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MAGNESIUM IN MEDICINE AND TREATMENT

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Abstract

Magnesium (Mg^{2+}) plays a critical role in numerous metabolic function in our body. Normal levels of both intra- and extra cellular magnesium are necessary for correct cellular processes. The specific clinical conditions in which Mg^{2+} deficiency has been implicated to play a pathophysiological role include depression, ischaemic heart disease, arrhythmias, preeclampsia, asthma, intradialytic hypotension or critical illness. Correct administration of magnesium can eliminate perioperative pain and muscle spasms, keep blood flowing smoothly, and prevent platelet stickiness. Although magnesium sulphate is now widely used to prevent or control eclamptic convulsions, there is no consensus on the optimal dosage and concentration of magnesium sulphate for the management of eclamptic seizures. Owing to its bronchodilating and anti-inflammatory effects, Mg^{2+} is an encouraging adjuvant therapy for paediatric patients, although its use is often limited to patients who do not respond to conventional treatment. Studies have also suggested that magnesium might be useful as an agent to control the rigidity and spasms of severe tetanus or for the enhancement of neuromuscular blockade during anaesthesia, but its actual efficacy as an anticonvulsant or an adjuvant to analgesics and anaesthetics to induce and maintain anaesthesia remains unclear. Moreover, a negative correlation has been shown between intradialytic changes of the serum magnesium and hypotensive episodes during dialysis sessions. Low Mg^{2+} haemodialysis solution resulted in both hypomagnesaemia and hypocalcaemia. Mg^{2+} compounds are now becoming recognized as safe, effective and cost-efficient alternatives to other phosphorus binders, with a significant added benefit of substantially reducing the risk and impact of cardiovascular diseases.

It seems that magnesium is underused in clinical conditions, considering its therapeutic capacity. On the other hand, numerous studies have found conflicting results, questioning the implicit efficacy of magnesium in several clinical conditions.

Key words: magnesium, eclampsia, asthma, tetanus, intradialytic hypotension, anesthetic.

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Abstrakt

Magnez (Mg^{2+}) odgrywa kluczową rolę w wielu procesach metabolicznych w organizmie ludzkim. Odpowiednie stężenie magnezu, zarówno wewnątrz- jak i zewnątrzkomórkowego, zapewnia prawidłowe funkcjonowanie komórki. Niedobór Mg^{2+} może odgrywać rolę w patofizjologii depresji, choroby niedokrwiennej serca, zaburzeń rytmu serca, drgawek rzucawkowych, astmy, hipotonii śródzabiegowej czy stanach krytycznych. Stosowanie odpowiednich dawek magnezu może zmniejszać ból okołooperacyjny, łagodzić skurcze mięśni, warunkować zachowanie płynności krwi czy zmniejszać ryzyko zakrzepów lub zatorów. Pomimo że siarczan magnezu jest powszechnie stosowany w celu zapobiegania lub kontroli drgawek rzucawkowych, brak jest jednomyślności co do optymalnej dawki czy stężenia roztworu siarczanu magnezu. Rozszerzające oskrzela oraz przeciwzapalne właściwości Mg^{2+} zachęcają do wykorzystania preparatów magnezowych w celu uzupełnienia terapii w leczeniu astmy, szczególnie dziecięcej, jednak jego użycie często ogranicza się do pacjentów, którzy nie reagują na leczenie konwencjonalne. Badania sugerują również, że terapia magnezowa może być pomocna w opanowaniu skurczu oraz sztywności mięśni u chorych na tężec lub może wzmacniać blokadę nerwowo-mięśniową w trakcie znieczulenia. Jednak skuteczność Mg^{2+} jako rzeczywistego czynnika przeciwdrgawkowego lub czynnika uzupełniającego leki przeciwbólowe czy anestetyk pozostaje niejasna.

Liczne badania wykazały ujemną korelację między śródzabiegowymi zmianami stężenia magnezu w surowicy pacjentów a częstością występowania hipotensji podczas dializy. Stosowanie płynu dializacyjnego o niskim stężeniu Mg^{2+} powoduje nie tylko hipomagnezemię, lecz również hipokalcemię.

