of its action as a calcium antagonist, both on an intracellular and extracellular level, others suggest it acts directly on cerebral endothelial cells[21]. Indeed Mg may act as a vasodilator in the peripheral and brain vessels[22,23] and decrease peripheral vascular resistance or relieve vasoconstriction[24]. Moreover, it is believed to reduce the formation of cerebral edema by protecting the blood-brain barrie[25], or through a central anticonvulsant action[26]. The most plausible effect of Mg is connected to a paradox. Eclampsia is no more than a form of posterior reversible encephalopathy syndrome (PRES, see also in the "miscellaneous" section) that is caused from high arterial blood pressure levels which are involved in vessel dilation, loss of blood-brain barrier impermeability, and consequently cerebral edema[27]. So, the administration of a vasodilator like $MgSO_4$ should not be a treatment but a co-cause of eclampsia. In reality, the vasodilatory effect of Mg is exerted in an extremely more effective way in the peripheral and mesenteric vessels than in cerebrovascular system[28]. So, the Mg effect is mediated by a blood pressure reduction obtained through a peripheral enlargement of the vascular system. About the blood-brain barrier and edema reduction, some authors suggest a direct effect on the calcium-binding protein in endothelial brain cells. This action on the endothelial cell actin cytoskeleton could reduce fluid movements through the cell, inducing a down-regulation in pinocytosis. The protective effect of Mg on the blood-brain barrier by reducing cerebral edema

is noticeable in other conditions like head trauma[29], confirming the existence of direct action on endothelial brain cells. The latter proposed mechanism is a direct anticonvulsant activity. Seizures are started and spread through the mediation of glutamate receptors. $MgSO_4$ has a direct effect on the N-methyl-d-aspartate (NMDA) antagonist receptors, which are a type of glutamate receptors[30]. On the other hand, a reduction in NMDA binding activity is registered under Mg therapy. It is not clear which is the most significant pathway, and other authors disagree with this evidence by citing the impermeability of the brain-blood barrier to Mg, but the anti-seizure effect cannot be denied[31]. Studies in which Mg was compared to other anti-epileptic or hypotensive drugs demonstrated a superiority of the first. In particular, the multinational Collaborative Eclampsia Trial showed that the risk of recurrent seizures in eclamptic women was reduced by 52% with magnesium compared to diazepam, and by 67% when compared to phenytoin[32]. Similar effects were obtained in other trials with Mg *versus* nimodipine, phenytoin, diazepam, and placebo[33-36]. On the other hand, in a recent trial by Khooshideh at al[37], while the efficacy of Mg was confirmed, it was stressed that there are risks of tocolytic effects during the first months of pregnancy, which were significantly higher than in phenytoin group ($p < 0.001$), and the number of cesarean sections ($p = 0.040$) was higher as well. In Brazil in 2016 Lotufo et al[38] performed a situational analysis, showing that there is no access to $MgSO_4$ in primary care facilities for eclampsia or for the obstetric care staff for emergency and clinical protocols. This is very dangerous because Mg is the drug of choice for seizure prevention and control in the management of severe eclampsia. A similar study[39] was made in India in 2017 and they found that the availability of $MgSO_4$ should be improved, and clinical guidelines around its administrations should be made. Training health care providers on the identification and treatment of preeclampsia/eclampsia could lead to notable improvements in maternal and infant mortality. The benefits of $MgSO_4$ for eclampsia had already been observed[40] in a retrospective study that found a remarkable reduction in the fatality rate due to eclampsia in those who received $MgSO_4$ therapy with minimal increase in costs, when compared with diazepam therapy. Recently, it is being used in pre-eclamptic women undergoing elective cesarean sections for its analgesic effect[41].

Magnesium and cardiovascular diseases

Hypomagnesemia is a frequent finding in patients suffering from heart failure, especially if they are being treated with diuretics; in an old study[42] where 297 patients were enrolled, hypomagnesemia was observed in 37% of them. Furthermore, normal levels of serum Mg do not necessarily correspond to normal Mg values at tissue level; in fact, it was observed that in patients with heart failure treated for several years with diuretic therapy, the magnesium tissue values were lower than normal and tended to normalize after magnesium supplementation[43]. Diuretic therapy is not the only cause of hypomagnesemia in such patients; a disproportionate activation of the renin-angiotensin-aldosterone system can also produce hypomagnesemia[44]; moreover, the increase in circulating catecholamines occurring during congestive heart failure increases the release of intracellular magnesium resulting in renal loss[45].

Magnesium and Atrial and Ventricular Arrhythmia

Hypomagnesemia appears to promote the development of some atrial and ventricular arrhythmias. The administration of Mg has been reported to suppress Multifocal Atrial Tachycardia (MAT) in hypomagnesemic patients and, at times, in patients with normal Mg plasma levels[46,47]. The importance of Mg in treating and preventing ventricular arrhythmias, especially after acute myocardial infarction, has been known for several decades. In 1978 Chipperfield et al[48] showed a highly significant decrease in Mg concentration in sudden-death patients. In the same period, Johnson et al[49] found that the Mg levels were low in sudden-death patients who had a history of angina pectoris. We know that low potassium levels are frequently associated with low Mg levels and this type of dyselectrolytemias are common in patients treated with diuretics[50]. One must note that frequently, at variance with potassium, low levels of Mg remain undiagnosed and untreated[51]. In these patients, a potassium supplementation does not increase the potassium serum levels, but the administration of Mg sulfate causes an increase in the cellular potassium content and decreases the frequency of arrhythmias. Administration of Mg in these patients is very important because the arrhythmias caused by Mg deficiency are resistant to both antiarrhythmic drugs and electrical cardioversion[52]. In a recent meta-analysis of all data resources on the effect of $MgSO_4$ on cardiovascular events after coronary revascularization, Salaminia

