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Magnesium in pain control - mechanisms of action in perioperative pain, neuropathic pain and migraine

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Abstract

Introduction:

Magnesium is a crucial macroelement with widespread effects on the nervous and muscular systems.. Due to its role as an NMDA receptor antagonist, magnesium has garnered significant attention in pain management research, particularly for its potential to modulate both acute and chronic pain. This article provides an overview of magnesium's therapeutic applications in neuropathic pain, migraine, and perioperative pain, drawing on research from PubMed and Google Scholar published between 1988 and 2025.

Aim of study:

This review aims to present the state of knowledge about magnesium’s possible role in pain control and present mechanism of its influence on the nociceptive stimuli reception.

Materials and methods:

Publication research was made using databases PubMed and Google Scholar, primarily focusing on articles published in the last 10 years, with exemptions concerning basic knowledge about magnesium as a macroelement and basic physiological knowledge which was based on articles published previously. Keywords used in research were among others: magnesium, pain, neuropathic pain, migraine, perioperative pain, magnesium deficiency.

Current state of knowledge:

Magnesium plays a crucial role in the management of various pain conditions, including perioperative, neuropathic, and migraine pain, through its multifactorial mechanisms. These include NMDA receptor antagonism, calcium channel blockade, anti-inflammatory effects, and muscle relaxation, all of which contribute to its analgesic properties. Evidence suggests that magnesium supplementation can reduce opioid use, counteract central and peripheral sensitization, and potentially prevent migraine attacks, highlighting its potential as an effective adjuvant in pain management strategies.

Summary (Conclusions):

Magnesium offers significant therapeutic potential in managing perioperative, neuropathic, and migraine pain through mechanisms such as NMDA receptor antagonism, calcium channel blockade, and neuroinflammation modulation. Its use can reduce opioid consumption, enhance pain relief, and improve outcomes, highlighting the need for further research into its clinical applications in pain management.

Key words: magnesium; pain; NMDA receptor; perioperative pain; neuropathic pain; migraine;

Introduction

Magnesium is a macroelement widely known for its omnidirectional influence on both nervous and muscular systems. Plurality of magnesium functions can be easily seen by the symptoms of its deficiency, which can vary from irritation, through muscle fatigue, seizures, to heart rhythm disturbances and many more.

For pain management the most important magnesium application effects are those connected with the nervous system. Magnesium is a N-methyl-D-aspartate (NMDA) receptor antagonist. That is why magnesium takes part in avoiding extensive peripheral sensitization. It is the reason why magnesium has started to become the object of plenty of research, examining its possible utility in both chronic and acute pain control.

In this article authors attempt to present the overview of possible magnesium usage in acute pain, as well as the chronic with examples of neuropathic and migraine.

Research was made among the articles in databases PubMed and Google Scholar published in the years 1988 - 2025. Key words used during the research were among others: magnesium, pain, neuropathic pain, migraine, perioperative pain, magnesium deficiency.

Perioperative pain

Perioperative pain can be considered a severe, acute pain which implies that it should be overcome quickly and strongly. Usage of magnesium as an adjuvant for perioperative pain therapy can help to achieve this goal by multidirectional mechanisms, explained below.

1. NMDA antagonism

Probably the most important magnesium feature for immediate pain soothing is its antagonist influence on the N-methyl-D-aspartate (NMDA) receptors. As the NMDA receptors take part in signal transduction, this influence helps to avoid central hypersensitivity for pain stimuli. [1,2,3]

2. Blockade of the calcium channels

Another mechanism that plays an important role in perioperative pain management is a calcium channel blockade. By competition with calcium, magnesium lowers the possibility for nerve cells to depolarize. Stabilization of the neuron can decrease the amount of released neurotransmitters that are involved in pain transmission. [4,5,6]

3. Improving opioid - efficacy

Magnesium is proven to improve the biological answer to opioids, by enhancing the binding affinity of opioids to their receptors. With reinforced analgesic power, the amount of opioid drugs used during perioperative analgesia and post-operative period can decrease significantly. Using reduced opioids doses, can also lessen the presence of opioid-connected side effects like constipation, nausea, vomiting. Decresing the probability of respiratory depression, which is also a derivative of dose administered, can increase the safety of analgosedation significantly. [7,8,9,10]

4. Reduction of inflammatory reaction

Inflammation starts right after the tissue is being damaged during the operation, as the defense reaction. This process is one of the main sources of generation of acute, especially somatic pain. Level of proinflammatory cytokines released can be lowered by magnesium. Beside that, magnesium modulates the inflammatory reaction directly. This characteristic can also reduce the pain by weakening the main cause of its origination. [11,12,13]

5. Enhancement of the local anesthesia

Combining a local anesthesia with the systemic use of medicaments, as well as, using it as the only counter-pain measure, both can be a strategies for dealing with the perioperative pain. [14,15,16]

6. Muscle relaxation

Following mechanism that participates in magnesium pain counteraction is its impact on the intensified muscle tension. Excessive muscle tension or spasms are often associated with perioperational period, being one of the ingredients that compose on complex pain sources. Muscle relaxation is also important in safe and easy intubation. Use of magnesium can reduce the amount of conventional myorelaxant used or can be used separately depending on type of operation and method of airway protection used. [17,18,19,20]

8. Anxiety Reduction

Magnesium is also known for its calming effects on the central nervous system, which can help reduce anxiety and stress around surgery, both of which can exacerbate the perception of pain.[21,22]

In summary, magnesium plays a multi-faceted role in perioperative pain management, from modulating pain transmission through NMDA receptors to reducing inflammation and enhancing muscle relaxation. Its use as an adjuvant in pain management protocols can lead to reduced opioid requirements and better overall recovery outcomes. Magnesium supply can also increase the safety of anesthesia, by lowering the side-effects possibility of the other medicaments dosage.