Związki magnezowe stają się obecnie uznawane za bezpieczne, skuteczne i opłacalne w porównaniu z innymi związkami wiążącymi fosforany. Na ich korzyść przemawia dodatkowo fakt, że Mg^{2+} zmniejsza ryzyko lub łagodzi skutki chorób układu krążenia. Biorąc pod uwagę terapeutyczne możliwości, jakie ma magnez, wydaje się, że jest on niewystarczająco wykorzystywany w warunkach klinicznych. Jednakże liczne badania wykazują sprzeczne wyniki, kwestionując oczekiwaną skuteczność magnezu.

Słowa kluczowe: magnez, rzucawka, astma, tężec, hipotonia śródzabiegowa, anestetyk.

INTRODUCTION

Magnesium (Mg^{2+}) is the second most abundant intracellular divalent cation and is a cofactor for hundreds of metabolic reactions in the body, such as glycolysis, Krebs cycle, ß-oxidation, activation of amino acids, synthesis and breakdown of DNA, neurotransmission or ion transport across cell membranes (Pasternak et al. 2010). Mg^{2+} also causes vasodilation by direct action as well as indirectly by sympathetic blockade and inhibition of catecholamine release. Magnesium dilates both the epicardial and resistance coronary arteries. It balances cholesterol and is essential for endocrine stability and function. Most importantly, magnesium prevents calcification of the cardiac tissues. Magnesium has been directly implicated in hypokalaemia, hypocalcaemia, tetany and dysrhythmia. Moreover, it regulates enzymes controlling intracellular calcium, thereby affecting smooth muscle vasoconstriction, which is important to the pathophysiology of several critical illnesses (Tong,

Rude 2005). Because of these vital roles, the magnesium level may be affected by stressors to the body, such as in certain disease states. Supplementation with magnesium may have therapeutic effects in these situations (Guerrera et al. 2009). Correct administration of magnesium can reduce perioperative pain (Seyhan et al. 2006) and muscle spasms (Elsharkawy et al. 2006, Bichara, Goldman 2009), keep blood flowing smoothly and prevent platelet stickiness.

The specific clinical conditions in which magnesium deficiency has been implicated to play a pathophysiological role include ischaemic heart disease, arrhythmias (Herroeder et al. 2011), prec-eclampsia (Euser, Cipolla 2009, Palmer, Newby 2009), asthma (Cheuk et al. 2005), intradialytic hypotension (Elsharkawy et al. 2006, Pakfetrat et al. 2010) or critical illness (Tang, Rude 2005); magnesium deficiency is a common yet underdiagnosed problem in an intensive care unit (ICU). The problem is that the extracellular level of the ion may not reflect its intracellular deficiency, because only 1% of the total body Mg^{2+} is in the extracellular fluid. Moreover, one cannot clearly define a patient's response to magnesium treatment based on his/her magnesium serum level.

ECLAMPSIA

Magnesium sulphate is recommended as the first-line medication for prophylaxis and treatment of eclampsia (Palmer, Newby 2009). Though the specific mechanisms of action remain unclear, the effect of magnesium sulphate in the prevention of eclampsia seems to be multi-factorial, including its action as a vasodilator, with effects produced either peripherally or through the cerebral circulation, and an agent protecting the blood-brain barrier (BBB) to decrease cerebral oedema formation; and acting as a central anticonvulsant by inhibiting N-methyl-D-aspartate receptors (Euser, Cipolla 2009). The most commonly used administration methods are the so-called Pritchard's and Zuspan's regimens. In the Pritchard's regimen, a loading bolus dose of 4 g of $MgSO_4$ is given slowly intravenously over 5-10 minutes and this is followed by 10 g given intramuscularly (5 g in each buttock). Subsequently, 5 g is given intramuscularly into alternate buttocks every 4 h. According to the Zuspan's regimens, a loading dose of 4 g is given intravenously over a period of 10 minutes with a maintenance dose of 1-2 g every hour by controlled infusion pump (Tukur 2009). The above doses should be respected due to the risk of overdosing side effects: muscle atonia, respiratory failure leading to death. The absence of a knee jerk may indicate magnesium overdosing. It must be remembered that doses exceeding 30 mg may result in the CNS depression, respiratory problems and reduced Apgar scores in neonates. A daily dose of $MgSO_4$ should *not exceed* 20-24 g. Patients with the renal failure after a loading dose are administered i.v. magnesium sulphate at a dose of 1.0 g h^{-1} under the control of serum magnesium concentration. It has been noticed that magnesium sulphate is superior to phenytoin and diaze-

