Key Words: magnesium, pain, CRPS, CPP, fibromyalgia

Intravenous Magnesium for the Management of Chronic Pain: An Updated Review of the Literature

By Henry Onyeaka, Janet Adeola, Rebecca Xu, Adlai Liburne Pappy, Marchelle Smucker, Wisdom Ufondu, Moyasar Osman, Jamal Hasoon, Vwaire Orhurhu

ABSTRACT ~ **Background:** *Available therapeutic options are currently limited by their modest efficacy. As a result, novel pharmacotherapeutic treatments with different mechanisms have recently attracted empirical attention. Magnesium, a divalent cation, is postulated to provide analgesic and anti-nociceptive effect through its action at the N-methyl-D-aspartate (NMDA) receptor.* **Objective:** *Considering the evidence surrounding magnesium's potential as a therapeutic modality for chronic pain, we conducted a narrative review on the evidence of magnesium's therapeutic effects in chronic pain.* **Methods:** *A review of the PubMed, and Google scholar databases was undertaken in May 2022 to identify completed studies that investigated the effectiveness of magnesium in the treatment of chronic pain from database inception to May 2022.* **Results:** *A total of 33 studies were included in the narrative review, out of which 26 were randomized controlled trials. Findings on available studies suggest that intravenous infusion of magnesium is an emerging and promising option that may alleviate pain in some clinical populations. Our narrative synthesis showed that evidence for intravenous magnesium is currently equivocal for a variety of chronic pain syndrome. Findings indicate that evidence for efficacy is poor or equivocal for: CRPS, neuropathic pain, chronic low back pain, and migraine prophylaxis. However, there is good evidence supporting the efficacy of intravenous magnesium for treating renal colic pain and pelvic pain related to endometriosis.* **Conclusion:** *Magnesium may be a promising pharmacologic solution for chronic pain. Future investigation is warranted on elucidating the neurobiological mechanisms of magnesium in attenuating pain signaling pathways.*
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Onyeaka, MBCHB, MPH, Department of Psychiatry, Harvard Medical School, Boston, MA, USA; Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; Department of Psychiatry, Mclean Hospital, Belmont, MA, USA. Adeola, MD, MS, Xu, MD, Pappy, MD, MBA, Department of Anesthesiology and Pain Medicine, Brigham and Women's Hospital, Boston, MA, USA. Smucker, BS, Edward Via College of Osteopathic Medicine, USA. Ufondu, Department of Biology, Program in Liberal Medical Education (PLME), Brown University, Providence, RI, USA. Osman, Department of Psychology, New York University, New York, NY, USA. Hasoon, MD, Department of Anesthesiology, University of Texas Health Science Center at Houston, Houston, TX, USA. Orhurhu, University of Pittsburgh Medical Center, Susquehanna, Williamsport, PA, USA; MVM Health, East Stroudsburg, PA, USA.

To whom correspondence should be addressed: Vwaire Orhurhu, MD, MPH, University of Pittsburgh Medical Center, Susquehanna, Williamsport, PA, USA. Phone: (507) 351-9579. E-mail: vwo569@mail.harvard.edu

Introduction

The opioid epidemic in the United States has highlighted the deleterious effects of persistent opioid therapy. Further, there is great interest in multimodal and non-opioid analgesics that can mitigate opioid consumption, which is a priority in chronic pain research. Magnesium represents one of these opioid-sparing agents. Magnesium is a physiological ion that is involved in several cellular processes. Clinically, magnesium therapy is well-tolerated and widely used, most commonly for the treatment of preeclampsia, arrhythmias and severe asthma.[2] Magnesium is also an analgesic that is used in the management of acute and chronic pain. Prior literature has demonstrated that magnesium is effective in alleviating postoperative pain, neuropathic pain, complex regional pain syndrome, migraine headaches and several other chronic pain conditions.[3–7]

Magnesium is a N-methyl–D-aspartate (NMDA) receptor antagonist. The NMDA receptor is a ligand (glutamate and glycine) gated ion channel. Through inhibition of the NMDA receptor, magnesium prevents the intracellular entry of calcium and halts the potentiation of central sensitization (wind –up phenomenon) that occurs secondary to peripheral tissue injury.[8] Central sensitization is due to repetitive nociceptive activation, resulting in a reduction in pain threshold and enhanced pain hypersensitivity.[8] Availability of intracellular calcium is critical in mediation and attenuation of pathways involved in central sensitization. Extracellular magnesium binds NMDA receptors and prevents this crucial step in the central transmission of peripheral nociception.

This present narrative review analyzes randomized control trials to present an updated and comprehensive review of the use of magnesium for the management of several pain pathologies. Specifically, we investigate the use of magnesium in the management of complex regional pain syndrome (CRPS), neuropathic pain, chronic low back pain, migraine/non-migraine headaches, postoperative pain, renal and chronic pelvic pain syndrome. This current study extends prior work by focusing on randomized control trials, which have the advantage of providing a comparative analysis while minimizing biases and confounders.

Drug/Compound

Magnesium has a diverse physiologic profile as one of the body's essential minerals. It is a required cofactor in many enzymatic processes, including protein synthesis, nucleic acid stability, maintenance of cell membrane potential, and neuromuscular function.[9] Clinically,

magnesium has become a staple in treating preeclampsia/eclampsia and torsades de pointes;[9] however, more recently, it has gained attention for its anti-nociceptive effects.

