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The Role of Magnesium in Pathophysiology and Migraine Treatment

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Abstract
Migraine is one of the most common recurrent types of headache and is the seventh cause of disability. This neurological disorder is characterized by having pain in head and other various symptoms such as nausea, emesis, photophobia, phonophobia, and sometimes visual sensory disorders. Magnesium (Mg) is a necessary ion for human body and has a crucial role in health and life maintenance. One of the main roles of Mg is to conserve neurons electric potential. Therefore, magnesium deficiency can cause neurological complications. Migraine is usually related to low amounts of Mg in serum and cerebrospinal fluid (CSF). Deficits in magnesium have significant role in the pathogenesis of migraine. Mg has been extensively used in migraine prophylaxis and treatment. This review summarizes the role of Mg in migraine pathogenesis and the potential utilizations of Mg in the prevention and treatment of migraine with the emphasis on transdermal magnesium delivery.

Keywords Migraine · Magnesium · Headaches · Pathogenesis · Treatment

Introduction

Migraine is defined as a headache accompanied by nausea or photophobia and phonophobia, which can be exacerbated by routine physical activity [1, 2]. Approximately, 18% and 6% of women and men in the USA and also 17.6% and 8% of women and men in Europe have migraine headaches, respectively, while in 51% of the cases, the decreased work or school productivity throughout attacks have been reported [3, 4]. Patients mostly experience migraines without aura. Migraine aura is a transitory focal neurological discrepancy characterized by visual, language/speech, sensory, or motor anomalies that is experienced in almost one-third of patients [5]. Patients with migraine may have a genetically induced hyper-excitable brain [6]. Novel investigations have revealed that the genetic load, based on communal polygenic variation, is more responsible in familial migraine cases than in non-familial ones. It is also higher for migraine with aura and hemiplegic migraine [7]. At least 19 different genes are detected to play a key role in this regard. When a genetically primed neuron is stimulated by an alteration in either external or internal environment, it prompts the brain pathways that generally conduct head pain and causes the symptoms of migraine to appear [8]. Migraine is considered as an intense unilateral throbbing headache, accompanied by osmophobia, anorexia, vomiting, diarrhea, and movement sensitivity [9]. Untreated migraine may last for about 4 to 72 h. During the headache phase, patients may experience cognitive impairments, conjunctiva injection, nasal congestion, or rhinorrhea [10]. Aura happens during or before migraine attacks. Additionally, patients commonly experience visual disturbances such as zigzag vision, flashes of light, language/speech turbulences, sensory, and motor abnormalities [11]. In the postdrome phase, patients feel a common sense of general fatigue, confusion, and weakness which possibly lasts for some hours to 1 day [12]. Migraine is typically associated with other neurological or psychiatric disorders such as stroke, epilepsy, and depressive disorders [13, 14]. In migraine patients, low levels of serotonin and saliva magnesium have been reported. Low level of serotonin is the cause of neuropeptides

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release by trigeminal nerves that are transferred to the meninges leading to migraine pain [15]. Deficiency in brain magnesium also triggers a sequences of processes initiated by platelet aggregation and glutamate release causing 5-hydroxytryptamine (5-HT) formation which acts as a vasoconstrictor in the final point [16]. Magnesium deficiency also causes cerebral artery spasm and enhanced release of pain intermediaries [16]. Decreased mitochondrial phosphorylation potential between headaches is also reported in migraine patients [17]. This phenomenon is the basis for the use of magnesium supplement to elevate mitochondrial function in migraine treatment. In this review, we have summarized migraine pathogenesis with the emphasis on the role of magnesium and the efficiency of intravenous, oral, and transdermal administration of magnesium in migraine treatment.