et al[53] described how the use of Mg would decrease ventricular and supraventricular arrhythmias. In recent years, some studies are focusing on the possible relation between Mg deficiency and atrial fibrillation (AF)[54]. In particular, in 2013 Kham et al[55] analyzed 3530 participants of the Framingham Offspring Study finding a moderated association between low serum Mg and the development of AF in individuals without cardiovascular disease during up to 20 years of follow up. These data were confirmed by Morkovits et al[56] in 2016 analyzing the Health Maintenance Organization database in which hypomagnesemia was associated with the incidence of AF over prolonged periods. Given these premises, Mg has been noted as a potential drug for the treatment of AF due to its membrane-stabilizing properties. A significant reduction below 100 bpm in heart rate during a rate control approach seems to be achieved in two studies[57,58] mostly with digoxin as background therapy. Furthermore, researches[59] focused on the role of Mg for rhythm control in acute AF along with antiarrhythmics drugs, demonstrating an increased success of cardioversion but without a dose standardization. However, the role of intravenous infusion of Mg by itself in the treatment of AF is not clear. Rajagopalan et al[60] in a recent trial randomized patients to receive Mg or placebo before electrical cardioversion: Mg infusion did not statistically increase the rate of successful cardioversion of AF, but its excellent safety profile and its properties would seem to make Mg a good option to use in facilitating electrical cardioversion. This observation reinforces Sultan's et al thesis[61] that a solution of Mg and potassium administered before electrical cardioversion could reduce the required energy. Since AF is the most common arrhythmia after cardiac and thoracic surgery, many studies in the last twenty years have looked for a way to prevent it. Two large meta-analyses[62,63] focused on arrhythmia prevention, analyzing its association with Mg, both in cardiac[62] and in thoracic surgery[63]. The current literature supports the tolerability of Mg administration that appears to reduce AF without significant adverse events, but there is limited evidence to support the routine administration of Mg for prevention of arrhythmias during and after cardiothoracic surgery.

Magnesium and Torsade De Pointes

Torsade de pointes (TdP) is a form of polymorphic ventricular proarrhythmia associated with QT interval prolongation. This condition can be congenital or iatrogenic. Iatrogenic QT interval prolongation is associated with the use of many drugs such as antiarrhythmics (especially class Ia and III), phenothiazines and butyrophenones, tricyclic antidepressants, non-sedative antihistamines, antibiotics (such as macrolides), antifungals, organophosphates, and cocaine. QT interval prolongation can also be associated with bradycardia and subarachnoid hemorrhage[64]. The effectiveness of Mg in TdP has been evaluated since 1990 by Tzivoni et al[65], but an optimal dosing regimen of $MgSO_4$ has not been established. When VF/pulseless VT cardiac arrest is associated with TdP, it can be useful to administer an IV/IO bolus of $MgSO_4$ at a dose of 1 to 2 g diluted in 10 mL[66].

Digitalis Toxicity

Digitalis is an antiarrhythmic drug that acts by inhibiting the sodium-potassium pump, which causes an increase in intracellular sodium and subsequently an increase in Na/Ca exchange with an increase in intracellular Ca. Digitalis toxicity can induce arrhythmias by increasing early afterdepolarizations and delayed afterdepolarizations[67]. Hypomagnesemia, like hypokalemia, predisposes to arrhythmias induced by digitalis toxicity. Hypomagnesemia can coexist with normal serum Mg values, especially in patients treated with long-term diuretics therapies, as previously stated. In one study[68] it was found that intravenous bolus of $MgSO_4$, followed by intramuscular Mg repletion, abolished the digitalis-toxic arrhythmias.

Magnesium and pulmonary diseases

Magnesium in Chronic Obstructive Pulmonary Disease

$MgSO_4$ given intravenously did not seem to have an immediate bronchodilator effect, however, it appears to potentiate the bronchodilator effect of inhaled beta-2 agonists. The increase in peak expiratory flow rate was larger in those who received Mg compared to placebo, without significant differences in dyspnea scores, hospital admission rates, or emergency department readmission rates compared to placebo[69]. Intravenous Mg was used in addition to standard bronchodilator therapy in acute exacerbation of COPD, showing improvements in FEV1 (the percentage change in FEV1 was 27.07% with Mg *versus* 11.39% in placebo group); similar improvements were noticed with FVC in Mg group[70]. Intravenous Mg *versus* nebulized ipratropium bromide

(IB) was studied in COPD exacerbations. It was noted that there were no significant differences between the drugs with regard to hospital admission, intubation, and hospital death rates treated in the Emergency Department. However, patients given IB in average had a greater improvement in peak expiratory flow rate compared to $MgSO_4$ and there was a significant reduction in $PaCO_2$ compared to baseline values in IB group but not in $MgSO_4$ group. There was a nonsignificant statistical trend toward a decrease in dyspnea score in both groups and adverse events were very similar[71]. Nebulized Mg was also studied as an adjuvant in the treatment of acute exacerbations of COPD in adults, but Edwards et al[72] found that, given as an adjuvant to salbutamol in the setting of COPD, it has no effect on FEV_1.