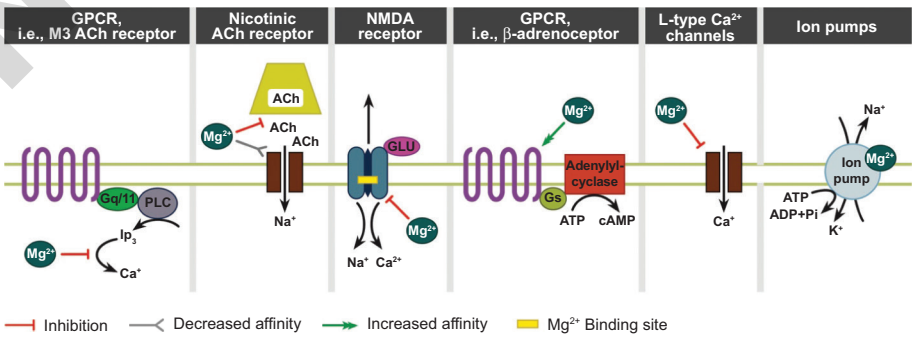
A major contributor to these effects includes magnesium's antagonistic relationship to cellular calcium channels. Blocking these channels prevents neurotransmitter release in the hippocampus, inhibits the secretion of acetylcholine at the neuromuscular junction, and antagonizes the NMDA receptor in the central nervous system.[9] Figure 1, from Shin et al. shows several of these abbreviated mechanisms on which magnesium exerts its effects.[8]

In particular, the NMDA receptor (NMDAR) has been shown to potentiate nociceptive pathways and contribute to central sensitization.[8] The NMDAR is a ligand-gated ion channel interspersed throughout the central nervous system. The binding of glutamate and glycine to the NMDAR opens the ion channel. However, under resting conditions, magnesium obstructs the channel. Depolarization of the cell membrane expels magnesium from the channel in a voltage-dependent manner, allowing sodium and calcium to enter the cell while potassium ions are permitted to move extracellularly. By this mechanism, the NMDAR not only potentiates cell depolarization but also employs calcium as a potent secondary messenger.[10] These mechanisms contribute to long-term potentiation, learning, and memory. However, excessive stimulation and subsequent intracellular calcium accumulation can maladaptively influence gene expression and cause cell damage.[8] This is the basis of central sensitization, which occurs in response to repeated nociceptive stimuli; large influxes of calcium move into neuronal cells in the dorsal horn of the spinal cord and result in pain hypersensitivity.[8]

As magnesium is a natural antagonist of this process, it has gained interest in the field of anesthesiology and pain medicine. Magnesium is absorbed in the intestines and exists in the plasma mostly in its ionized

FIGURE 1

Abbreviated Mechanisms Involving Magnesium



form before it is renally excreted. Normal physiologic levels are considered between 1.7–2.4 mg/dl.[9] Magnesium can be administered orally or in the form of magnesium sulfate via intravenous (IV), intrathecal, or epidural routes. In trials for perioperative pain, IV magnesium sulfate was given with a loading dose of 30–50 mg/kg and a maintenance dose of 6–20 mg/kg.[8] Although this is typically given as a continuous infusion, studies have shown that a single bolus of magnesium sulfate can reduce opioid consumption postoperatively for up to 24 hours.[11] Magnesium toxicity typically does not occur in the absence of renal disease, making it a relatively safe compound with few adverse effects in individuals with adequate kidney function.[9]

Results

Complex Regional Pain Syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a chronic condition characterized by spontaneous and evoked pain, usually in a distal extremity after trauma (e.g., surgical intervention or injury).[12] The Budapest Criteria is the most widely used diagnostic tool for CRPS.[13] CRPS is categorized as type I or type II based on the presence or absence of clinically significant peripheral nerve injury (such as abnormal nerve conduction test) respectively.[12] In CRPS, the ongoing pain is disproportionate to the inciting trauma and associated tissue damage.[13] The affected limb is characterized by considerable autonomic and inflammatory dysregulation. Clinically, this manifests as hyperalgesia, allodynia, changes in skin color, temperature, and hair growth, and in severe cases tremors and dystonia.[14]

The exact pathophysiology of CRPS remains elusive, but there are several speculative models that attempt to explain the mechanism of the tissue changes observed in this pain syndrome. Regardless of the driving factor, most of the disease models agree that CRPS is due to a complex interplay of central and peripheral processes.[12] After tissue injury, the nervous system is particularly sensitive to nociceptive and inflammatory changes in the affected area.[12] This appears to be a protective mechanism to prevent further injury.[12] In the central nervous system (CNS), ongoing painful stimuli after injury may result in central sensitization. As previously described in this analysis, central sensitization results in the enhancement of pain transmission and perception. In the periphery, the noxious stimuli result in increased firing of primary afferent fibers. Tissue injury results in central and peripheral sensitization through the release of pro-nociceptive and pro-inflammatory neuropeptides. The release of these neuropeptides is also thought to result in sympathetic nervous system dysregulation.[15] These physiological changes account for the symptoms observed in CRPS.

TABLE 1

Table for Studies on Complex Regional Pain Syndrome

N	Author and Study Year	Study Design	Pain Pathology	Intervention Group: Dose, Frequency, Route of MG Administration	Control Group/ Placebo	Adjuvant Pain Treatment	Primary Outcome	Duration of Effect	Secondary Outcome	Adverse Effects
56	Fischer et al. 2013	Randomized double-blind placebo-controlled	CRPS Type I	IV MgSO4 70 mg/kg In 4 hours over 5 consecutive days	IV NaCl 0.9% In 4 hours over 5 consecutive days	Physical therapy	Pain scores (BOX-11 & McGill assessment) and level of impairment (impairment level sum score)	No difference	Functional limitations and quality of life	Flushing, dizziness
30	Van der Plas et al. 2013	Double-blind placebo-controlled crossover	CRPS	Intramuscular magnesium sulphate. 1000 mg in week 1, 1,500 mg in week 2, and 2,000 mg in week 3	Intramuscular Sodium chloride .9%	2.5 gram of lidocaine-prilocaine 5% cream to puncture site to reduce unblinding	Change in Burke-Fahn-Marsden scores after 3 weeks of therapy	No effect	Difference in change after 3 weeks between interventions on measures other than the BFM scale.	Injection pain, subcutaneous hematoma, Mild allergy