Migraine Pathogenesis

Migraine attacks begin by the prophetic signs such as fatigue, speaking and reading trouble, and sensual sensitivity. However, these attacks are extremely prognostic in many patients, usually 12 h before the beginning of attacks [18]. Despite the fact that the pathogenesis of migraine has not been fully clarified, two pathways through which migraine may advance are via mitochondrial dysfunction and abnormal cortical information processing. Both cause the stimulation of hyperexcitable trigeminovascular system [19]. Defects in oxidative energy metabolism in migraine are generalized. Riboflavin and coenzyme Q10, physiologically involved in mitochondrial respiratory chain functioning, are effective in migraine prophylaxis [20]. Migraine headache begins with the slow stimulation of neurons and glia along with hyperemia involving spreading activation happening in different areas of the brain [21]. Nurokinin A, substance P (SP), nitric oxide (NO), and calcitonin gene-related peptide (CGRP) are also combined with blood vessel walls and produce neurogenic inflammation, dilation, and protein extravasation. These factors are then being carried towards cortex and thalamus forming pain, ultimately [22]. CGRP is essential for the migraine progression and is presumed to be contributed in pain formation [23]. Glutamate levels are higher in the brain and also in the peripheral circulation in migraine patients, predominantly during attacks. Studies on population genetics have identified different migraine-associated polymorphisms in genes being involved in glutamate signaling and genes encoding probable regulators of glutamate receptor trafficking or glutamate release [24]. Furthermore, decrease in serotonin levels during migraine attacks causes neuropeptides release from trigeminal nerves, which is transferred towards meninges causing migraine pain [25]. Sensitization procedure is another pathophysiological mechanism causing alterations in migraine attacks from acute to acute recurrent, chronic non-progressive, and chronic progressive [26]. Peripheral sensitization has essential role in pulsating (throbbing) the quality of migraine headaches and worsening symptoms of physical activity [26, 27]. The last phases of migraine attacks and the extreme sensitivity in brain are triggered by central sensitization procedure [28]. Activation and sensitization of trigeminovascular neurons, and connections of these neurons to subcortical and brainstem structures, and other dysfunctional sensory processing cause central sensitization [29]. Central sensitization is because of hyperactivity of brain sensory systems and dysfunction of inhibitory or modulatory systems that include neurotransmitters for example dopamine [30]. The superior salivatory nucleus is involved in intermediating the cranial autonomic symptoms detected in the premonitory stage in the nonexistence of pain [29]. The amygdala is a large gray matter complex in the limbic system, and plays a key role in the neurolimbic pain-modulating in migraine pathogenesis [31]. Some studies confirmed that amygdala involves in migraine pain modulation including the modulation of synaptic transmission by cortical spreading depression (CSD) and the periaqueductal gray matter (PAG) network and chronic migraine [31]. The activation of meningeal vasodilation, neurogenic inflammation, and central sensitization is eventually perceived as head pain. Furthermore, many neuropeptides are purported to be involved in the migraine circuitry both peripherally and centrally [32].

Role of Magnesium in Migraine Pathophysiology

Magnesium is the second common intracellular cation existing in all tissues influencing a number of neurochemical processes [33]. This ion is a crucial cofactor for more than 350 enzymes particularly those necessitating adenosine triphosphate (ATP) to be fully functional including the numerous protein kinases, proteins contributed to nucleic acid metabolism or ATPases involved in various ions transportation [34, 35]. Magnesium balance in the body is mainly regulated through renal reabsorption and gastrointestinal absorption. Altered gastrointestinal absorption can cause negative body Mg balance [36]. Mg deficiency is normally specified by measuring serum Mg concentrations which are placed between 0.7 and 1.05 mmol/L in healthy individuals [34]. Mg deficiency has an essential role in the pathogenesis of migraine headaches by neurotransmitter secretion change, CSD stimulation, and the platelet aggregation increase [37]. The spreading depression (SD) is specified by the breakdown of ion homeostasis is related to a temporary cessation of neuronal function, and is understood to play role in migraine pathogenesis and needs the release of glutamate. N-methyl-D-aspartate (NMDA) receptors play a critical role in the propagation of this procedure [38]. Previous investigations have reported that by confirmation of magnetic resonance spectroscopy (MRS) in brain, the decreased levels of Mg in serum, saliva, and cerebrospinal fluid (CSF) of migrainous patients are obvious during and between migraine attacks [39, 40]. Mg deficiency influences the neuroinflammation, serotonin receptor affinity, NMDA receptor