Magnesium in Acute Asthma

Asthma is a chronic respiratory condition characterized by airway inflammation, constriction of airway smooth muscles, and structural alteration of the airways that is at least partially reversible. Exacerbations of asthma can be life-threatening and place a significant burden on healthcare services. Several guidelines have been published to inform management personnel in acute settings; several include the use of a single bolus of intravenous Mg in cases that do not respond to the first-line treatment. A 2014 systematic review[73] provides evidence that a single infusion of 1.2 g or 2 g of $MgSO_4$ over 15 and 30 min reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulized short-acting beta2-agonists, and corticosteroids. An adjuvant bolus of intravenous Mg in acute bronchospasm appears statistically beneficial in improving spirometric airway function[74] and is widely used for acute asthma, usually for patients with severe or life-threatening asthma who have not responded to initial treatment. Nebulized $MgSO_4$, by contrast, is hardly used[75]. In 2016 some scholars[76] investigated the efficacy of nebulized Mg in the treatment of moderate to severe asthma attacks. They found that adding Mg to standard therapy leads to greater and faster improvements in peak expiratory flow rate, oxygen saturation, and respiratory rate. It also reduced hospitalization rates in this patient population. Nebulized $MgSO_4$ alone or combined with salbutamol has a clinically significant bronchodilator effect in acute asthma and leads to clinical improvements[77-79]. Long-term oral Mg supplementation does not lead to improved control in adult asthma, but many meta-analyses[80] of randomized controlled trials have confirmed the efficacy of both intravenous and inhaled (as an adjuvant to salbutamol nebulizer solution) Mg therapy in severe asthma.

Anesthesia and Pain Control

In anesthesia, Mg has an important role because its deficiency has been demonstrated in 7-11% of the hospitalized patients and it has been found to coexist with other electrolyte disorders, particularly hypokalemia or hypophosphatemia, hyponatremia, and hypocalcemia. Hypomagnesemia needs to be detected and corrected to prevent increased morbidity and mortality[81]. $MgSO_4$ was used during general balanced anesthesia in patients with arterial hypertension. Mg, acting as a natural calcium-channel blocker, induces direct and indirect vasodilatation, playing a role in the treatment of arterial hypertension, thus it can be used for cardiovascular stability during general anesthesia[82]. Mebazaa et al[83] have shown that the administration of Mg by intrathecal route is safe and extends the effect of spinal anesthesia. This study need further investigations. Mg oral supplementation was also used to reduce pain in patients with the severe peripheral arterial occlusive disease. It has been found that Mg may aid in maximizing the effectiveness of opioids while reducing their dose, and thus the severity of side effects. In addition to its NMDA-blocking properties, Mg has vasodilatory effects, improves endothelial function and exerts an antidepressant action[84]. In postoperative pain, $MgSO_4$ was studied as a noncompetitive antagonist NMDA receptor to modify nociceptive modulation. Intravenous administration of Mg can improve postoperative analgesia and decreases the requirement for postoperative opioids, but the effects are inconsistent and have not been reliably accompanied by a reduction in the incidence of morphine-related adverse events[85]. $MgSO_4$ was compared to ketorolac in the treatment of patients with renal colic. In a double-blind clinical trial study[86] they found that $MgSO_4$ does not influence renal colic pain relief. Another double-blind study[87] showed that $MgSO_4$ could be used as an add-on drug in the treatment of patients suffering from a renal colic.

Magnesium and Migraines

Assarzadegan et al[88] that investigated the possible pathogenetic role of Mg deficiency in migraines. This connection is based on the fact

that serum Mg levels are lower in patients with migraine, both during and in-between the attacks[88] than in non-cephalalgic ones. However, the mechanism is not clear and it is noted that the levels of serum ionized Mg, and the active form of the ion, were not different in the two groups[89]. A more practical approach to the problem has also been tried, and there are many different studies that have analyzed the use of intravenous Mg as a therapy for patients with acute migraines. In outpatient clinics, a study showed the effectiveness of IV Mg in rapidly reducing pain, but in the ED there were contradictory results; in one study no benefit was found from the protocol[90]. A second study compared IV administration of Mg, metoclopramide, and placebo and found no differences between the three[91]. A third one showed that IV $MgSO_4$ reduced pain more rapidly and effectively than dexamethasone and metoclopramide combined[92]. A fourth one argued that administering IV Mg was not only a fast and satisfactory treatment, but that it was better than ketorolac both one and two hours after the treatment[93]. The last one compared the use of 2 g of intravenous Mg to 60 mg of IV caffeine citrate and proved that the first option greatly outweighed the second one[94]. In summary, the connection between Mg levels and migraines, and the therapeutic possibilities that this implies are not disproven, but there is a great need for further investigations.

Miscellaneous

Mg was also compared with other antihypertensive drugs in the ED[95]. There was no significant difference in systolic or diastolic blood pressure between three groups (IV $MgSO_4$, parenteral or oral antihypertensive, MgSO4, and antihypertensive agent). Intravenous $MgSO_4$ is as effective as an antihypertensive drug at lowering blood pressure (BP) in the emergency department. In acute stroke, Saver et al[96,97] tried to test the prehospital use of Mg as a neuroprotective drug. The therapy was safe but did not improve disability outcomes at 90 days. In 2018, Zeng et al[98] analyzed a possible neuroprotection effect of $MgSO_4$ infusion after non-cardiac surgery, but at the moment there are not enough studies in literature to confirm or refute this hypothesis. Hypomagnesemia might participate in the cascade leading to Posterior Reversible Encephalopathy Syndrome, a serious neurological condition for which the cause was not yet found. From a retrospective work, we know that all the patients with available serum Mg levels presented hypomagnesemia. These results[99] require larger investigations to assess the importance of acute hypomagnesemia in PRES and the possible need to treat PRES with $MgSO_4$. Mg could have a role in the management of the Irukandji syndrome, a condition that results from the contact with the venom of a certain box jellyfish. But a systematic review[100] found insufficient evidence to support any clear recommendation regarding the use of Mg, nor was there clear evidence to recommend its use in the Irukandji syndrome.