There are limited randomized control trials that provide evidence on the standard treatment for CRPS. The first-line therapies for CRPS include bisphosphonates, calcitonin, ketamine, steroids, and focused physical and occupational therapy.[12,16] IV magnesium has been shown to reduce sensory disturbances in acute stages of CRPS Type I.[17] Magnesium appears to have limited efficacy in the treatment of chronic CRPS Type I.[6] A randomized control trial demonstrated that overall, there was no difference in pain scores between patients who received intravenous magnesium compared to counterparts who received placebo.[6] In the study, efficacy of treatment was measured using several metrics including the BOX-11 and Impairment level Sum Score (ISS) which are pain severity rating scale and impairment rating scale, respectively. Of note, the study demonstrated a statistically significant and clinically relevant improvement in CRPS sensory symptoms in the magnesium cohort as graded by the McGill Pain scale (NWCt).[6] While the findings are not immediately translatable to clinical practice, the marginal improvement in CRPS sensory symptoms suggests that magnesium may have anti-inflammatory properties that might mediate its role in the treatment of acute CRPS.[6]

In another randomized control trial,[7] the use of magnesium for the treatment of dystonia in CRPS patients was investigated. In addition to central changes, there are physiological changes at the neuromuscular junction that mediates the development of dystonia in CRPS. Muscle contraction is highly dependent on calcium influxes and magnesium can counter this effect through its activity at the NMDA receptor.[7] Intramuscular magnesium was proposed to serve as a muscle relaxant that can potentially decrease the clinical manifestation of dystonia.[7] The study was unable to demonstrate that intramuscular magnesium (at doses as high as once gram twice daily) was efficacious in alleviating dystonia in CRPS patients.[7] Overall, the benefits of magnesium therapy appear to be limited to acute CRPS, with unclear benefits in later stages of this pain syndrome.

Neuropathic Pain

Neuropathic pain is due to injury to the somatosensory system; this includes damage to nerves in the central and peripheral nervous systems. At the physiological level, there is a lesion to a sensory or mixed peripheral nerve, cutaneous nerve branch or damage to a central somatosensory pathway. Like CRPS and other chronic pain conditions, there is the presence of peripheral and central sensitization.

Clinically, neuropathic pain presents as a sensory deficit in a specific region of the body. Patients might experience hypersensitivity (paresthesia, allodynia) or hyposensitivity (mechanical or thermal hypoalgesia) to sensory stimuli, with presence of pain being a defining feature.[18,19] Besides pain, other associated sensory features observed in neuropathic pain are based on the nerve fibers that are affected.[18] If large diameter afferent fibers are affected, this presents as loss of mechanical or vibratory perception. If small diameter fibers or central processing pathway such as the spinothalamic tracts are affected, this presents as loss of noxious and thermal sensation. It can be difficult to diagnose neuropathic pain and distinguish it from nociceptive pain. The critical distinguishing feature in neuropathic pain is the presence of somatosensory abnormalities.[18,19] In nociceptive pain, the nociception is secondary to damage of non-neural tissue and is a result of activation nociceptors with an intact somatosensory system. It is possible to have components of both nociceptive and neuropathic pain, which is known as mixed pain syndrome.

The first-line treatment options for neuropathic pain include pregabalin, gabapentin, tricyclic antidepressants, and serotonin-noradrenalin-reuptake inhibitors (duloxetine, venlafaxine).[19] The use of magnesium has been proposed in the management of neuropathic pain syndromes. A study that investigated the use of magnesium infusion in the treatment of postherpetic neuralgia (PHN) found that magnesium reduced PHN pain in comparison to the placebo treatment.[4] In the study, mean pain scores during magnesium infusion decreased from 6.9 to 1.7.[4] While magnesium decreased pain scores in the PHN cohort, it did not relieve symptoms of allodynia.[4] This was thought to be due to the fact that allodynia is not entirely mediated by central sensitization, a process which magnesium inhibits.[4] Another study that assessed the use of magnesium in PHN patients demonstrated clinically significant analgesic effects of magnesium.[20] This study is clinically relevant as it demonstrated that magnesium could be an effective therapeutic agent in PHN patients who are refractory to first-line therapies.[20] The study also compared the analgesic effects of magnesium to ketamine and demonstrated a higher response rate in the ketamine cohort, although this did not achieve statistical significance. Of note, the doses of magnesium used in the aforementioned PHN studies were lower than the dose of magnesium used in the treatment of preeclampsia.[4,20] More recently, an analysis demonstrated that injection of magnesium, a local anesthetic and steroid into the transforaminal epidural space can be efficacious in the treatment of lower limb radicular pain.[3]