pam in preventing the recurrence of seizures and maternal death in patients with eclampsia (Nalewczyńska et al. 2008). Magpie and co-authors' trial showed that the reduction in the risk of eclampsia following prophylaxis with magnesium sulphate was associated with a 16% decrease in the risk of death or serious morbidity potentially related to pre-eclampsia 2-3 years later (Magpie et al. 2007). In 2006 and then in 2008, the maximum recommended concentration of magnesium sulphate for i.v. infusion was set at 20% in the British Columbia Perinatal Health Program and later, by the Society of Obstetricians and Gynaecologists of Canada. Because the 20% concentration of $MgSO_4$ was much higher than the 2% to 8% concentrations used previously there were concerns about a potential increase in the incidence of phlebitis. So Palmer and Newby undertook a retrospective chart audit for patients who had received magnesium sulphate (2% to 8% or 20% solution) for eclampsia prophylaxis, concluding the lack of any evidence of documented cases of phlebitis as well as fewer side effects when 20% magnesium sulphate was used (Palmer, Newby 2009).

Nowadays, researchers aim to investigate whether low dose $MgSO_4$ regimens might assure less toxicity and an improved neonatal outcome without significant adverse effects in control of eclamptic convulsions. Seth et al. demonstrated that both maternal and fetal outcomes were comparable in either low dose (4 g i.v. loading dose continued with 2 g i.m. every 3 h), single loading dose (4 g i.v. and 5 g i.m. only) or the standard Pritchard's regimen of magnesium sulphate; a low dose as well as a single dose were associated with significantly lower toxicity related to magnesium sulphate (Seth et al. 2010). Similarly, Ekele et al. showed that limiting the dosage of magnesium sulphate to 14 grams loading dose (4 g intravenous and 10 g intramuscular) was effective as an anticonvulsant in 92.6% of eclampsia patients and only 7% of the patients needed the continuation of maintenance doses (Ekele et al. 2009). Chowdhury et al. also proved that a much lower maintenance dose of 0.6 g h^{-1}, considerably less than 1-2 g h^{-1} advocated by Zuspan, was as effective in Asian women as the Pritchard's i.m. regimen and could prevent the recurrence of convulsions. Thus, researchers found that lower dosage of $MgSO_4$ may increase the safety margin without compromising effectiveness and, moreover, one might prefer to avoid the possibility of painful injections in the i.m. regimen. On the other hand, they guessed that since the study in a western population showed that an ideal serum magnesium level was obtained with either the Pritchard's i.m. regimen or the i.v. regimen with a maintenance dose of $\geq$2 g h^{-1}, the difference in the response between western and Asian women was only because the former had a higher body weight than the latter (Chowdhury et al. 2009).

Although magnesium sulphate is now widely used to prevent or control eclamptic convulsions, there is no consensus on the optimal dosage and concentration of magnesium sulfate for the management of eclamptic seizures.

ASTHMA

In the smooth muscle of bronchi, magnesium decreases the intracellular calcium level by blocking its entry through non-voltage-operated channels and its release from the endoplasmic reticulum. Mg^{2+} acting as Ca^{2+} antagonist may directly inhibit actin-myosin interactions, which results in muscle cell relaxation. The magnesium ion also reduces muscle fibre excitability by inhibiting the release of acetylcholine from cholinergic nerve-endings. Additionally, magnesium stimulates nitric oxide and prostacyclin synthesis, which might depress asthma severity; as well as this, it also stabilizes T cells and inhibits mast cell degranulation, alleviating inflammation (Bichara, Goldman 2009). Magnesium deficiency in asthmatic patients may potentiate the calcium intracellular flow into the smooth muscle cells, thereby leading to increased myosin phosphorylation and thus to the enhanced contractility of muscles. Since a decrease in magnesium concentration was noted during adrenaline or salbutamol infusion, which are used in acute asthma, it is suggested that the magnesium flow between extracellular and intracellular compartments may be under the influence of β-adrenergic receptors. During a stress reaction, i.e. acute asthma exacerbation, magnesium escapes from cells while calcium enters them. Hypomagnesaemia increases acetylcholine cell depolarization, causing an increase in the excitability of bronchial smooth muscles and their contraction. Additionally, the shortage of Mg enhances the muscle's reactivity to catecholamines and reduces the relaxant action of prostaglandins (Kowal et al. 2007).

