

**REVIEW PAPER**

**THE ROLE OF MAGNESIUM  
IN MIGRAINE PATHOGENESIS.  
POTENTIAL USE OF MAGNESIUM  
COMPOUNDS IN PREVENTION  
AND TREATMENT OF MIGRAINE  
HEADACHES**

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Abstract

One of the major functions of magnesium is the maintenance of proper electric potential of neurons. Pathological conditions associated with systemic magnesium deficiencies may be associated with disturbance of numerous neurophysiological processes. These may include neuron function, transmission of nerve impulses, neuromuscular transmission, muscle contraction and vasomotor reflex. Therefore, magnesium deficiencies, particularly those associated with hypomagnesemia, are a source of problems for neurologists.

Migraine is one of the most common neurological disorders. Despite many years of research, pathophysiology of migraine has not been elucidated. The predominant opinion is that the onset of migraine headaches is associated with cerebral vascular spasms. Based on the available knowledge of biological functions of magnesium, at least several feasible mechanisms for prevention or reduction of the intensity of migraine attacks by magnesium ions have been proposed. The goal of this review is to summarize the literature re-

ports on magnesium in the pathogenesis of migraine and to identify the potential uses for magnesium compounds in prevention and treatment of migraine headaches.

Key words: magnesium, migraine, migraine headache prevention, treatment of migraine attacks.

## **ROLA MAGNEZU W PATOGENEZIE MIGRENY. MOŻLIWOŚCI ZASTOSOWANIA ZWIĄZKÓW MAGNEZU W PROFILAKTYCE I LECZENIU MIGRENOWYCH BÓLÓW GŁOWY**

### **Abstrakt**

Jedną z najważniejszych funkcji magnezu jest utrzymywanie odpowiedniego potencjału elektrycznego komórek nerwowych. W stanach patologii związanych z ogólnoustrojowymi niedoborami magnezu może dochodzić do zakłócenia rozmaitych procesów neurofizjologicznych. Należą do nich m.in.: funkcjonowanie neuronów, przewodzenie impulsu nerwowego, przekaźnictwo nerwowo-mięśniowe i skurcz mięśni oraz odruch wazomotoryczny. Z powyższych względów stany niedoborów magnezu, zwłaszcza te przebiegające z hipomagnezemią, stały się problemem w praktyce klinicznej lekarza neurologa.

Migrena jest jednym z najczęściej występujących schorzeń neurologicznych. Pomimo wielu lat badań, jej patofizjologia nie została jednoznacznie wyjaśniona. Aktualnie dominuje pogląd, iż pojawianie się migrenowych bólów głowy ma związek ze skurczem naczyń mózgowych. Na podstawie dostępnej wiedzy dotyczącej biologicznych funkcji magnezu zasugerowano istnienie przynajmniej kilku możliwych mechanizmów, za których pośrednictwem jony magnezu mogłyby zapobiegać pojawianiu się ataków migreny lub ograniczać ich nasilenie. Celem pracy było podsumowanie dostępnych w piśmiennictwie doniesień dotyczących roli magnezu w patogenezie migreny, a także wskazanie możliwości wykorzystania preparatów magnezu w profilaktyce i leczeniu migrenowych bólów głowy.

Słowa kluczowe: magnez, migrena, profilaktyka migrenowych bólów głowy, leczenie napadów migreny.

## **INTRODUCTION**

Magnesium is present in all tissues, being the second most common intracellular cation (after potassium). Magnesium plays many roles in the human system: it contributes to intracellular energy storage and expenditure, acts as a cofactor for more than 300 enzymes, is required for the proper course of nucleic acid synthesis, and is involved in cell division and growth, as well as in operation of ion channels, receptors and transport systems.

One of the major functions of magnesium is the maintenance of proper electric potential of neurons (Hu et al. 2006). In order for this function to be carried out properly, the system must be armed with structures protecting the central nervous system from sudden drops of magnesium levels. These include the blood-brain barrier and choroid plexus, which effectively prevent fluctuations in cerebrospinal fluid magnesium levels in physiological condi-

tions (MCKEE et al. 2005). Pathological conditions associated with systemic magnesium deficiencies may be associated with disturbance of numerous neurophysiological processes. These may include neuron function, transmission of nerve impulses, neuromuscular transmission, muscle contraction and vasomotor reflex (SONTIA, TOUYZ 2007, DRIBBEN et al. 2010). Therefore, magnesium deficiencies, particularly those associated with hypomagnesemia, are a source of problems for neurologists. These problems are very serious since, as demonstrated in studies conducted by independent teams of researchers, the number of patients with hypomagnesemia is usually underestimated (DE FEO 2009). In addition, low plasma magnesium levels are more common in patients presenting at hospital admission rooms or emergency units and may affect as much as 65% of population with proper creatinine levels, contributing to increased mortality among these patients (WHANG, RYDER 1990, SAFAVI, HONARMAND 2007).