TABLE 2

Table for Studies on Neuropathic Pain and Low Back Pain

N	Author and Study Year	Study Design	Pain Pathology	Intervention Group; Dose, Frequency, Route of Mg Administration	Control Group/ Placebo	Adjuvant Pain Treatment	Primary Outcome
7	Brill et al. 2002	Double-blind, placebo-controlled, cross-over	Postherpetic neuralgia	Mg IV infusion at 30 mg/kg over 30 minutes	IV infusion of 0.9% saline 100 ml over 30 minutes	N/A	Change in Visual Analog scale (VAS) 10 minutes, 20 minutes and 30 minutes
10	Felsby et al.	Double-blind placebo-controlled	Neuropathic pain	Mg 0.16 mmol/kg bolus followed by infusion for 1 hour. Infusion done in 3 sessions	NaCI (9 g/l) bolus then infusion for 1 hour. Infusion done in 3 sessions	N/A	VAS score, evoked-allodynia
30	Kim et al.	Randomized double-blind, uncontrolled	Postherpetic neuralgia	IV magnesium sulfate (30 mg/kg per hour) in 0.9% NS; final volume of 100 mL and infused over 1 hour for 3 days	Uncontrolled study	Midazolam for sedation	Pain score using Visual Analog scale (VAS)
80	Yousef and Al-deeb 2013	Double blind Randomized Controlled Trial (RCT)	Low back pain with a neuropathic component	IV magnesium 1 g daily infusion for 2 weeks followed by oral magnesium oxide 400 mg and magnesium gluconate 100 mg BID for 4 weeks	Placebo with normal saline and sugar capsules	Gabapentin 300 mg TID, amitriptyline 25 mg nightly, celecoxib 200 mg BID, interferential current therapy	Pain score 6 months 0 to 10	Lumbar spine range of motion	None

Other studies have been unable to reproduce the effectiveness of magnesium's analgesic properties. Felsby et al demonstrated that magnesium infusion did not reduce pain and allodynia in patients with peripheral neuropathic pain.[5] In this study, the dose of magnesium that was used was higher than the dose that was administered in the aforementioned PHN studies. An analysis that explored the use of oral magnesium in neuropathic pain failed to demonstrate improvement in pain scores or quality of life metrics after one month of magnesium therapy when compared to the placebo.[21] The study did observe a decrease in pain paroxysm and emotional component in the magnesium cohort compared to the patients' baseline. This finding was thought to be due to magnesium's role in cognitive and neuropsychiatric pathways.[21] The clinical significance of this finding and its role in treatment of neuropathic pain requires further evidence from studies. The equivocal results in the use of magnesium for neuropathic pain syndromes demonstrate that further research is needed to elucidate patient characteristics that make certain patients more responsive to magnesium therapy than others.

Chronic Low Back Pain

Low back pain is highly prevalent among Americans and remains a difficult condition to treat. It represents a growing health problem with significant socioeconomic burden and disability. Etiologies of chronic low back pain include myofascial pain, facet joint pain, sacroiliac joint pain, spinal stenosis, radiculopathy, discogenic pain, and failed back surgery syndrome.

A randomized controlled trial performed in Egypt (n = 80) investigated the role of magnesium in treating chronic low back pain with a neuropathic component. The patients in the magnesium group received IV magnesium sulfate 1 g administered over four hours daily for two weeks, followed by oral magnesium oxide 400 mg and magnesium gluconate 100 mg capsules given twice daily for four weeks. All patients, including those in the control group, were given gabapentin, amitriptyline, and celecoxib as adjunctive therapy. Additionally, all patients received interferential current therapy three times per week and underwent back muscle strengthening exercises. While all patients in the study reported significantly improved pain and had a greater spinal range of motion at two weeks, the magnesium group reported persistently improved symptoms even six months later in the follow-up period. This difference suggests that acute treatment with magnesium can lead to long-term improvements in chronic neuropathic low back pain. Of note, the authors excluded those with acute low back pain and back pain of non-neuropathic etiology. Therefore, the role of magnesium in these patients remains unclear.[22]

Headaches

Migraines

According to the International Classification of Headache Disorders, migraine is defined as "recurrent, moderate to severe headache attacks lasting 4–72 h with associated features including nausea and/or vomiting".[23] It is a chronic and disabling condition with multifactorial etiology.

Multiple randomized controlled trials have studied the role of magnesium in preventing or treating migraine headache intensity and frequency. Three studies (n = 190 total) evaluated the efficacy of oral magnesium, dosages ranging from 486 to 600 mg daily, as a prophylactic medication for migraine.[24–26] Two of the studies found that magnesium successfully reduced migraine attack frequency over a three-month period.[24,26] However, the third trial was stopped early due to poor response rates in both the magnesium and control groups and a lack of significant differences between the two groups. Of note, this study utilized magnesium aspartate rather than magnesium citrate.[25] The most recent trial of the three found that magnesium treatment was associated with increased cortical blood flow and decreased visual evoked potential latency and amplitude. (Köseoglu et al. 2008) This suggests that magnesium modulated the vascular and neurogenic pathophysiology of migraine.[26] Side effects of oral magnesium were relatively common but mild, with 10% to 18% of patients reporting soft stool and diarrhea and 4.7% to 5% reporting gastric irritation.[24–26]

IV magnesium sulfate appears to be an effective treatment for acute migraine attacks. Four trials (n = 340 total) found that a single dose of IV magnesium sulfate, 1 to 2 g, successfully reduced migraine intensity more effectively than control medications in emergency room settings.[27–30] In one study, all patients in the magnesium group reported either complete resolution of pain (86.6%) or improvement in pain (13.4%) as well as complete resolution of accompanying symptoms such as nausea and photophobia (100%) immediately after receiving the treatment. Conversely, the placebo group only had 1 patient reporting improved pain and 3 patients reporting resolution of accompanying symptoms.[27] Magnesium was more effective than a dexamethasone/metoclopramide combination, metoclopramide alone, and dihydroergotamine alone in head-to-head trials.[28–30] Magnesium also worked faster than dexamethasone/metoclopramide and metoclopramide, with significant differences in pain reduction noted as early as 20 minutes after administration.[28,29] In another trial, magnesium was superior to dihydroergotamine only at the 60- and 90-minute intervals.[30] Common side effects of magnesium included flushing (8% to 82%),[27,29] decrease in blood pressure (13.3% in one study),[27] and nausea (11.4% in one study).[28]