Pediatric Population: a General Overview

As previously described in adults, $MgSO_4$ in emergency is strongly indicated in cases of TdP or pulseless VT associated with TdP. Limited data are available for many conditions in which Mg seems to have a precipitating or even pathogenic role, but solid studies are missing. In recent years some authors[101,102] have discussed the relation between Mg plasma levels and children with attention-deficit hyperactivity disorder (ADHD) or autism spectrum disorder. However, these findings are controversial and further researches may be needed to investigate the influence of low Mg levels and its association with brain growth. Recently, Baek et al[103] found that hypomagnesemia seems to be more common in children with febrile seizures than in controls, maybe due to a modern diet containing processed food low in Mg, but a potential role of Mg in therapy has not yet been studied.

Magnesium and Asthma

Mg use is recommended by various guidelines in cases of acute refractory asthma status, and its use has now entered clinical practice[104] for this indication. Nebulized $MgSO_4$ seems to have no particular benefit in moderate asthma exacerbations[105], but intravenous use may reduce the need for hospital admission in children presenting to the ED with severe asthma exacerbations, with a favorable "cost-benefit"[106] and safety[107] profile. However, the evidence is limited by the number and size of studies[108]. Moreover, a randomized trial of Alansari et al[109] tried to determine the utility of intravenous use of $MgSO_4$ in acute bronchiolitis when added to supportive care, but it does not seem to provide any particular benefit, although Kan et al[110] would seem to encourage the use of inhaled $MgSO_4$in the same condition, in addition to standard therapy.

Magnesium and Fetal Neuroprotection

Antenatal administration of $MgSO_4$ has an important role in the neuroprotective strategy for preterm infants[111,112]. Strong evidence from five randomized controlled trials and five meta-analyses has demonstrated that $MgSO_4$, when administered before the preterm delivery, significantly reduces the risk of cerebral palsy at two years, in absence of serious adverse effects in both pregnant women and neonates[113-117]. The mechanisms underlying this neuroprotective effect are not well established; however, studies have indicated several hypotheses. Mg can prevent excitotoxicity via NMDA receptor antagonistic action and a reduction in extracellular glutamate[118] and can exert anti-inflammatory effects by reducing oxidative stress and pro-inflammatory cytokines[119]. All the international guidelines uniformly recommended the use of $MgSO_4$ in preterm birth, although the maximum term of administration (from 29 + 6 WG to 33 + 6 WG), the duration of the maintenance dose (from 12-24 h), and the possibility of re-treatment varies.

Conclusions

Magnesium is one of the most common cations in the human body and its role is well known in human biology. Many researchers in the last decades focused on studying its role as an aid or even a therapy for different conditions, some of which are life-threatening. However, solid large prospective studies are lacking. One of the most critical points concerning Mg research is about the right therapeutic dose. A slow intravenous bolus of 2 g of $MgSO_4$, infused in not less than 20 min, seems to be the preferred dose in most investigations to minimize the side effects of a rapid administration while exploiting its full potential. Up to now the use of Mg in the ED has entered the daily routine in the treatment of many conditions, but often this is due to personal experiences and not to codified international guidelines, and in any case, in the absence of a solid scientific basis. The only emergency conditions in which $MgSO_4$ infusion has shown efficacy by itself are eclampsia, Torsade de Pointes, acute refractory asthma status and fetal neuroprotection. Nevertheless, mild rhythm disturbances like symptomatic extrasystole or multifocal atrial tachycardia in stable patients can benefit from Mg infusion, especially in association with standard therapy; however, in these conditions, there is an important lack of clinical studies which waits to be filled.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

1) Chesley LC. History and epidemiology of pre-eclampsia-eclampsia. Clin Obstet Gynecol 1984; 27: 801-820.
2) Kaye P, O'Sullivan I. The role of magnesium in the emergency department. Emerg Med J 2002; 19: 288-291.
3) Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients 2015; 7: 8199-8226.
4) Wallace C. Magnesium. Emerg Med 2003; 15: 92-96.
5) Chesley LC. Parenteral magnesium sulfate and the distribution, plasma levels, and excretion of magnesium. Am J Obstet Gynecol 1979; 133: 1-7.
6) Taber EB, Tan L, Chao CR, Beall MH, Ross MG. Pharmacokinetics of ionized versus total magnesium in subjects with preterm labor and preeclampsia. Am J Obstet Gynecol 2002; 186: 1017-21.
7) Humphrey S, Kirby R, Rudloff E. Magnesium physiology and clinical therapy in veterinary critical care. J Vet Emerg Crit Care (San Antonio) 2015; 25: 210-225.
8) Biesenbach P, Mårtensson J, Lucchetta L, Bangia R, Fairley J, Jansen I, Matalanis G Bellomo R. Pharmacokinetics of magnesium bolus therapy in cardiothoracic surgery. J Cardiothorac Vasc Anesth 2018; 32: 1289-1294.
9) Flink EB. Magnesium deficiency. Etiology and clinical spectrum. Acta Med Scand Suppl. 1981; 647: 125-137.
10) Fatuzzo P, Zanoli L, Scollo V, Portale G, Gaudio A, Pani A, Granata A. Review: UPDATE on magnesium metabolism. G Ital Nefrol 2016; 33: pii: gin/33.6.2. 1724-5590.
11) Kala J, Abudayyeh A. Magnesium: an overlooked electrolyte. J Emerg Med 2017; 52: 741-743.
12) Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clin Pharmacokinet 2000; 38: 305-314.
13) Haider DG, Lindner G, Ahmad SS, Sauter T, Wolzt M, Leichtle AB, Fiedler GM, Exadaktylos AK, Fuhrmann V. Hypermagnesemia is a strong independent risk factor for mortality in critically ill patients: results from a cross-sectional study. Eur J Intern Med 2015; 26: 504-507.
14) Pritchard JA. The use of the magnesium ion in the management of eclamptogenic toxemias. Surg Gynecol Obstet 1955; 100: 131-140.
15) Lazard EM. A preliminary report on the intravenous use of magnesium sulphate in puerperal eclampsia. Am J Obstet Gynecol 1925; 9: 178-188.
16) Gordon R, Magee LA, Payne B, Firoz T, Sawchuck D, Tu D, Vidler M, de Silva D, von Dadelszen P. Magnesium sulphate for the management of preeclampsia and eclampsia in low and middle income countries: a systematic review of tested dosing regimens. J Obstet Gynaecol Can 2014; 36: 154-163.