## **MIGRAINE**

Migraine is one of the most common neurological disorders. According to different sources, migraine affects 4 to 20% of population and is a common cause of patients' referral to the neurologist's office. The disorder is more common in females than in males, albeit the age of onset is younger in males (KURTH et al. 2009). Although most reports mention the disorder as affecting adults, it has been recently pointed out that children might also be affected, with the incidence in this age group being underestimated (ABU-AREFEH et al. 2010). Migraine headaches come 19<sup>th</sup> in the WHO rank of disorders excluding patients from normal functioning in their environment. It was estimated that employees in the US miss a total of 110 million work-days per year, which significantly reduces the productivity index (HU et al. 1999, STANG et al. 2001, BUSE et al. 2009).

Although migraine headaches have been the subject of research for many decades, and the term "migraine" dates back to the ancient times, migraine classification criteria were developed by the International Headache Society relatively recently, i.e. in 1988 (DIB 2008). According to these criteria, migraine is classified as one of the primary (spontaneous) headaches, which include also cluster headaches, tension headaches and other spontaneous headaches (OLESEN, STEINER 2004).

Migraine is characterized by recurrent paroxysmal headaches lasting 4 to 72 hours, usually pulsating, unilateral and most commonly involving the parietal, temporal and periorbital regions. The pain may be provoked by multiple factors. The disorder is exacerbated by emotional stress and physical activity (GOADSBY et al. 2005). The classification proposed by the International Headache Society identifies two types of migraine: migraine without aura and less common migraine with aura, which usually lasts 5 to 60 minutes (GOADSBY et al. 2005). In the case of the latter type, the onset of headache is preceded by focal neurological cerebral or brain stem symptoms.

Despite many years of research, pathophysiology of migraine has not been elucidated. The predominant opinion is that the onset of migraine headaches is associated with cerebral vascular spasms (KURTH 2007, TIETJEN 2007).

### **THE ROLE OF MAGNESIUM IN MIGRAINE PATHOGENESIS**

DEMIRKAYA et al. (2000) demonstrated a relationship between migraine headaches and magnesium levels within human body, pointing out several possible mechanisms for the anti-migraine activity of magnesium. Maintenance of normal plasma levels of magnesium ions is required for proper function of vascular endothelium and proper vascular contractility. Thus, hypomagnesemia is a factor predisposing patients to vascular spasm (GRUBB 2005, SCHRUCKS et al. 2010). The likelihood of cerebral vascular spasm underlying the migraine headache was shown to be proportional to the ratio of calcium and magnesium ion levels in plasma. Magnesium ions are known to modulate the tone of the smooth muscles of cerebral and peripheral vessels. Magnesium acts as a calcium antagonist on vascular smooth muscle tone. (WEINBERGER 2006, BO, PISU 2008).

By acting as NMDA receptor antagonists, magnesium ions prevent propagation of glutamatergic transmission-dependent of cortical depression, which is associated, among others, with the onset of migraine aura. *In vitro* studies showed that low concentration of magnesium within the cerebral tissue leads to earlier onset and easier propagation of cortical depression (LAURITZEN 2001, SUN-EDELSTEIN, MAUSKOP 2009). In addition, hypomagnesemia is associated with induction of platelet aggregation or vascular endothelial function damage (ROMANI 2008, WOLF et al. 2008). Hypomagnesemia is also a factor predisposing patients to increased serotonin secretion, thus potentiating the vasoconstrictive action of this biogenic amine. Earlier exposure to magnesium ions was shown to inhibit serotonin-dependent vascular spasm (GRUBB, CARMO JORGE 2000).

Other suggested mechanisms responsible for migraine headaches include the reduction of vasodilatory effect of prostacyclin (KOSEOGLU et al. 2008). Possibility of migraine attacks was pointed out for conditions usually associated with lowered plasma magnesium levels, e.g. during pregnancy, menstruation, stress, abuse of alcohol or as a consequence of chronic intake of certain drugs, such as diuretics (ALTURA 1985).

Although there are papers that question the relationship between hypomagnesemia and migraine, most authors have no doubt that such a relationship exists (SMEETS et al. 1994, MISHIMA et al. 1997). GALLAI et al. (1992) showed that individuals suffering from migraine headaches were characterized by lower plasma and saliva magnesium levels between the attacks compared to the control group. According to RAMADAN et al. (1989), lowered intracellular magnesium levels are also observed in brain structures in this period in migraine patients. Moreover, additional decrease in magnesium levels is observed during the migraine attack in plasma, erythrocytes and mononu-

clear blood cells, as well as in the cerebrospinal fluid (GALLAI et al. 1992, SUN-EDELSTEIN, MAUSKOP 2009). All these observations seem to support the hypothesis proposed in the 1970s by Durlach stating that the increased urinary excretion of magnesium ions during migraine attacks was associated with the loss of magnesium from plasma, thus leading to hypomagnesemia (DURLACH 1976).