TABLE 3

Table for Studies on Migraines

N	Author and Study Year	Study Design	Pain Location/ Pathology	Intervention Description	Control Group/ Placebo	Any Adjunctive Pain Treatment?	Primary Outcome(s)	Duration of Effect(s)	Secondary Outcome(s)	Adverse Effect(s)
40	Köseoglu, Talaslioglu, Gönül, Kula 2008	Double blind RCT	Migraine without aura	Magnesium citrate 300 mg BID (n = 30)	Placebo (n = 10)	Simple analgesics, acute migraine treatment medication (not allowed to take >10 days per month)	Migraine attack frequency, migraine attack severity (pain scale 0 to 10)	3 months	Visual evoked potential latency and amplitude, statistical parametric mapping of brain single photon emission computerized tomography (cortical blood flow)	Soft stool and diarrhea (10%), gastric irritation (5%)
69	Pfaffenrath et al. 1996	Double blind RCT	Migraine without aura	Magnesium-u-aspartate hydrochloride trihydrate (MAH) granulate 10 mmol BID (total 20 mmol (486 mg) daily)	Placebo granulate	None reported	At least 50% reduction in intensity or duration of migraine attacks measured on 100-mm visual analogue scale	12 weeks	Migraine duration and intensity, number of migraine days and attacks, accompanying symptoms, analgesic consumption, global efficacy assessment, EEG, CBC, GOT, GPT, GGT, bilirubin, magnesium, calcium, sodium, potassium, creatinine	Soft stool (14.3%), diarrhea (14.3%), palpitations 8.6%

(Continued)

TABLE 3 *(Continued)*

Table for Studies on Migraines

N	Author and Study Year	Study Design	Pain Location/ Pathology	Intervention Description	Control Group/ Placebo	Any Adjunctive Pain Treatment?	Primary Outcome(s)	Duration of Effect(s)	Secondary Outcome(s)	Adverse Effect(s)
81	Peikert, Wilimzig, Köhne-Volland 1996	Double blind RCT	Migraine	Magnesium citrate 600 mg granular powder daily (n = 43)	Placebo (n = 38)	Patients were free to use symptomatic medications such as NSAIDs, antiemetics, ergotamines, sumatriptan, etc.	Frequency at weeks 9–12 compared to baseline	12 weeks	Reduction in number of days with migraine, duration of attacks, intensity of attacks (pain scale 0 to 10), symptomatic medication consumption	Diarrhea (18%), gastric irritation (4.7%)
30	Demirkaya, Vural, Dora, Topçuoğlu 2001	Single blind RCT, crossover design	Acute moderate to severe migraine attack	Magnesium sulfate 1 g IV over 15 minutes (n = 15)	Normal saline (n = 15) All received magnesium sulfate as well	Oral acetaminophen if pain still present 2 hours later	Pain severity (categorized as no pain, mild, moderate, severe)	Immediately after treatment, 30 minutes later, 2 hours later	Nausea, irritability, photophobia, side effects	Burning sensation in face/neck, flushing (82%), decrease in blood pressure by 5–10 mm Hg (13.3%)

70	Shahrami et al. 2015	Double blind RCT	Acute migraine attack	IV magnesium sulfate 1 g over 15 min (n = 35)	Intravenous dexamethasone 8 mg and metoclopramide 10 mg over 15 min (n = 35)	Rescue medication at provider's discretion if pain still present 20 minutes after treatment	Pain severity (0–10 scale)	20 minutes, 1 hour, 2 hours after treatment	Need for additional medication	Nausea (11.4%)
120	Cete et al. 2005	Double blind RCT	Acute migraine attack	IV magnesium sulfate 2 g over 10 min	IV metoclopramide 10 mg, normal saline	Rescue medication with 0.75 mg/kg meperidine (if needed after 30 minutes and 1 hour after treatment)	Pain severity on 100-mm visual analogue scale after 30 minutes	0 minutes, 15 minutes, 30 minutes after treatment	Need for rescue medication, recurrence at 24 hours	Flushing (8%)
120	Rahimdel, Eslami, Zeinali 2007	Double blind RCT	Acute migraine attack	IV magnesium sulfate 1 g	Dihydroergotamine	None reported	Pain severity on 0–10 visual analogue scale	30 minutes, 60 minutes, 90 minutes after treatment	Gender, migraine type (classical or common)	Not reported

Non-Migraine Headaches

Two trials studied IV magnesium sulfate in acute benign headaches, which included migraines and non-migraine headaches; magnesium was not effective in either trial.[31,32] One study found that magnesium sulfate was significantly worse at reducing headache intensity than prochlorperazine. Additionally, only 1 patient in the prochlorperazine group reported side effects, whereas 5 of 16 patients (31%) in the magnesium group reported side effects, notably burning at the IV line site (25%) and vomiting (6.25%).[31] The second study compared magnesium against placebo, but the trial was stopped early after an interim analysis found no benefit and increased side effects with magnesium. Of the patients in the magnesium group, 42.9% reported flushing, 4.7% reported decreased blood pressure, and 4.7% reported burning at the IV line site.[32]