Magnesium sulphate is not recommended for *routine use* in asthma exacerbations. However, in some cases of severe asthma attacks, a single dose of i.v. $MgSO_4$ is appropriate and recommended by the Global Initiative for Asthma (GINA). It applies to adults having the baseline forced expiratory volume in 1 s (FEV1) 25-30% of the predicted value; adults who do not respond to conventional treatment; children whose FEV1 remains less than 60% of the predicted value after an hour of treatment. Magnesium is administered intravenously at a dose of 2 g in a single 20-minute infusion. Additional monitoring is unnecessary and no side effects of such treatment are indicated (Silverman et al. 2002).

Several clinical trials regarding the use of magnesium in adults and children with asthma were summarized by Rowe et al. (2000), Cheuk et al. (2005), Blitz et al. (2005) as well as Mohammed and Goodacre (2007). Rowe et al. and Cheuk et al. examined the effect of i.v. magnesium sulphate while Blitz et al. studied its inhaled form in the treatment of asthma exacerbations, whereas Mohammed and Goodacre's meta-analysis included both intravenous and nebulised magnesium sulphate usage in patients presenting with acute asthma.

Rowe and co-authors' thorough review on the effect of i.v. $MgSO_4$ versus placebo used in patients with acute asthma demonstrated that hospital admission was not statistically reduced owing to the use of $MgSO_4$ and patients

receiving magnesium sulphate displayed non-significant improvement in the peak expiratory flow rates (PEFR) together with clinically unimportant changes in vital signs and lack of side effects (Rowe et al. 2000). The meta-anlysis written in 2005 by Cheuk et al., which compared i.v. magnesium sulphate to placebo in treating paediatric patients with moderate to severe asthmatic attacks, with co-therapies of inhaled β_2 agonists and systemic steroids, showed that $MgSO_4$ was effective in preventing hospitalisation and led to significantly improved outcomes of short-term pulmonary function tests and clinical symptom scores (Cheuk et al. 2005). A meta-analysis of six trials made by Blitz et al. investigating usage of inhaled $MgSO_4$ combined with a β_2-agonist for an acute asthma exacerbation confirmed beneficial effects with respect to improved pulmonary function, although there was no evidence of its positive impact on hospital admission rates (Blitz et al. 2005). Contrary, in the study of Aggarwal et al., who compared nebulized (thrice at intervals of 20 min) magnesium sulphate (500 mg) with salbutamol (0.5 mg) or salbutamol alone in the treatment of acute asthma, there was no significant rise in PEFR at any point in patients nebulized $MgSO_4$. The researchers concluded there was no therapeutic advantage in adding $MgSO_4$ to salbutamol nebulisation in the treatment of patients with acute, severe or life threatening asthma (Aggarwal et al. 2006). Mohammed and Goodacre completed a meta-analysis of randomised and quasi-randomised trials of intravenous or nebulised MgSO4 in acute asthma, which showed that the i.v. treatment was associated with weak evidence of any effect on the respiratory function in adults, no significant effect on hospital admission, and a significant effect on respiratory function and hospital admission in children. With respect to the nebulised treatment, it was associated with weak evidence of its effect on respiratory function and on hospital admission in adults or else no significant effect on the respiratory function in children (Mohammed, Goodacre 2007).

Thus, intravenous magnesium sulphate seems to be beneficial in the treatment of moderate to severe asthma in children. Owing to its bronchodilating and anti-inflammatory effects, magnesium is an encouraging adjuvant therapy for paediatric patients, but its use is often limited to patients who do not respond to conventional treatment. A cross-sectional online survey of two national paediatric emergency physician associations in Canada and the United States conducted using a modified Dillman's technique showed that although 88% of participants report knowing that Mg^{2+} is effective, only 14 of 199 (7%) and 142 of 199 (71%) give it to prevent hospitalizations and to prevent admissions to an intensive care unit (ICU), respectively (Schuh et al. 2010).