blockage, calcium channel, and glutamate and NO activity [33, 41]. Mg counteracts both vascular and neurogenic mechanisms of migraine. Mg has also been suggested as a treatment choice for migraines due to its NMDA receptor blockage property, a receptor identified as an important contributor to pain transmission [42]. Additionally, magnesium sustains calcium homeostasis by NMDA receptor binding, moderating the substance P release, and controls NO production [43]. Decreased level of serum ionized magnesium (IMg^{2+}) and increased serum ionized calcium (ICa^{2+}) to IMg^{2+} ratio will possibly raise the serotonin affinity for serotonin receptor sites in cerebral vascular muscle inducing cerebral vasoconstriction. Vasoconstriction, prompted through serotonin, can be obstructed via Mg pretreatment [44]. Biochemical studies have recommended that the dysregulation of Ca^{2+} ions, because of mitochondrial dysfunction, modifies neurons signaling properties. This phenomenon has been associated with peripheral pain mechanisms [45]. Mg could usefully target diverse features of the neuroinflammation which progresses mitochondrial oxidative phosphorylation, 5-hydroxytryptamine (5-HT) neurotransmission, and the NO system [39, 46]. The serotonin receptors 5-HT is the most important receptor in headache pathway. 5-Hydroxytryptamine-1D (5HT1D) and 5-hydroxytryptamine-1B (5-HT1B) receptors are also detected in trigeminal sensory neurons and smooth muscle cells in meningeal vessels, respectively [47]. These agents can help headache to be tranquilized by terminating or stopping neuropeptide release in the periphery and obstructing neurotransmission in trigeminocervical complex (TCC) [48]. Furthermore, low Mg levels increases glutamate activity [49]. Higher levels of glutamate have also been reported in migraine patients CSF as well as in the saliva of episodic and chronic migraine patients [42]. Moreover, Mg can regulate the glutamate uptake in astrocytes and restricts the function of NMDA receptor attenuating migraine [50]. The block of NMDA receptor in the voltage-dependent manner by Mg is an important phenomenon in neurosciences [51]. Function of NMDA receptor is related to magnesium levels. By acting as NMDA receptor antagonists, magnesium ions stop the dissemination of glutamatergic-dependent transmission of cortical depression that is related to the initiation of migraine aura [44]. Furthermore, patients with migraine are hypotensive throughout attacks which can be attributed to the enhanced levels of NO [52]. NO is a significant vasodilator and modulator of brain blood flow. Decreased Mg levels, as an inhibitor of NO production can also increase NO levels [53, 54]. It has been reported that Mg influences CGRP circulating levels [37]. Numerous new pharmacotherapeutic selections for the preventive treatment of migraine include monoclonal antibodies and small molecule antagonists that target CGRP pathway [55]. Vulnerability to migraine is powerfully inclined by genetics. The probability of an intersection or overlap between genetics of migraine and magnesium homeostasis is known and must be additionally considered [56].

Prevention and Treatment of Migraine with Magnesium

Prophylactic treatment should be deliberated in migraine patients at least twice a week or longer in attacks above 48 h, or in cases with unsuccessful earlier treatment [57, 58]. The main aim of migraine prophylaxis is to decrease attacks recurrence rate and patient debility, while elevating their quality of life. A well-operated prophylactic therapy should decrease the rate of recurrence of migraine attacks down to the minimum of 50% [36]. The present guiding principle regarding migraine prophylaxis includes a wide range of utilizing beta-blockers and other antihypertensive drugs, anticonvulsants, antidepressants, nutraceutical containing magnesium, and the injection of botulinum toxin type A in chronic migraine [59]. Mg has been categorized as a suggested macroelement in the prevention of migraine headaches by the United States Headache Consortium (USHC) [60, 61]. Oral Mg compounds are also used to prevent migraine. Based on the references of Canadian Ministry of Health, the maximum dose of Mg should not be exceeded from 350 mg/day [62]. Mg oxide is also frequently suggested for migraine prophylaxis in the pediatric population at the dose of 400 mg/day [63]. Additionally, few side effects containing abdominal pain, nausea, and diarrhea have been reported for Mg supplementation. Mg can also temporarily decrease the blood pressure [64]. Furthermore, it is considered as a safe supplement during pregnancy [64]. However, clinical trials have reported controversial results for the possible efficiency of oral Mg in migraine prevention [63].