Today, hypomagnesemia is also mentioned as a cause of menstrual migraine headaches. The onset of these headaches was previously associated with the estrogen secretion profile which undergoes changes during the menstrual cycle. (SILBERSTEIN, GOLDBERG 2007). It should be noted that IHS classification of 1988 does not include menstrual migraine. However, a relationship between changes in plasma magnesium levels during the menstrual cycle and the attacks is currently proposed. Headaches associated with the menstrual cycle occur in stages in which the lowest magnesium levels, and thus the highest calcium-to-magnesium ratios are recorded (SILBERSTEIN, GOLDBERG 2007, DULLO, VEDI 2008).

Demonstration of the relationship between hypomagnesemia and migraine headaches contributed to the advances in studies aimed at identification of potential uses of magnesium compounds in prevention and treatment of migraine attacks.

## **THE ROLE OF MAGNESIUM IN PREVENTION OF MIGRAINE ATTACKS**

Initiation of prophylactic treatment should be considered in patients with migraine attacks occurring at least twice a week or lasting above 48 hours, or in cases in which earlier treatment had failed (SILBERSTEIN 2000, DIAMOND et al. 2007, DEMAGD 2008). Prophylactic migraine treatment should last three to twelve months and involve daily administration of selected compounds (SILBERSTEIN 2000, DIAMOND et al. 2007, DEMAGD 2008).

Magnesium has been classified by the United States Headache Consortium (USHC) as a macroelement recommended in prevention of migraine headaches. It is listed as one of the so-called second line compounds. At the same time, magnesium compounds were pointed out to be relatively safe. Side effects of treatment with magnesium compounds are relatively rare and mild, which is particularly important in prophylactic treatment lasting at least 3 months (D'AMICO, TEPPER 2008). Moreover, magnesium compounds are the only compounds used for migraine prevention falling into the highest FDA pregnancy category, allowing their use by pregnant women (PRINGSHEIM et al. 2010).

Oral magnesium compounds are used for migraine prevention. According to the recommendations of the Canadian Ministry of Health, the maximum dose of magnesium should not exceed  $350 \text{ mg day}^{-1}$  (PRINGSHEIM et al. 2010). To date, prophylactic administration of magnesium compounds has

been considered in the cases of migraine both associated and not associated with aura (FACCHINETTI et al. 1991, PEIKERT et al. 1996, PFAFFENRATH et al. 1996, WANG et al. 2003). One of the first randomized studies of prophylactic administration of magnesium was carried out by Facchinetti and included a group of 20 women suffering from menstrual migraine. Patients received magnesium pyrrolidinecarboxylate at the dose of 360 mg day<sup>-1</sup>. The compound was initiated on Day 15 of the menstrual cycle and continued until the first day of bleeding. The regimen was repeated for two subsequent cycles (FACCHINETTI et al. 1991). The method of treatment initiation was strictly correlated with changes in plasma magnesium levels occurring during the menstrual cycle (ALLAIS et al. 2005). The study confirmed a beneficial effect of magnesium compounds in the prevention of menstrual migraine. In addition, magnesium salts were shown to be efficient in reducing the symptoms of the premenstrual syndrome (FACCHINETTI et al. 1991).

Studies conducted by Peikert et al (1996) showed that administration of magnesium citrate for 3 months reduced the incidence of migraine attacks by 41.6%, as compared to a reduction of less than 16% in patients receiving placebo. Pain intensity and duration of an attack were also reduced as compared to the control group, although the differences were not statistically significant (PEIKERT et al. 1996).

However, not all studies support the efficacy of magnesium compounds in migraine prophylaxis. Such efficacy was not demonstrated in studies by PFAFFENRATH et al. (1996), who administered 480 mg of magnesium to a group of 68 patients. Due to these discrepant reports regarding the efficacy of magnesium in migraine prevention, magnesium compounds are classified as category B. (EVANS, TAYLOR 2006, MOODI, LOWDER 2006).

## **THE ROLE OF MAGNESIUM IN THE TREATMENT OF MIGRAINE ATTACKS**

Oral administration of magnesium compounds is rather unhelpful in treating migraine attacks. As evidenced by the available literature, oral application of magnesium has limited efficacy in the treatment of migraine after as long as several months of supplementation (MAUSKOP et al. 1996, DEMIRKAYA et al. 2001). Results of studies of the headache relief efficacy of intravenous administration of magnesium compounds are ambiguous. The efficacy could not be demonstrated in some of the studies, while results of other studies supported the analgesic activity of magnesium compounds.