TETANUS

Magnesium is a presynaptic neuromuscular blocker with properties of a vasodilator, catecholamine release blocking agent and an anticonvulsant, all of which are desirable for the control of spasticity and autonomic dysfunction

in tetanus (Karanikolas et al. 2010). Thwaites et al. reported the results of a randomised placebo controlled trial of magnesium sulphate infusions for the treatment of severe tetanus, which showed that magnesium did not reduce the need for mechanical ventilation in adults with severe tetanus but it reduced the requirement for other drugs to control muscle spasms and cardiovascular instability (Thwaites et al. 2006). In the later study, Thwaites et al. confirmed that the patients who received Mg^{2+} had significantly less autonomic dysfunction and required less cardiovascular stabilizing drugs; additionally, the researchers noticed that patients had lower urinary concentrations of adrenaline. Therefore, they suggested that adrenaline was important in the pathophysiology of severe tetanus, and magnesium controlled the autonomic dysfunction by decreasing the adrenaline release, which affected its urinary excretion (Thwaites et al. 2008). Karanikolas et al. observed that even a high-dose (total Mg dose 758 g) prolonged (26 days) intravenous Mg therapy, if carefully titrated and monitored, could be continued for a long time without obvious side effects or major organ toxicity. They reported that the i.v. Mg^{2+} therapy resulted in an excellent muscle contraction control by patients within hours, without the need for additional administration of muscle relaxants. However, because of the persistence of painful muscle rigidity during their daily wake-up tests, i.v. Mg^{2+} infusions were continued for a long period (26 days) in two of three patients (Karanikolas et al. 2010). In contrast, Mathew et al. reported that the intravenous magnesium therapy might not be useful as a sole agent to control the rigidity and spasms in severe tetanus, therefore additional sedative adjuncts were required to control the disease (Mathew et al. 2010).

Since magnesium therapy can cause serious adverse effects, including muscle weakness, paralysis and hypotension, further research is needed before recommending Mg^{2+} as the first-line therapy for tetanus (Karanikolas et al. 2010).

DIALYSIS

Intradialytic changes in the serum Mg^{2+} affect systemic hemodynamics, especially when haemodialysis is performed with a low calcium dialysate. Since Mg^{2+} exerts direct modulatory action on cardiac excitability and vascular smooth muscle contraction and relaxation (Elsharkawy et al. 2006), hypomagnesaemia in haemodialysis patients *can result in impaired myocardial contractility,* thereby favouring hypotension. Moreover, in haemodialytic (HD) patients, reduced Mg^{2+} level may lead to increased atherosclerosis susceptibility, because it has shown that both serum and intracellular Mg had a significant and independent negative association with the carotid intima-media thickness, which is a predictor of future vascular events and a marker of early atherosclerosis (Navarro-González et al. 2009). Additionally, Mg-based phosphate binders have always been used with excellent results (de Francisco et al. 2010).

Kyriazis et al. investigated the way dialysate Mg^{2+} concentrations could affect blood pressure during hemodialysis. The researchers identified a dialysis solution containing 0.25 mmol l^{-1} Mg^{2+} and 1.25 mmol l^{-1} Ca^{2+} as a significant risk factor for developing intradialytic hypotension (IDH), and showed that increasing the Mg^{2+} level to 0.75 mmol l^{-1} could prevent frequently seen IDH. Moreover, the low-Mg haemodialysis solution resulted in both hypomagnesaemia and hypocalcaemia (decreasing serum magnesium and calcium levels by 35% and 8%, respectively), which was associated with an impairment of myocardial contractility not compensated by total peripheral resistance (Kyriazis et al. 2004). These results coincide with the studies by Pakfrtrat et al. or Elsharkawy et al., linking intradialytic changes in the serum Mg^{2+} with hypotension episodes during a dialysis session (Elsharkwy et al. 2006, Pakfetrat et al. 2010). Turgut et al. observed magnesium supplementation (magnesium citrate orally at a dosage of 610 mg every other day for 2 months) was negatively associated with the common carotid intima-media thickness (IMT), so it may play an important protective role in the development and/or acceleration of arterial atherosclerosis in patients with chronic renal sufficiency (Turgut et al. 2008). This has confirmed some earlier research by Tzanakis et al., which had shown that both increased serum and intracellular Mg^{2+} levels significantly improve the carotid IMT in HD patients (Tzanakis et al. 2004).

In patients with chronic kidney disease (CKD) requiring haemodialysis, renal elimination of phosphate is impaired, resulting in hyperphosphataemia. Although certain magnesium salts have high phosphate-binding capacity, their use in the treatment of hyperphosphataemia is very limited, largely due to the fear of the occurrence of hypomagnesaemia.