17) Euser AG, Cipolla MJ. Magnesium sulfate treatment for the prevention of eclampsia: a brief review. Stroke 2009; 40: 1169-1175.
18) Zuspan FP. Problems encountered in the treatment of pregnancy-induced hypertension. A point of view. Am J Obstet Gynecol 1978; 131: 591-597.
19) Pritchard JA. Management of preeclampsia and eclampsia. Kidney Int 1980; 18: 259-266.
20) Okusanya BO, Oladapo OT, Long Q, Lumbiganon P, Carroli G, Qureshi Z, Duley L, Souza JP, Gülmezoglu AM. Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. BJOG 2016; 123: 356-366.
21) Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. Mg2+-Ca2+ interaction in contractility of vascular smooth muscle: Mg2+ versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Can J Physiol Pharmacol 1987; 65: 729-745.
22) Naidu S, Payne AJ, Moodley J, Hoffmann M, Gouws E. Randomised study assessing the effect of phenytoin and magnesium sulphate on maternal cerebral circulation in eclampsia using transcranial Doppler ultrasound. Br J Obstet Gynaecol 1996; 103: 111-116.
23) Euser AG, Cipolla MJ. Resistance artery vasodilation to magnesium sulfate during pregnancy and the postpartum state. Am J Physiol Heart Circ Physiol 2005; 288: H1521-H1525.
24) Belfort MA, Moise KJ Jr. Effect of magnesium sulfate on maternal brain blood flow in preeclampsia: a randomized, placebo-controlled study. Am J Obstet Gynecol 1992; 167: 661-666.
25) Garcia JG, Davis HW, Patterson CE. Regulation of endothelial cell gap formation and barrier dysfunction: role of myosin light chain phosphorylation. J Cell Physiol 1995; 163: 510-522.
26) Cotton DB, Hallak M, Janusz C, Irtenkauf SM, Berman RF. Central anticonvulsant effects of magnesium sulfate on N-methyl-D-aspartate-induced seizures. Am J Obstet Gynecol 1993; 168: 974-978.
27) Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, Pessin MS, Lamy C, Mas JL, Caplan LR. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996; 334: 494-500.
28) Belfort MA, Saade GR, Yared M, Grunewald C, Herd JA, Varner MA, Nisell H. Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia. Am J Obstet Gynecol 1999; 181: 402-407.
29) Li W, Bai YA, Li YJ, Liu KG, Wang MD, Xu GZ, Shang HL, Li YF. Magnesium sulfate for acute traumatic brain injury. J Craniofac Surg 2015; 26: 393-398.
30) Dingledine R, Hynes MA, King GL. Involvement of N-methyl-D-aspartate receptors in epileptiform bursting in the rat hippocampal slice. J Physiol 1986; 380: 175-189.
31) Hallak M. Effect of parenteral magnesium sulfate administration on excitatory amino acid receptors in the rat brain. Magnes Res 1998; 11: 117-131
32) No authors listed. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. Lancet 1995; 345: 1455-1463.
33) Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D; Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877-1890.
34) Belfort MA, Anthony J, Saade GR, Allen JC Jr; Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003; 348: 304-311.
35) Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database Syst Rev 2010; 12: CD000127.
36) Gordon R, Magee LA, Payne B, Firoz T, Sawchuck D, Tu D, Vidler M, de Silva D, von Dadelszen P. Magnesium sulphate for the management of preeclampsia and eclampsia in low and middle income countries: a systematic review of tested dosing regimens. J Obstet Gynaecol Can 2014; 36: 154-163.
37) Khooshideh M, Ghaffarpour M, Bitarafan S. The comparison of anti-seizure and tocolytic effects of phenytoin and magnesium sulphate in the treatment of eclampsia and preeclampsia: a randomised clinical trial. Iran J Neurol 2017; 16: 125-129.
38) Lotufo FA, Parpinelli MA, Osis MJ, Surita FG, Costa ML, Cecatti JG. Situational analysis of facilitators and barriers to availability and utilization of magnesium sulfate for eclampsia and severe pre-eclampsia in the public health system in Brazil. BMC Pregnancy Childbirth 2016; 16: 254.
39) Budhwani H, Shivkumar P, Purandare CN, Cataldo NA, Desai S, Bhatt P, Baswal D, Bhardwaj A. Examining the use of magnesium sulfate to treat pregnant women with preeclampsia and eclampsia: results of a program assessment of emergency obstetric care (EmOC) training in India. J Obstet Gynecol India 2017; 67: 330-336.
40) Okereke E, Ahonsi B, Tukur J, Ishaku SM, Oginni AB. Benefits of using magnesium sulphate (MgSO4) for eclampsia management and maternal mortality reduction: lessons from Kano State in Northern Nigeria. BMC Res Notes 2012; 5: 421.
41) Elsharkawy RA, Farahat TE, Abdelhafez MS. Analgesic effect of adding magnesium sulfate to epidural levobupivacaine in patients with pre-eclampsia undergoing elective cesarean section. J Anaesthesiol Clin Pharmacol 2018; 34: 328-334.
42) Wester PO, Dyckner T. Intracellular electrolytes in cardiac failure. Acta Med Scand Suppl 1986; 707: 33-36.
43) Lim P, Jacob E. Magnesium deficiency in patients on long-term diuretic therapy for heart failure. Br Med J 1972; 3: 620-622.
44) Horton R, Biglieri EG. Effect of Aldosterone on the Metabolism of Magnesium. J Clin Endocrinol Metab 1962; 22: 1187-1192.
45) Douban S, Brodsky MA, Whang DD, Whang R. Significance of magnesium in congestive heart failure. Am Heart J 1996; 132: 664-671.
46) Iseri LT, Fairshter RD, Hardemann JL, Brodsky MA. Magnesium and potassium therapy in multifocal atrial tachycardia. Am Heart J 1985; 110: 789-794.