Post-Surgical Pain

Post-surgical pain affects about 2–10% of adults undergoing surgery and remains a significant cause of disabling pain worldwide.[33] Perioperative IV magnesium sulfate was effective in reducing post-surgical pain in women undergoing open gynecologic surgeries in three recent randomized controlled trials (n = 130 total).[34–36] One study showed that the magnesium group consumed significantly less opioid intraoperatively (as determined by doses of pethidine needed for pain relief).[34] Two of the studies found that patients who received magnesium used less rescue analgesics (e.g., rescue doses of morphine).[35,36] Two of the three studies found significant pain reduction starting within 30 minutes from surgery.[34,36] Magnesium was superior to placebo in reducing pain for at least 12 hours postoperatively in all three studies. Of note, all three studies administered the magnesium slightly differently. One study gave patients a 50 mg/kg bolus followed by an 8 mg/kg/hour infusion as maintenance for the duration of surgery.[34] Another study administered a continuous 15 mg/kg/hour infusion for the duration of surgery.[35] The third study administered a single pre-induction dose of 50 mg/kg over 20 minutes.[36]

Another randomized controlled trial (n = 44) studied the use of intraoperative IV magnesium sulfate in patients undergoing two-stage total knee arthroplasties (TKAs) performed one week apart. Patients who received magnesium had significantly lower pain scores after both the first and second surgeries. Fentanyl patient-controlled anesthesia (PCA) usage was significantly lower in the magnesium group 48 hours after both surgeries. Notably, the control group reported higher pain scores with the second TKA compared to the first, but this was not observed in the magnesium group, suggesting that magnesium may prevent tertiary hyperalgesia.[37]

TABLE 4

Studies on Post-Surgical Pain

N	Author and Study Year	Study Design	Pain Location/ Pathology	Intervention Description	Control Group/ Placebo	Any Adjunctive Pain Treatment?	Primary Outcome(s)	Duration of Effect(s)	Secondary Outcome(s)	Adverse Effect(s)
50	Al-Rahmawy, Abd Al-Moteleb, El-Ebeidy, Hafez 2021	Double blind RCT	Post-mastectomy pain syndrome	Dexamethasone 4 ml (4 mg/mL), lidocaine 5 mL (20 mg/mL), and magnesium sulfate 1 mL (10%, 100 mg/mL) for total of 10 mL to stellate ganglion block (n = 25)	Dexamethasone, lidocaine, and normal saline for a total of 10 mL to stellate ganglion block (n = 25)	Gabapentin 300 mg q8h for patients with VAS >=4	Pain severity with visual analogue scale (0–10)	5 minutes after injection, 2 weeks, 1 month, 2 months, 3 months after injection	Shoulder movement, skin temperature of ipsilateral arm, time to first request of analgesia, doses of gabapentin needed, number of next injections needed, development of complications and side effects	Hypotension (40%), voice hoarseness (12%); not significantly different compared to control
44	Shin et al. 2016	Double blind RCT	Post staged bilateral total knee arthroplasty	Intravenous magnesium sulfate 50 mg/kg over 15 min at anesthesia induction, followed by continuous magnesium sulfate infusion (15 mg/kg/hr) for the duration of each surgery	Normal saline	Midazolam premedication 0.3 mg/kg; femoral nerve block with 1% lidocaine; lumbar subarachnoid block with 0.5% hyperbaric bupivacaine and fentanyl; periarticular injection in operative field with ropivacaine,	Pain severity with 100-mm visual analogue scale	24 hours, 48 hours after surgery	Amount of rescue analgesics used, cumulative amounts of PCA 48 hours after surgery	Not reported

(Continued)

TABLE 4 *(Continued)*

Studies on Post-Surgical Pain

N	AUTHOR AND STUDY YEAR	STUDY DESIGN	PAIN LOCATION/ PATHOLOGY	INTERVENTION DESCRIPTION	CONTROL GROUP/ PLACEBO	ANY ADJUNCTIVE PAIN TREATMENT?	PRIMARY OUTCOME(S)	DURATION OF EFFECT(S)	SECONDARY OUTCOME(S)	ADVERSE EFFECT(S)
						morphine, ketorolac, epinephrine, cefuroxime; perioperative multimodal analgesia (pregabalin, celecoxib, acetaminophen, dexamethasone, fentanyl PCA), IV ramosetron for PONV, IV ketoprofen PRN, metoclopromaide PRN				
30	Asadollah, Vahdat, Yazdkhasti, Nikravan 2015	Double blind RCT	Hysterectomy and/or myomectomy	IV magnesium sulfate (50 mg/kg over 10 min), followed by 8 mg/kg/hr as maintenance	Normal saline	Midazolam premedication 0.2 mg/kg; induction with propofol and fentanyl; maintained with propofol and remifentanil infusion; fentanyl 1 mg/kg IV at end of operation; meperidine 30 mg as rescue medication for VAS >4 q3h PRN	Pain severity with visual analogue scale (0–10)	30 min, 2 hours, 4 hours, 12 hours after first receiving magnesium	Amount of rescue medication needed, postoperative nausea, vomiting, respiratory rate, blood pressure, heart rate, deep tendon reflexes, level of consciousness	No difference between groups, specific data not reported

40	Haryalchi et al. 2017	Double blind RCT	Total abdominal hysterectomy	IV magnesium sulfate infusion (15 mg/kg/hr) starting 15 minutes before induction of anesthesia (n = 20)	Normal saline (n = 20)	Induction with sodium thiopental 5 mg/kg, fentanyl 1 mcg/kg, succinylcholine; maintenance with N_2O/O_2, isoflurane, atracurium, fentanyl Meperidine 20 mg PRN as rescue medication for pain score >4	Pain severity with numeric rating scale (0–10)	0 hour, 6 hours, 12 hours, 24 hours after the operation	Amount of rescue medication needed, serum beta-endorphin levels	No postoperative hypotension, nausea, or vomiting
60	Jarahzadeh et al. 2016	Double blind RCT	Abdominal hysterectomy	IV magnesium sulfate 50 mg/kg over 20 minutes, given 30 minutes after induction of anesthesia	Lactated Ringer's	Premedication with midazolam 2 mg, fentanyl 2 mcg/kg, induction with propofol and atracurium, IV morphine 5 mg 30 min after induction; morphine as rescue medication	Pain severity with visual analogue scale	0 hour, 1 hour, 2 hours, 6 hours, 12 hours after the surgery	Amount of rescue morphine consumed	No differences