Tzanakis et al. carried out a study in hemodialytic patients to evaluate the efficacy and safety of $MgCO_3$ as a phosphate-binder when given with a concurrent low dialysate magnesium solution. The study showed that $MgCO_3$ administered in the mean daily dose of 6.21 tablets (range 3-9) containing 441 mg of elemental magnesium (range 213-639 mg) might be an effective and inexpensive way to control serum phosphate levels in HD patients, and the administration of $MgCO_{3,}$ in combination with a low dialysate Mg^{2+} concentration (0.48 mmol l^{-1}) prevented the risk of severe hypermagnesaemia (Tzanakis et al. 2008). Similarly, McIntyre et al. demonstrated that fermagate, a calcium-free iron and magnesium hydroxycarbonate binder, administered (1 g or 2 g) three times daily just before meals for 21 days was associated with statistical reductions in the mean serum phosphate from 2.16 mmol l^{-1} to 1.71 and 1.47 mmol l^{-1}, respectively, in HP patients. Adverse event (AE) incidence in the 1 g dose of fermagate was statistically comparable to the placebo group but the 2 g arm was associated with a statistically higher number of patients reporting AEs than the 1 g arm, particularly gastrointestinal AEs, as well as a higher number of discontinuations, thus complicating the interpretation of the efficacy this dose. Thus, the study proved

that the efficacy and tolerability of fermagate were dose-dependent and a daily oral 1g dose of the medicament might be promising in the treatment of hyperphosphatemia in patients who are receiving haemodialysis (McIntyre et al. 2009). Another study investigated the effect of calcium acetate/magnesium carbonate (CaMg) on serum phosphorus levels compared with sevelamer hydrochloride (HCl). Patients received calcium acetate 435 mg containing 110 mg elemental calcium combined with magnesium carbonate 235 mg containing 60 mg elemental magnesium (OsvaRen®) or sevelamer-HCl 800 mg (Renagel®) for 24 weeks. A starting dose of the drugs was at least four tablets per day. Thereafter, the dose was increased by one to three tablets per day to achieve an adequate phosphate level in serum. The researchers showed CaMg was non-inferior to the comparator at controlling serum phosphorus levels and it had a good tolerability profile, so it might represent an effective treatment of hyperphosphataemia *(*de Francisco et al. 2010).

Although the use of dialysis fluid containing 0.25-0.4 mmol l^{-1} Mg^{2+} usually keeps magnesaemia within normal limits, magnesium compounds are not widely used in HD patients because nephrologists have an inordinate fear of hypermagnesaemia and the belief that Mg^{2+} administration is frequently accompanied by gastrointestinal disorders. However, currently magnesium compounds are becoming recognised as safe, effective and cost-efficient alternatives to other phosphorus binders with the significant added benefit of substantially reducing the risk and impact of cardiovascular diseases.

ANAESTHESIA

Because Mg^{2+} ions block the open N-methyl-D-aspartate (NMDA) channel in a voltage-dependent manner, they may contribute to the anesthetic, amnesic as well as anticonvulsant properties of propofol. Moreover, Mg^{2+} competes with calcium ions at the neuromuscular junction and enhances the effect of neuromuscular blockers by decreasing presynaptic acetylcholine release. It also has an inhibitor effect on the postsynaptic potential, thereby reducing the excitability of the muscular fiber membrane.

A study by Cizmeci and Ozkose (2007) showed that magnesium sulphate can be used safely as an adjuvant to total i.v. anesthesia for day case surgeries, with the effect from potentialization of neuromuscular blockade. The patients received 15% $MgSO_4$ 50 mg kg^{-1} in 100 ml of saline before induction of anesthesia, followed by 8 mg kg^{-1} h^{-1} infusion of magnesium sulphate until the end of surgery. The researchers noticed that propofol requirements were significantly lower in patients received $MgSO_4$ than in those who received only saline, and the haemodynamic variables were similar in the two groups. Moreover, the neuromuscular potency of vecuronium was greater and the verbal numeric scale values for pain were found to be significantly lower in the Mg^{2+} group compared to the control one (Cizmeci, Ozkose 2007). The serum magnesium level was in the normal range at the induction of anesthesia in the both groups, but its *postoperative concentration* was significantly