The study by Facchinetti et al. [65] on 20 women suffering from menstrual migraine receiving Mg pyrrolidinecarboxylate at the dose of 360 mg/day showed Mg salts as an effective agent in menstrual migraine prevention which decreased the symptoms of premenstrual syndrome [65]. Additionally, during oral treatment, Mg levels were significantly elevated in lymphocytes and polymorphonuclear cells (PMN); however, no significant alteration in plasma Mg levels was established [65]. These data indicate Mg supplementation as an additional means for menstrual migraine prophylaxis, and show that a minor migraine threshold is correlated with Mg deficiency. Peikert et al. [66] showed that oral administration of 600 mg trimagnesium dicitrate daily for 3 months decreased the occurrence of migraine attacks down to 41.6% when compared with the controls. Additionally, pain severity and attack duration were also decreased. Results from this study revealed that high-dose oral Mg is effective in migraine prophylaxis [66]. The data from single-blind clinical trial conducted by Tarighat et al. [67] also revealed that Mg supplementation significantly promoted the mean level of serum Mg and caused pain relief in migraine patients. The results revealed that concurrent oral

use of magnesium oxide (MgO) and L-carnitine supplementation exhibited synergic effects of magnesium and L-carnitine in migraine prophylaxis, nevertheless trials with bigger samples size are required to approve these preliminary results [67].

However, a randomized double-blind multicenter trial showed that a combination of 600 mg/day Mg, 400 mg/day riboflavin, and 150 mg/day Q10 did not statistically decrease migraine days [68]. Although, after 3 months of supplementation therapy, decreased migraine pain and disease burden were observed. This combinative supplement also diminished the number of migraine days for nearly 2 days. Additionally, the severity of migraine pain was significantly decreased in the supplement group [68]. The advantage of this study is the prospective, double-blind, and placebo-controlled design. The adverse effects associated with this combination were principally abdominal discomfort and diarrhea because of high volumes of Mg, but there were no serious adverse events reported in this trial [68].

The results of a recent open-trial study highlighted the efficiency of combination of tanacetum parthenium, 5-hydroxytryptophan (5-HTP) and Mg in migraine prophylaxis [69]. Aurastop (derived from the combination of tanacetum parthenium (150 mg extracted of active parthenolide), griffonia simplicifolia (20 mg of 5-HTP) and Mg (185 mg of magnesium pidolatum)) [70] which was administered twice a day for 3 months, significantly decreased recurrence rate and the period of migraine attacks and pain severity in most patients [69]. In general, this combination looks as a hopeful association of molecules for migraine prophylaxis with a satisfactory safety profile. Further clinical trials are necessary to examine the capacities of this compound either given alone or in combination with other molecules [69]. Another study was conducted to confirm the efficiency and safety of the Aurastop in the prophylactic treatment of episodic migraine without aura (MO) another study. Eighty patients with MO, with a monthly frequency of 3 to 8 attacks and 4 to12 headache days, were treated with Aurastop twice daily for 3 months. A significant decrease in the number of headache days, number of attacks per month, and pain severity was observed post-treatment. These results revealed that this combination might act synergistically on neuroinflammation, neural transmission, and central sensitization. Regardless of the methodological limitations of this observational pilot study due to the absence of placebo group, this results highlighted the prospective effect of Aurastop® on the complex physiopathological mechanisms of migraine [71]. Another observational study concluded that the proprietary supplement Antemig® (contained 100 mg of feverfew, 100 mg of coenzyme Q10, 112.5 mg of Mg, and 1.4 mg of vitamin B6), at the dose of one tablet per day for up to 3 months, can be operative and well tolerated for the prophylaxis of migraine in adults [72]. Treatment for 3 months significantly decreased the average number of migraine days. The proportion of patients with anxiety and depressive symptoms decreased between baseline phase and third month of supplementation. The findings suggested that this supplement could be advantageous and safe for the prevention of migraine in adult patients [72]. In a single-center, randomized, double-blinded controlled, and crossover trial, the effectiveness of Mg oxide in comparison with valproate sodium to prevent migraine attacks was evaluated. The intervention group received 500 mg Mg oxide and the control group received 400 mg valproate sodium two tablets per day (every 12 h) for 8 weeks [73]. The main efficiency was reduction in the number of migraine attacks, number of days with moderate or severe headache, and number of hours with headache (duration) per month in the final 8 weeks when compared with the baseline. Without important adverse effect, 500 mg magnesium oxide seems to be efficient in migraine prophylaxis like valproate sodium. This study was limited by the absence of placebo control and by the absence of data on the serum variations of Mg levels before and during treatment. But the research can be a base for prospect studies with larger number of participants [73].