A recent trial found that magnesium sulfate was an effective adjunct to dexamethasone and lidocaine in stellate ganglion blocks for women suffering from post-mastectomy pain syndrome, although the therapeutic effect only persisted for one month. Further, patients who received magnesium had a longer period of time before requesting additional analgesia (average difference of 14 days, $p = 0.016$) and also utilized fewer milligrams total of adjunctive gabapentin ($p = 0.006$).[38]

In all of the above studies, there were either no differences in side effects between the magnesium groups and control groups, or there were no side effects reported.[34–38]

Renal Pain/Colic

Renal colic is a debilitating pain condition and a leading cause of emergency department visits.[39] It is typically caused by urinary and kidney stones leading to severe pain from obstruction, inflammation and spasm of the pelvicalyceal smooth muscles. Due to anatomical location, renal colic typically manifests as pain in the lumbar, flank and hypogastric region, and it can sometimes radiate to the testes.

Ahmed et al.[40] conducted a randomized double-blind study that evaluated the effectiveness of IV magnesium in patients with acute renal colic pain and observed better and immediate pain relief (measured on the visual analogue scales) 30 minutes and 1 hour after a single infusion of magnesium. However, in the same year, another randomized, double-blind, placebo-controlled trial investigated the effectiveness of magnesium sulfate compared to ketorolac in 87 patients with acute renal colic and reported contrasting results.[41] In their study, both groups of patients received an IV infusion of 30 mg of ketorolac, however, in addition, the intervention group received 50 mg/kg of IV magnesium sulphate while the placebo group received 100 mL of normal saline. The results indicated that after 30 minutes, the pain score was significantly reduced in both groups and the cohort receiving IV magnesium reported no difference in pain intensity versus the cohort placebo. No differences in hemodynamic parameters were observed. In another study, Jokar et al.[42] randomized 100 patients with acute renal colic to 2 groups; the control group received the standard protocol (intravenous infusion of 0.1 mg/Kg morphine sulfate, 30 mg of Ketorolac), and 100 mL normal saline while the intervention group received the standard protocol plus 15 mg/Kg of IV magnesium sulfate. At 30 and 60 minutes, mean pain score and additional morphine requirement were lower in the intervention group compared to the control group. Also, there was no significant differences in hemodynamic measures and adverse effects between the two groups.

TABLE 5

Table for Studies on Renal Colic/Renal Pain

N	Author and Study Year	Study Design	Pain Pathology	Intervention Group; Dose, Frequency, Route of Mg Administration	Control Group/Placebo	Adjuvant Pain Treatment	Primary Outcome	Duration of Effect	Secondary Outcome	Adverse Effects
96	AHMED et al. 2019	Randomized Double-blind, controlled	Renal Colic	15 mg/Kg of IV magnesium sulfate 50% in 100 ml normal saline infused within 15 minutes	30 mg of IV Ketorolac and IV infusion of 0.9% saline 100 ml over 30 minutes	N/A	Change in Visual Analog scale (VAS) at 30 minutes and 60 minutes	1 hour	Need for morphine addition	None reported
87	Maleki Verki et al. 2019	Double-blind placebo-controlled	Renal Colic	30 mg IV Ketorolac + 50 mg/kg of IV magnesium sulphate	30 mg IV Ketorolac + 100 mls of Normal saline	N/A	VAS scores change at 15 minutes and 30 minutes	30 minutes	N/A	None reported
100	Jokar et al. 2017	Randomized double-blind, uncontrolled	Renal Colic	IV infusion of 0.1 mg/Kg morphine sulfate + 30 mg of Ketorolac), + 100 ml normal saline	IV infusion of 0.1 mg/Kg morphine sulfate + 30 mg of Ketorolac), + 15 mg/Kg of IV Mg sulfate 50%/100 ml normal saline	0.1 mg/Kg morphine sulfate	Pain score using Visual Analog scale (VAS)	1 hr	Need for additional amount of morphine	None reported
90	Majidi & Derakhshani et al. 2020	Randomized double-blind, uncontrolled	Renal Colic	IV Mg sulphate; 2cc of 50% solution diluted with normal saline solution until reaching 100 ml injected during 15 minutes	IV morphine (0.1 mg/kg dose), instilled in 100mls of normal saline	N/A	VAS scores change at 20, 30, 60, 120, and 180 minutes	N/A	N/A	N/A
80	Zolfaghari Sadrabad et al. 2021	Randomized double blind controlled trial	Renal Colic	50 mg/kg IV magnesium sulfate	0.1 mg/kg intravenous morphine	N/A	Pain ratings using Numerical Rating Scale at 10 and 20 minutes	NA	NA	Nausea, vomiting, flushing, dizziness

Two studies were conducted in 2020 and 2021 to compare the effectiveness of IV magnesium versus IV morphine for the management of renal colic pain.[43,44] In one study, authors[43] conducted a randomized double-blind trial on 90 patients with acute renal colic pain comparing IV magnesium to IV morphine sulphate and found that IV magnesium was equally effective as IV morphine in decreasing pain severity (assessed by visual analogue scale) up to 180 minutes after drug administration. A similar observation was reported in the study by.[44] Their findings favored a recommendation that magnesium sulfate can be safely added as adjunct treatment in reducing renal colic pain and reduced the need for rescue analgesics without affecting hemodynamic measures.