lower in the saline than in the $MgSO_4$ group. Altan et al. confirmed that the amount of propofol used in the maintenance of anesthesia was lower in the presence of magnesium sulphate (30 mg kg^{-1} as a bolus before induction and 10 mg kg^{-1} h^{-1} by infusion; moreover, they noticed that anesthetic induction was more rapid in patients who received $MgSO_4$ (Altan et al. 2005). Seyhan et al. demonstrated that magnesium (40 mg kg^{-1} bolus followed by 10 mg kg^{-1} h^{-1}) infusion caused significant reductions in intraoperative propofol, atracurium as well as postoperative morphine consumption, although increasing the magnesium dosage further did not offer any advantages, but induced haemodynamic consequences (Seyhan et al. 2006). Ray et al. agreed that the perioperative use of magnesium sulphate (30 mg kg^{-1} as a bolus before induction and 10 mg kg^{-1} h^{-1} by infusion) was able to attenuate the haemodynamic response to tracheal intubation. On the other hand, they noticed Mg^{2+} may cause bradycardia and hypotension as well as result in a delay in recovery. Thus, the researchers concluded that $MgS0_4$ needed careful management to be used as an adjuvant agent to general anaesthetics (Ray et al. 2010).

Ghatak et al. indicated positive effects of magnesium as an adjuvant to epidural bupivacaine (19 ml of epidural bupivacaine 0.5% along with 50 mg magnesium), Mg^{2+} reduced the time of onset and establishment of the epidural block up to T6 level without any side effects (Ghatak et al. 2010). Shoeibi et al. found that an intrathecal injection of 0.5 ml magnesium sulphate 10% with 1.5 ml lidocaine 5% for spinal anesthesia resulted in a significant enhancement of the duration of analgesia after spinal anesthesia and surgery. It is possible that the analgesic effect of magnesium occurred at the supra -spinal level and might be related to its systemic absorption (Shoeibi et al. 2007). Ko et al. confirmed an inverse relation between cumulative postoperative analgesic consumption and the cerebrospinal fluid (CSF) magnesium concentration. On the other hand, researchers showed that perioperative i.v. administration of $MgSO_4$ (50 mg kg^{-1} intravenous magnesium sulfate as a bolus dose followed by a continuous infusion of 15 mg kg^{-1} h^{-1} for 6 h) did not increase the CSF magnesium concentration and had no effects on postoperative pain. Thus, they suggested that perioperative intravenous magnesium infusion may not be useful for preventing postoperative pain (Ko et al. 2001). Because magnesium prolongs muscle relaxation, continuous monitoring of neuromuscular function during surgery is required, and muscle relaxants should be applied accordingly.

Although the above studies suggest a clinically relevant effect of magnesium, its actual efficacy as an adjuvant to analgesics and anaesthetics to induce and maintain anaesthesia remains unclear **(**Herroeder et al. 2011). Clinicians are therefore very often hesitant to use magnesium in perioperative treatment. This issue requires evaluation in large clinical trials.

SUMMARY

In conclusion, it seems that magnesium is used insufficiently in comparison to its therapeutic capacity. Primary limitations associated with the use of Mg^{2+} in treatment are due to the fear of overdose. The problem is to determine the best magnesium dosage regime: dose, i.v. or i.m. administration. However, experiments have shown that administration of 2 g $MgSO_4$ (16 mEq) in a bolus enhanced the magnesium serum concentration from 1.8 to 3.1 mEq l^{-1} (0.9-1.55 mmol l^{-1}) 30 minutes after the infusion and that administration of 2-4 g $MgSO_4$ (16-32 mEq) to patients with normal renal function over 30-60 minutes has a low probability of side effects. Fast infusions (1-2 min) of 2 g $MgSO_4$ (16 mEq) also caused minimal side effects, but they required patient monitoring (Silverman et al. 2002). On the other hand, numerous studies have found conflicting results, questioning the implicit efficacy of magnesium in several clinical conditions. In short, future studies are required to know how magnesium contributes to pathological processes, whether Mg^{2+} administration serves the purpose of merely correcting an underlying deficiency state or how to use a specific pharmacologic effect of magnesium as well as to clearly determine under what circumstances should it be used therapeutically and what doses should be recommended.

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