Studies conducted by MAUSKOP et al. (1998) showed that intravenous administration of magnesium sulfate reduces the severity of migraine, cluster and tension headaches in 80% of patients. As mentioned before, this effect was most probably caused by the interaction between magnesium and serotonin receptors. Besides, potential mechanisms of action of magnesium ions that would determine its analgesic efficacy include the impact on the syn-

thesis and secretion of nitric oxide (which has a vasodilatory effect) and interaction with NMDA receptors, as well as the influence on many other receptors and neurotransmitters important for headache pathogenesis (MAUSKOP, ALTURA 1998).

Studies conducted by BIGAL et al. (2002) showed that intravenous administration of 1 g of magnesium sulfate had no effect on the course of headache attacks in patients suffering from migraine without aura. However, reduction of pain discomfort, photophobia and hypersensitivity to sounds were observed in patients suffering from migraine with aura compared to the placebo group. No reduction in the incidence of nausea accompanying migraine attacks was observed.

The efficacy of magnesium sulfate was reported also by ZIDVERC et al. (2001). A thirty-minute infusion of magnesium sulfate during an acute migraine attack had similar pain relieving efficacy as sumatriptane, a selective 5-HT<sub>1D</sub> serotonin receptor agonist. Unfortunately, earlier recurrence of headaches was observed in some of the patients receiving magnesium, compared to sumatriptane group.

As mentioned before, some reports do not support sufficient efficacy of magnesium compounds in interrupting migraine attacks. These include, for example, observations by CORBO et al. (2000), who found that intravenous addition of 2 g magnesium sulfate to methoclopramide administered during the attack had no pain relief efficacy, and even reduced the efficacy of the antiemetic drug. Similar results were published by CETE et al. (2005).

Diverse responses of patients to magnesium sulfate are attributed to numerous factors, including low baseline levels of magnesium ions in plasma (MAUSKOP et al. 1995). However, this opinion is not shared by GINDER et al. (2000), who found no relationship between the plasma magnesium levels and the responses to MgSO<sub>4</sub> treatment. It cannot be excluded that different responses of patients to intravenous magnesium treatment may be due to individual-specific factors. However, such factors could not be identified to date.

## SUMMARY

Magnesium is a cation required for proper course of many important physiological processes, disturbances of which are associated with migraine pathogenesis (SUN-EDELSTEIN, MAUSKOP 2011). Hypomagnesemia is a factor predisposing patients to the onset and propagation of cortical depression and changes in neurotransmitter secretion, intensifying the synthesis and secretion of P substance, increasing platelet aggregation and, most of all, causing vascular spasms (SUN-EDELSTEIN, MAUSKOP 2011). Based on the available knowledge of biological functions of magnesium, at least several feasible mecha-

nisms for prevention or reduction of the intensity of migraine attacks by magnesium ions have been proposed (TAYLOR 2011). Although hypomagnesemia has been associated with migraine pathogenesis for many years, the breakthrough in the research in this field was possible only after ion-selective electrodes were invented. In contrast to earlier methods, the use of ion-selective electrodes allows the measurement of ionized magnesium, i.e. the magnesium pool directly associated with physiological effects of this element (SUN-EDELSTEIN, MAUSKOP 2011).

Migraine is a chronic disorder that occurs with periodical exacerbations or attacks that significantly reduce the quality of life of the patients (LIPTON et al. 2003, PRINGSHEIM 2010). Despite different classifications as well as prevention and treatment standards being introduced and modified, the incidence of migraine is still considered to be underestimated (Antonaci 2010). There are two aspects to the migraine treatment strategy, namely prevention and interruption of migraine attacks (ANTONACI 2010). In this study, attention was drawn to potential use of magnesium compounds in both prevention and interruption of migraine attacks. This approach proved efficient in many cases, for instance in prevention of menstrual migraine (MAUSKOP et al. 2002). With regard to intravenous administration of magnesium compounds in order to interrupt acute pain, results of available studies remain ambiguous (CORBO et al. 2000, BIGAL et al. 2002). However, analysis of available reports may lead to conclusion that reports that confirm at least partially beneficial effect of magnesium are predominant (MAUSKOP et al. 1995, MAUSKOP 2001). Doubtless, the results of these studies justify further efforts to obtain more unambiguous answers to questions regarding the role of individual sensitivity in responses to magnesium compounds, which might allow a more efficient prophylactic and therapeutic treatment. Currently, it is also pointed out that extracellular levels of magnesium ions may be largely genetically determined. This was confirmed by the study of SHUEN et al. (2009), who demonstrated a significant correlation between estrogen receptor gene-1 (ESR1) polymorphism and total magnesium levels in plasma (SHUEN et al. 2009). Perhaps examination of this issue would open a path to understanding the correlation between the use of magnesium compounds and the patient's response to the treatment.

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