47) McCord JK, Borzak S, Davis T, Gheorghiade M. Usefulness of intravenous magnesium for multifocal atrial tachycardia in patients with chronic obstructive pulmonary disease. Am J Cardiol 1998; 81: 91-93.
48) Chipperfield B, Chipperfield JR. Differences in metal content of the heart muscle in death from ischemic heart disease. Am Heart J 1978; 95: 732-737.
49) Johnson CJ, Peterson DR, Smith EK. Myocardial tissue concentrations of magnesium and potassium in men dying suddenly from ischemic heart disease. Am J Clin Nutr 1979; 32: 967-970.
50) Boyd JC, Bruns DE, Wills MR. Frequency of hypomagnesemia in hypokalemic states. Clin Chem 1983; 29: 178-179.
51) Ryzen E, Elkayam U, Rude RK. Low blood mononuclear cell magnesium in intensive cardiac care unit patients. Am Heart J 1986; 111: 475-480.
52) David L. Reich, Joel A. Kaplan, Joseph S. Savino, Steven N. Konstadt. Kaplan's Cardiac Anesthesia. 5th ed., Saunders, Philadelphia, 2003.
53) Salaminia S, Sayehmiri F, Angha P, Sayehmiri K, Motedayen M. Evaluating the effect of magnesium supplementation and cardiac arrhythmias after acute coronary syndrome: a systematic review and meta-analysis. BMC Cardiovasc Disord 2018; 18: 129.
54) Kotecha D. Magnesium for atrial fibrillation, myth or magic? Circ Arrhythm Electrophysiol 2016; 9: pii: e004521.
55) Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, Magnani JW, Ellinor PT, Benjamin EJ, Wang TJ. Low serum magnesium and the development of atrial fibrillation in the community. Circulation 2013; 127: 33-38.
56) Markovits N, Kurnik D, Halkin H, Margalit R, Bialik M, Lomnicky Y, Loebstein R. Database evaluation of the association between serum magnesium levels and the risk of atrial fibrillation in the community. Int J Cardiol 2016; 205: 142-146.
57) Ho KM, Sheridan DJ, Paterson T. Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. Heart 2007; 93: 1433-1440.
58) Davey MJ, Teubner D. A randomized controlled trial of magnesium sulfate, in addition to usual care, for rate control in atrial fibrillation. Ann Emerg Med 2005; 45: 347-353.
59) Wang A. Efficacy of class III antiarrhythmics and magnesium combination therapy for atrial fibrillation. Pharm Pract (Granada) 2012; 10: 65-71.
60) Rajagopalan B, Shah Z, Narasimha D, Bhatia A, Kim CH, Switzer DF, Gudleski GH, Curtis AB. Efficacy of intravenous magnesium in facilitating cardioversion of atrial fibrillation. Circ Arrhythm Electrophysiol 2016; 9: pii: e003968
61) Sultan A, Steven D, Rostock T, Hoffmann B, Müllerleile K, Servatius H, Drewitz I, Lüker J, Meyer P, Salukhe T, Willems S. Intravenous administration of magnesium and potassium solution lowers energy levels and increases success rates electrically cardioverting atrial fibrillation. J Cardiovasc Electrophysiol 2012; 23: 54-59.
62) Fairley JL, Zhang L, Glassford NJ, Bellomo R. Magnesium status and magnesium therapy in cardiac surgery: a systematic review and meta-analysis focusing on arrhythmia prevention. J Crit Care 2017; 42: 69-77.
63) Zhao BC, Huang TY, Deng QW, Liu WF, Liu J, Deng WT, Liu KX, Li C. Prophylaxis against atrial fibrillation after general thoracic surgery: trial sequential analysis and network meta-analysis. Chest 2017; 151: 149-159.
64) Viskin S. Long QT syndromes and torsade de pointes. Lancet. 1999; 354: 1625-1633.
65) Tzivoni D, Keren A. Suppression of ventricular arrhythmias by magnesium. Am J Cardiol 1990; 65: 1397-1399.
66) Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, Kudenchuk PJ, Ornato JP, McNally B, Silvers SM, Passman RS, White RD, Hess EP, Tang W, Davis D, Sinz E, Morrison LJ. Part 8: adult advanced cardiovascular life support: 2010 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010; 122(18 Suppl 3): S729-S767.
67) Tangvoraphonkchai K, Davenport A. Magnesium and cardiovascular disease. Adv Chronic Kidney Dis 2018; 25: 251-260.
68) Cohen L, Kitzes R. Magnesium sulfate and digitalis-toxic arrhythmias. JAMA 1983; 249: 2808-2810.
69) Shivanthan M, Rajapakse S. Magnesium for acute exacerbation of chronic obstructive pulmonary disease: a systematic review of randomised trials. Ann Thorac Med 2014; 9: 77-80.
70) Mukerji S, Shahpuri B, Clayton-Smith B, Smith N, Armstrong P, Hardy M, Marchant G, Marsh E. Intravenous magnesium sulphate as an adjuvant therapy in acute exacerbations of chronic obstructive pulmonary disease: a single centre, randomised, double-blinded, parallel group, placebo-controlled trial: a pilot study. N Z Med J 2015; 128: 34-42.
71) Nouira S, Bouida W, Grissa MH, Beltaief K, Trimech MN, Boubaker H, Marghli S, Letaief M, Boukef R. Magnesium sulfate versus ipratropium bromide in chronic obstructive pulmonary disease exacerbation: a randomized trial. Am J Ther 2014; 21: 152-158.
72) Edwards L, Shirtcliffe P, Wadsworth K, Healy B, Jefferies S, Weatherall M, Beasley R; Magnesium COPD Study Team. Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults: a randomised double-blind placebo-controlled trial. Thorax 2013; 68: 338-343.
73) Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. Cochrane Database Syst Rev 2014; (5): CD010909.
74) Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. Ann Emerg Med 2000; 36: 191-197.
75) Jones LA, Goodacre S. Magnesium sulphate in the treatment of acute asthma: evaluation of current practice in adult emergency departments. Emerg Med J 2009; 26: 783-785.
76) Hossein S, Pegah A, Davood F, Said A, Babak M, Mani M, Mahdi R, Peyman H. The effect of nebulized magnesium sulfate in the treatment of moderate to severe asthma attacks: a randomized clinical trial. Am J Emerg Med 2016; 34: 883-886.