Intravenous (i.v.) administration of Mg has also been recommended as a treatment choice for migraines. Mauskop et al. [74] reported that 80% of patients after being treated with 1 g intravenous magnesium sulfate ($MgSO_4$) became pain-free for 15 min and nearly all had brief flushing. Photophobia and phonophobia as well as nausea were broadly eradicated in patients treated with $MgSO_4$. These results show the potential role of IMg^{2+} deficiency in the etiology and development of headaches and recommend a possible efficiency of intravenous $MgSO_4$ in the acute treatment of many patients with different headaches. Therefore, measuring serum IMg^{2+} levels can help to discover its first routine use in clinical practice [74]. Demirkaya et al. [75] compared 1 g intravenous $MgSO_4$ with normal saline (NS) as placebo. Seventy percent of the patients had migraine with aura. Afterward magnesium administration, larger percent of patients became pain-free in 30 min after the administration. In 93.3% of patients, the attack was ended; in 6.6%, pain severity was decreased; and in all patients, associated symptoms disappeared. 86.6% of the patients in both groups experienced mild adverse effects including flushing and face or neck burning. These results confirmed that the effect of $MgSO_4$ in acute migraine should be studied in large-scale studies [75]. In another study by Corbo et al. [76], intravenous administration of 2 g $MgSO_4$ and 20 mg metoclopramide on 44 patients (21 patients received metoclopramide with Mg and the other 23 were treated with metoclopramide and placebo as controls) showed that magnesium and metoclopramide combination therapy decreased the efficiency of metoclopramide in migraine relief. Actually, those women who received metoclopramide plus $MgSO_4$ had less promising response to treatment when compared with the patients who received metoclopramide plus placebo. Flushing was also the most common side effect among

patients. These results could not be generalizable to men as most of the participant in this study were women [76]. In a phase II placebo-controlled trial, intravenous administration of 1 g $MgSO_4$ for 1 migraine attack treatment among patients with aura showed better pain-free at 1 h; however, pain relief at 1 h in patients without aura was not statistically significant when compared with the placebo group [77]. In summary, intravenous $MgSO_4$ could be a practical option for the acute treatment of migraine with aura. Results revealed that $MgSO_4$ can be administered alone to treat migraine with aura, or as an adjuvant therapy for the related symptoms in migraine with and without aura [77]. Frank et al. [78] also showed that administration of 2 g intravenous Mg in patients with acute benign headache who referred to the emergency department (ED) caused no significant differences in pain relief according to visual analog scale (VAS) at 30 min when compared with the controls. Thus, no i.v. magnesium was not advantageous in treating patients with acute benign headache who referred to the ED [78]. Another phase II study compared the administration of 10 mg of intravenous metoclopramide with 2 g of intravenous magnesium sulfate in treating migraine attack. Each group had more than a 25-mm improvement in VAS score at 30 min. [79]. However, 3% and 8% of patients taking metoclopramide and magnesium experienced dystonia and flushing, respectively. The recurrence rate in 24 h was similar between the groups. Even though patients receiving placebo needed rescue medication more than the others, so metoclopramide and magnesium have an analgesic effect like to placebo in migraine attacks [79]. A meta-analysis that reviewed 1203 abstracts and five randomized controlled trials (RCTs) exhibited that i.v. administration of Mg caused 7% lower relief rate at 30 min after the administration and a greater 37% side effect response rate. Nevertheless, i.v. use of Mg was significantly efficient for migraine relief in patients with aura, 1 h after administration [80]. These meta-analyses were unsuccessful to validate advantageous effects of i.v. Mg in terms of decreasing pain relief in acute migraine in adults. It actually revealed that patients treated with Mg were likely to describe more adverse events [80]. In a cross-sectional study performed by Kasmaei et al. [81], the efficacy of 30 mg ketorolac and 1 g $MgSO_4$ in migraine pain management were assessed. Based on the results of this study, both ketorolac and $MgSO_4$ were significantly efficient in migraine pain management; however, $MgSO_4$ exhibited higher efficiency when compared with ketorolac, 1 and 2 h after drug administration [81]. This study still cannot demonstrate anything with great certainty; however, it can be considered as a pilot study to conduct further double-blind RCTs [81]. Another study by Baratloo et al. [82] also revealed that both intravenous caffeine and $MgSO_4$ decreased the severity of pain, even though, the $MgSO_4$ exhibited efficiency than caffeine citrate after 1 and 2 h. Furthermore, 2 g intravenous $MgSO_4$ was more effective for short-term managing of migraine in EDs when compared with 60 mg intravenous caffeine citrate [82]. The sample size of this study is somewhat smaller and it did not evaluate the long-term effectiveness of the drugs. Also, there were statistical differences on the subjects' age and sex of the studied groups that caused a bias in this study. As a result, the management of acute episodes should be individualized case by case because of the idiosyncratic effects of available agents. Further well-planned RCTs to approve the results of this study are needed [82].