Neuropathic pain

Treatment of the neuropathic pain has constantly been a challenge for clinicians. Managing this type of pain is often insufficient, that is why it often leads to permanent disability. [23,24]

There are a lot of causes that may lead to developing neuropathic pain. Most common in clinical practice are those of diabetic or herpetic origin. Also often observed are problems connected with former mechanical nerve destruction caused by trauma or surgery. [25,26]

1. Mechanisms of a neuropathic pain

Mechanisms leading to appearance of the neuropathic pain after the action of those factors are as follows: central sensitization, peripheral sensitization, neuroinflammation.

Central sensitization is a process in which the central nervous system (CNS) becomes hyperresponsive to both nociceptive and non-nociceptive stimuli, leading to an amplification of pain perception. [27,28] There are studies which shows that pain which is the result of the central sensitization may be of a higher intensity that the primary nociceptive stimuli.[29]

Peripheral sensitization is the phenomenon of increased sensitivity of nociceptors to injury or inflammation, leading to enhanced pain perception in case damage occurs. The reasons are changes in the peripheral nervous system, such as lowered thresholds for activation and an increased release of inflammatory mediators, which contribute to the development of neuropathic pain symptoms.[28,30,31]

Neuroinflammation is the following mechanism that leads to origination of neuropathic pain by activating the immune cells in the nervous system as microglia and astrocytes. They release pro-inflammatory cytokines and chemokines, which exacerbate neuronal excitability and alter pain signaling pathways. [32,33,34]

2. Magnesium role in overcoming neuropathic pain

Magnesium plays an important role in proper nerve functioning by neuroprotection especially by stabilizing neurons' cell membranes. This characteristic helps to avoid new damages in the nervous system, both central and peripheral. [5,35]

By its anti-inflammatory properties magnesium may also help to avoid new breakages, and by thus lower the neuropathic pain or protect from its intensification. [36,37,38]

Another important mechanism of magnesium is its NMDA - receptors antagonism, which was described earlier in the case of the perioperative pain. Preventing central and peripheral sensitization, by blocking the NMDA receptors, plays a crucial role in chronic pain creation. It precludes the possibility of sensitization, as well as, lowering hypersensitivity after it has already occurred. [39,40,41]

Migraine

Migraine is a specific type of pain which is defined as a partly neuropathic pain by some authors, but it also has a large nociceptive component. [42,43]

Treatment of migraine comprises two parts: long-term attacks prevention and acute pain control during attack.

In the long - term strategy it is crucial to avoid magnesium deficiency, which is proven to enhance the amount of attacks, as well as its intensity. [44,45,46] This can be achieved by diet treatment, with increased consumption of magnesium-rich food like (eg. fish, whole grains, cocoa, seeds, nuts, legumes, leafy green vegetables) or oral supplementation.

Coping with acute migraine pain during attack, with magnesium use as an adjuvant, is done with its intravenous intake in the form of a sulphate. [47,48] It can be beneficial for patients, even if there is no evidence of magnesium deficiency, because of the direct magnesium mechanisms of action.[49,50]

All the anti-nociceptive magnesium mechanisms presented previously play a role in migraine, but there are some with particular meaning in this case. First one is the influence of magnesium in so-called cortical spreading depression (CSD), which is the probable mechanism underlying the migraine attack induction. It is the wave of cortical depolarization, followed by post-depolarization depression - “silencing”. This phenomenon is connected with the presence of so-called “aura” preceding migraine attacks. Magnesium lower the possibility of depolarization by enhancing the neuro cell membrane stability.[44,46,51,52]
Second mechanism of specific importance in stopping or preventing the migraine attack is magnesium influence on lowering the vascular muscle constriction. It is still a subject of studies whether vasoconstriction is connected with cortical spreading depression or is it a separate mechanism leading to migraine pain.

Conclusions

Magnesium demonstrates significant potential as a therapeutic agent in the management of various pain conditions, including perioperative, neuropathic, and migraine pain. Its primary mechanisms of action—NMDA receptor antagonism, calcium channel blockade, and modulation of neuroinflammation—underpin its efficacy in attenuating both acute and chronic pain. In perioperative pain, magnesium's ability to prevent central sensitization, enhance opioid efficacy, reduce inflammation, and promote muscle relaxation contributes to improved analgesia and reduced opioid consumption, thereby mitigating opioid-related side effects.

In the context of neuropathic pain, magnesium's neuroprotective effects, mediated through stabilization of neuronal membranes and reduction of neuroinflammation, help prevent the exacerbation of pain. Furthermore, its blockade of NMDA receptors serves as a critical mechanism in preventing the development of central and peripheral sensitization, both of which are central to the pathophysiology of chronic pain states.

For migraine patients, magnesium addresses both the prevention and acute management of attacks. Long-term, magnesium deficiency has been implicated in increased frequency and severity of attacks, while supplementation can reduce attack occurrence. During an acute migraine, intravenous magnesium sulfate demonstrates efficacy by stabilizing neuronal membranes, reducing cortical spreading depression, and potentially mitigating vascular constriction, thus alleviating pain.

In summary, magnesium's multifactorial actions, ranging from neuroprotection to anti-inflammatory and analgesic effects, make it a valuable adjuvant in pain management across different pain syndromes. Its incorporation into clinical practice holds promise for improving pain control, reducing opioid consumption, and enhancing recovery, underscoring the need for further research into its optimal clinical application.

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