77) Sarhan HA, El-Garhy OH, Ali MA, Youssef NA. The efficacy of nebulized magnesium sulfate alone and in combination with salbutamol in acute asthma. Drug Des Devel Ther 2016; 10: 1927-33.
78) Gallegos-Solórzano MC, Pérez-Padilla R, Hernández-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjuvant management of severe asthma crisis in an emergency department. Pulm Pharmacol Ther 2010; 23: 432-437.
79) Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev 2017; (11): CD003898.
80) Beasley R, Aldington S. Magnesium in the treatment of asthma. Curr Opin Allergy Clin Immunol 2007; 7: 107-110.
81) Soave PM, Conti G, Costa R, Arcangeli A. Magnesium and anaesthesia. Curr Drug Targets 2009; 10: 734-743.
82) Vicković S, Pjević M, Uvelin A, Pap D, Nikolić D, Lalić I. Magnesium sulfate as an adjuvant to anesthesia in patients with arterial hypertension. Acta Clin Croat 2016; 55: 490-496.
83) Mebazaa MS, Ouerghi S, Frikha N, Moncer K, Mestiri T, James MF, Ben Ammar MS. Is magnesium sulfate by the intrathecal route efficient and safe? Ann Fr Anesth Reanim 2011; 30: 47-50.
84) Venturini MA, Zappa S, Minelli C, Bonardelli S, Lamberti L, Bisighini L, Zangrandi M, Turin M, Rizzo F, Rizzolo A, Latronico N. MAGnesium-oral supplementation to reduce PAin in patients with severe PERipheral arterial occlusive disease: the MAG-PAPER randomised clinical trial protocol. BMJ Open 2015; 5: e009137.
85) Bilir A, Gulec S, Erkan A, Ozcelik A. Epidural magnesium reduces postoperative analgesic requirement. Br J Anaesth 2007; 98: 519-523.
86) Maleki Verki M, Porozan S, Motamed H, Fahimi MA, Aryan A. Comparison the analgesic effect of magnesium sulphate and Ketorolac in the treatment of renal colic patients: double-blind clinical trial study. Am J Emerg Med 2018; pii: S0735-6757: 30683-30691.
87) Jokar A, Cyrus A, Babaei M, Taheri M, Almasi-Hashiani A, Behzadinia E, Yazdanbakhsh A. The effect of magnesium sulfate on renal colic pain relief; a randomized clinical trial. Emerg (Tehran) 2017; 5: e25.
88) Assarzadegan F, Asgarzadeh S, Hatamabadi HR, Shahrami A, Tabatabaey A, Asgarzadeh M. Serum concentration of magnesium as an independent risk factor in migraine attacks: a matched case-control study and review of the literature. Int Clin Psychopharmacol 2016; 31: 287-292.
89) Assarzadegan F, Asadollahi M, Derakhshanfar H, Kashefizadeh A, Aryani O, Khorshidi M. Measuring serum level of ionized magnesium in patients with migraine. Iran J Child Neurol 2015; 9: 13-16.
90) Frank LR, Olson CM, Shuler KB, Gharib SF. Intravenous magnesium for acute benign headache in the emergency department: a randomized double-blind placebo-controlled trial. CJEM 2004; 6: 327-332.
91) Cete Y, Dora B, Ertan C, Ozdemir C, Oktay C. A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the Emergency Department. Cephalalgia 2005; 25: 199-204.
92) 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: 69-76.
93) Delavar Kasmaei H, Amiri M, Negida A, Hajimollarabi S, Mahdavi N. Ketorolac versus magnesium sulfate in migraine headache pain management; a preliminary study. Emerg (Tehran) 2017; 5: e2.
94) Baratloo A, Mirbaha S, Delavar Kasmaei H, Payandemehr P, Elmaraezy A, Negida A. Intravenous caffeine citrate vs. magnesium sulfate for reducing pain in patients with acute migraine headache; a prospective quasi-experimental study. Korean J Pain 2017; 30: 176-182.
95) Bayir A, Kara H, Ak A, Cander B, Kara F. Magnesium sulfate in emergency department patients with hypertension. Biol Trace Elem Res 2009; 128: 38-44.
96) Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, Conwit R, Liebeskind DS, Sung G, Kramer I, Moreau G, Goldweber R, Sanossian N; FAST-MAG investigators and coordinators. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. N Engl J Med 2015; 372: 528-536.
97) Shkirkova K, Starkman S, Sanossian N, Eckstein M, Stratton S, Pratt F, Conwit R, Hamilton S, Sharma L, Liebeskind D, Restrepo L, Valdes-Sueiras M, Saver JL; FAST-MAG investigators and coordinators. Paramedic initiation of neuroprotective agent infusions: successful achievement of target blood levels and attained level effect on clinical outcomes in the FAST-MAG pivotal trial (field administration of stroke therapy - magnesium). Stroke 2017; 48: 1901-1907.
98) Zeng ZW, Zhang YN, Lin WX, Zhang WQ, Luo R. A meta-analysis of pharmacological neuroprotection in noncardiac surgery: focus on statins, lidocaine, ketamine, and magnesium sulfate. Eur Rev Med Pharmacol Sci 2018; 22: 1798-1811.
99) Chardain A, Mesnage V, Alamowitch S, Bourdain F, Crozier S, Lenglet T, Psimaras D, Demeret S, Graveleau P, Hoang-Xuan K, Levy R. Posterior reversible encephalopathy syndrome (PRES) and hypomagnesemia: a frequent association? Rev Neurol (Paris) 2016; 172: 384-388.
100) Rathbone J, Franklin R, Gibbs C, Williams D. Review article: role of magnesium sulphate in the management of Irukandji syndrome: a systematic review. Emerg Med Australas 2017; 29: 9-17.
101) Huang YH, Zeng BY, Li DJ, Cheng YS, Chen TY, Liang HY, Yang WC, Lin PY, Chen YW, Tseng PT, Lin CH. Significantly lower serum and hair magnesium levels in children with attention deficit hyperactivity disorder than controls: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2019; 90: 134-141.