Chronic Pelvic Pain

Chronic pelvic pain (CPP) refers to pain that originates from a complex group of heterogeneous pathologies of the pelvic organs. Pirnia et al.[45] in a prospective, randomized, double-blind, placebo-controlled clinical trial, evaluated 163 women with secondary dysmenorrhea caused by endometriosis. This study assessed pain intensity and quality of life after adding magnesium sulfate (50 mg/kg MgSO4 in 100 mL saline) to tincture of opium (TOP) and buprenorphine (BUP). Study participants were assigned into six groups. The first and second groups were the users of TOP, one group received MgSO4 (n = 26) and the second group received placebo (n = 28). The third and fourth groups were BUP users, the third group received MgSO4 (n = 27) and the fourth group received placebo (n = 25); and the fifth and sixth groups were opioid non-users. The fifth group received MgSO4 (n = 29) and the sixth group received placebo (n = 28). The study showed significant improvement in pain (visual analogue scale) and quality of life (QOL questionnaire) metrics in the intervention group compared to controls. These findings support that the concomitant use of IV magnesium with opioids is associated with pain reduction and the improvement of QOL in women with secondary dysmenorrhea.

A single-center, double-blind, randomized controlled trial conducted on 44 women diagnosed with chronic pelvic myofascial pain associated with trigger points investigated the efficacy of magnesium-based trigger point infiltration formulation vs lidocaine-only infiltration vs control group of participants who were waitlisted for a chronic pain clinic in treating chronic myofascial pelvic pain.[46] The study found that those who received magnesium-only infusions, and lidocaine-only infusions had a greater mean reduction in their immediate post-treatment pain than those in the waitlisted (control) group. Both treatment groups

saw improvements in pain with function and quality of life scores. The authors noted that their findings do not support the use of a magnesium-based trigger point infiltrate in the treatment of chronic myofascial pelvic pain over lidocaine-only infiltration, as both are equally effective.

Other Studies

A few studies have examined the potential for dietary nutrients including magnesium for treating chronic pain associated with fibromyalgia. Ali et al.[47] conducted a randomized, double-blind, placebo-controlled pilot study of 34 patients to investigate the efficacy of IV micronutrient therapy (IVMT) and specifically the Myers' Cocktail, for treating fibromyalgia syndrome. Study participants were randomly assigned either to treatment (weekly infusions of IVMT) or to placebo (weekly infusions of lactated ringer's solution) for 8 weeks. The study reported significant improvement in pain, tender points, quality of life and mood measures in both groups. The therapeutic effects of IVMT persisted at 4 weeks postintervention for tender points, pain, and quality of life, while therapeutic effects from placebo persisted for 4 weeks for tender points only. At the end of weeks 8 and 16, outcome measures did not differ significantly between both groups. One patient in the intervention group experienced dyspepsia, insomnia, depression, and elevated blood pressure. In another randomized double blinded controlled cross-over study,[48] Russell at el examined the efficacy of super Malic, a tablet containing malic acid (200 mg) and magnesium (50 mg), in the treatment of primary fibromyalgia syndrome (FM). 24 patients were randomized to super malic or placebo. The intervention group received 4 weeks of 3 super malic tablets dosed twice daily, followed by a 6-month, open label phase, with dose escalation up to 6 tablets bid. A 2-week, medication-free, washout period was required before receiving treatment, between blinded courses, and before starting open-label treatment. The outcomes of interest included pain, tenderness, physical functioning and psychological measures. The study reported no clear therapeutic effect from administration of low-dose Super Malic. However, there was significant improvement in pain and tenderness with longer duration and higher doses of super malic treatment. Similar findings regarding the efficacy of high dose malate and magnesium for treating pain in fibromyalgia patients were reported in the study.[49]

In 2020,[50] conducted a randomized study to compare the effect of magnesium and tryptophan enriched diet with traditional Mediterranean diet on sleep quality and psychological (mood, anxiety, self-image perception) outcomes among 22 women with fibromyalgia.

The intervention cohort received a Mediterranean diet enriched with high doses of tryptophan and magnesium (60 mg tryptophan and 60 mg magnesium), whereas the control group received the standard Mediterranean diet for 16 weeks. Pain outcomes were not assessed. The study found that tryptophan and magnesium-enriched Mediterranean diet reduced anxiety symptoms, mood disturbance, eating disorders, and dissatisfaction with body image, but did not improve sleep quality in women with fibromyalgia.

These studies offer initial evidence for the potential of magnesium in the treatment of fibromyalgia. While most of the studies thus far have examined dietary magnesium, more studies focusing on IV magnesium are warranted to further define magnesium's role in the treatment of pain in fibromyalgia.

Conclusion and Summary

Chronic pain imposes an enormous burden on health, quality of life and is associated with significant healthcare costs. Available pharmacological modalities for treating chronic pain have associated adverse effects and relatively modest efficacy. As a result, there is a critical need for improved pharmacological treatment choices. Magnesium is FDA-approved for many indications such as cardiac arrhythmias, eclampsia/preeclampsia seizure prevention, and hypomagnesemia. There is emerging evidence that magnesium may have analgesia and anti-nociceptive potential in multiple pain conditions. While there is substantial literature to support its tolerability and minimal adverse effect profile, so far, the available data suggest equivocal evidence and variable efficacy for managing pain in different chronic pain syndromes.

Magnesium's analgesic properties are not properly understood but it is theorized to modulate pain via its antagonism of the NMDA receptor. There is mixed evidence for the potential of dietary magnesium in the treatment of pain in fibromyalgia. Further studies focusing on IV magnesium are warranted to define further magnesium's role in the treatment of pain in fibromyalgia. ✤

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