Almost 38% of patients with episodic migraines can benefit from preventive therapy, but less than 13% take prophylactic medications. Preventive medication therapy decreases migraine frequency, severity, and headache-related distress [83]. Intravenous administration of Mg is usually considered for acute migraine management and prophylaxis, whereas oral use of Mg supplementation is approved for prophylaxis and it decreases the frequency and severity of migraine [84, 85]. Additionally, 600 mg/day of magnesium has also been suggested as a safe and affordable treatment for migraine care and can be increased to 1200 mg if tolerated [46].

Transdermal Magnesium Therapy

Transdermal drug delivery has been considered as an effective approach for many years which has made creams, gels, ointments, sprays, and lotions to be used for more than a century [86]. High local concentrations combined with low systemic levels is achieved with a transdermal formulation, ensuring maximum therapeutic effect at the site of action and minimal systemic and gastrointestinal adverse effects [86]. The transdermal use of Mg (magnesium-containing sprays) compared with oral use is particularly effective for its almost 100% absorption and lower side effects through bypassing the gastrointestinal tract [87]. Transdermal Mg therapy is also well tolerated, and every extra Mg will be excreted from the body [87]. Utilization of transdermal Mg is an easy, affordable, and functional method to raise cellular Mg level. Shealy et al. [88] claimed that the transdermal use of magnesium retrieved Mg deficiency during 4 to 6 weeks, while an oral supplementation was efficient after 4 to 12 months [88]. Transdermal Mg directly passed into the tissues through the skin and is immediately transported to the cells [89]. Due to its water solubility, magnesium chloride ($MgCl_2$) is possibly the most bioavailable form of Mg and increased absorption through spraying on topically [90]. $MgCl_2$ that includes 11.8% magnesium binds to 88.2% chloride. It is made over vaporization from saline (mostly sea) waters. After sodium chloride elimination, the remained bittern, is mostly consisted of $MgCl_2$ and $MgSO_4$ [91]. $MgCl_2$ can be also used as "magnesium oil" [91] on skin's surface and diffuses into the stratum corneum. Then, magnesium is transported into subcutaneous fat and finally the circulatory system [92, 93]. In a clinical study, 20 sprays of magnesium

oil were administered for 9 patients aged between 22 and 69 years over 12-weeks period to evaluate the cellular levels of Mg. The original treatment included daily spray of every location of the body, in addition to a 20-min foot soak by 100-ml magnesium oil (by means of a simple water foot-bath) two times weekly [94]. Results showed that cellular Mg levels elevated in 89% of subjects from − 7.1 to 262% with an average rise of 59.7%. Equivalent outcomes by means of oral supplementation have been described over 9–24 months. No data on serum Mg concentration was accessible [94]. This investigation confirms that transdermal application of magnesium Mg in the chloride form will increase Mg levels within the body over a comparatively short period of time [94]. Table 1 has summarized clinical trials' use of magnesium in migraine patients.