102) Bakian AV, Bilder DA, Korgenski EK, Bonkowsky JL. Autism spectrum disorder and neonatal serum magnesium levels in preterm infants. Child Neurol Open 2018; 5: 2329048X18800566.
103) Baek SJ, Byeon JH, Eun SH, Eun BL, Kim GH. Risk of low serum levels of ionized magnesium in children with febrile seizure. BMC Pediatr 2018; 18: 297.
104) Indinnimeo L, Chiappini E, Miraglia Del Giudice M; Italian Panel for the management of acute asthma attack in children Roberto Bernardini. Guideline on management of the acute asthma attack in children by Italian Society of Pediatrics. Ital J Pediatr 2018; 44: 46.
105) Turker S, Dogru M, Yildiz F, Yilmaz SB. The effect of nebulised magnesium sulphate in the management of childhood moderate asthma exacerbations as adjuvant treatment. Allergol Immunopathol (Madr) 2017; 45: 115-120.
106) Ohn M, Jacobe S. Magnesium should be given to all children presenting to hospital with acute severe asthma. Paediatr Respir Rev 2014; 15: 319-321.
107) Becker SM, Job KM, Lima K, Forbes TJ, Wagstaff J, Tran NK, Sherwin CM, Nelson DS, Johnson MD, Rower JE. Prospective study of serum and ionized magnesium pharmacokinetics in the treatment of children with severe acute asthma. Eur J Clin Pharmacol 2019; 75: 59-66.
108) Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. Cochrane Database Syst Rev 2016; (4): CD011050.
109) Alansari K, Sayyed R, Davidson BL, Al Jawala S, Ghadier M. IV Magnesium sulfate for bronchiolitis. Chest 2017; 152: 113-119.
110) Kan RX, Zhang CL, Zhen Q, Chen J. Magnesium sulfate micro air pump suction for bronchiolitis treatment in infants under two years old. Eur Rev Med Pharmacol Sci 2016; 20: 1180-1184.
111) Chollat C, Marret S. Magnesium sulfate and fetal neuroprotection: overview of clinical evidence. Neural Regen Res 2018; 13: 2044-2049.
112) Jayaram PM, Mohan MK, Farid I, Lindow S. Antenatal magnesium sulfate for fetal neuroprotection: a critical appraisal and systematic review of clinical practice guidelines. J Perinat Med 2018; 47: 262-269.
113) Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. Am J Obstet Gynecol 2009; 200: 595-609.
114) Costantine MM, Weiner SJ; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants. Obstet Gynecol 2009; 114: 354-364.
115) Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev 2009; (1): CD004661.
116) Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and safety of magnesium sulfate on neuroprotection: a meta-analysis based on PRISMA guidelines. Medicine (Baltimore) 2016; 95: e2451.
117) Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. JAMA 2003; 290: 2669-2676.
118) Kang SW, Choi SK, Park E, Chae SJ, Choi S, Jin Joo H, Lee GJ, Park HK. Neuroprotective effects of magnesium-sulfate on ischemic injury mediated by modulating the release of glutamate and reduced of hyperreperfusion. Brain Res 2011; 1371: 121-128.
119) Burd I, Breen K, Friedman A, Chai J, Elovitz MA. Magnesium sulfate reduces inflammation-associated brain injury in fetal mice. Am J Obstet Gynecol 2010; 202: 292. e1-9.