Dr. Shealy's Biogenics Magnesium Lotion Spray has about 275 mg of magnesium in 10 sprays two times per day. In this therapy, specialists propose fairly "thin" skin areas of body including forearms, underarms, and abdomen for use. To use Mg oil for migraine headaches management, spray on shoulders, neck, and upper back is recommended. After 15–20 min, most of the magnesium will be absorbed. The use of Mg oil spray 2 times per day (once in the morning and at night) can be also utilized when the patient feels a migraine attack to reduce its magnitude [88].

Conclusion

Migraine is more than a headache. No perfect treatment does exist for many individuals with migraine, who often have recurrent, enduring, and painful symptoms. Up to now, numerous drugs such as opium, nonsteroidal anti-inflammatory drugs (NSAIDs), neuroleptics, and triptans have been used to treat migraine headaches. Due to the side effects of these drugs, many individuals are in search of a preventive treatment for migraine. Mg is the second-line treatment for migraine patients with several effects on the nervous system, NMDA receptors, voltage-gated calcium channels inhibition, connexin channels, and other ion channels. These mechanisms could be contributed to Mg-mediated migraine control. Mg is also a supplement with moderately rare side effects and good indication for the progression of migraine symptoms. Generally, although current data indicates the beneficial effects of intravenous and oral Mg administration as treatment choices, RCTs with bigger sample sizes are required to improve the recognition on the effectiveness of Mg treatment. On the other hand, transdermal $MgCl_2$ solution is an ideal approach in migraines treatment because of its immediate absorption through the skin. In brief, we recommend further clinical trials to be done to give an improved estimation of the effects of magnesium in migraine prevention and treatment.

Table 1 Magnesium use clinical trials in migraine patients

Rout of Mg use	Study design	Outcomes	References
Oral	- 20 women with menstrual migraine - 360 mg/day magnesium pyrrolidinecarboxylate	- Increased Mg levels in lymphocytes and PMN - Prevented of menstrual migraine - Decreased premenstrual syndrome symptoms	[65]
Oral	- Magnesium citrate - For 3 months	- Reduced the migraine attacks frequency - Decrease the pain intensity and attack duration	[66]
Oral	- Simultaneous use of MgO and L-carnitine	- Increased the mean level of serum Mg - Reduced pain	[67]
Oral	- 600 mg/day Mg, 400 mg/day riboflavin and 150 mg/day Q10 - For 3 months	- Diminished migraine pain and disease burden - Reduced the number of migraine days	[68]
Oral	- Tanacetum parthenium, 5-HTP and Mg - Twice a day for 3 months	- Decreased the rate of recurrence - Decreased the period of migraine attacks - Decreased the pain intensity	[69]
Oral	- 500 mg MgO - 400 mg valproate sodium - Two tablets each day for 8 weeks	Mean number of migraine attacks - Magnesium group 1.72 ± 1.18 - Valproate group 1.27 ± 1.27	[73]
Intravenous	- 1 g Mg - For 15 min	- Caused to pain-free - Caused to brief flushing	[74]
Intravenous	- 1 g Mg compared with NS as placebo. - For 30 min	- Caused to pain-free - Experienced flushing and face or neck burning	[75]
Intravenous	- 1 g $MgSO_4$ for 1 migraine attack treatment	- Better pain-free in patients with aura at 1 h	[77]
Intravenous	- 2 g $MgSO_4$ compared with 10 mg metoclopramide - For the treatment of 1 migraine attack	- Decreased headache intensity at 30 min - Experienced dystonia and flushing	[79]
Intravenous	- 30 mg ketorolac compared with 1 g $MgSO_4$	- Decreased migraine pain	[81]
Intravenous	- 2 g $MgSO_4$ compared with 60 mg caffeine citrate	- Decreased migraine headaches	[82]
Transdermal	- 20 sprays Mg - For 9 patients - Over 12-weeks two times weekly	- Raised cellular magnesium levels are from − 7.1 to 262%.	[94]

5-HTP 5-hydroxytryptophan, *Mg* magnesium, *MgO* magnesium oxide, *$MgSO_4$* magnesium sulfate, *NS*, normal saline, *PMN* polymorphonuclear cells

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

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