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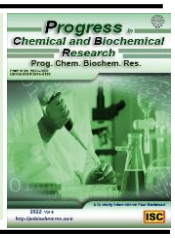

Review Article

Investigating the Beneficial Effects of Adding Intrathecal Magnesium to Spinal Anesthetic Solution in Lower Limb Orthopedic Surgeries: A Systematic Review

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ABSTRACT

Introduction: The safety of administration of intrathecal magnesium has been proven in many studies and this drug has no toxic effects in histopathological analyses. For example, in one study, the effects of intrathecal magnesium sulfate administration in preventing spinal cord ischemia during aortic cross-clamp have been proven and no histopathological damage has been observed. The aim of this systematic review is to investigate the beneficial effects of adding intrathecal magnesium to spinal anesthetic solution in lower limb orthopedic surgeries.

Methodology: The present study is a systematic review study that was conducted in the first quarter of 2023 at Tabriz University of Medical Sciences. At first, the basic keywords to search for articles published in all English-language databases were determined by both researchers of this study; These keywords include: magnesium, magnesium sulfate, intraspinal, spinal, intrathecal, anesthetic solution, lidocaine, bupivacaine, surgery, orthopedics, lower limb, pain, pain intensity, hemodynamic status, blood pressure, systolic, diastolic, opioid , opioid use, analgesic, analgesia, pain control, pain management, severe pain, acute and painful pain.

Results: The results indicated that the addition of intrathecal magnesium leads to a significant reduction in pain intensity after lower limb orthopedic surgeries; This means that whenever magnesium sulfate is injected into the spinal cord following the injection of intrathecal anesthetic, the intensity of pain after surgery is significantly reduced and the use of intrathecal magnesium leads to optimal and useful pain management.

Conclusion: Our study showed that adding 100 mg of magnesium sulfate to spinal anesthesia can prolong the duration of analgesia without side effects after orthopedic procedures. Also, the safety of higher intrathecal dose of magnesium sulfate was shown in this study.

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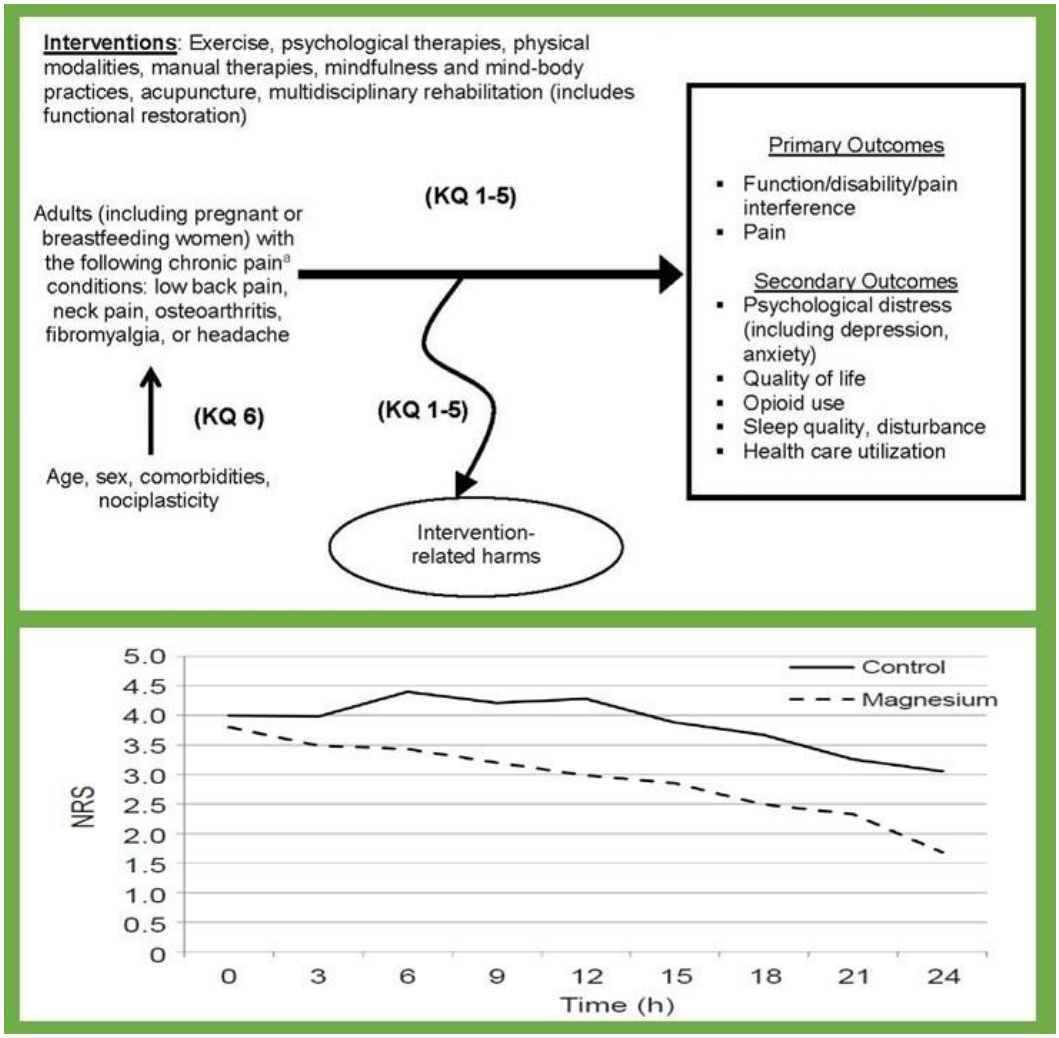
GRAPHICAL ABSTRACT



1. Introduction

Every year, more than 6 million patients in the world undergo surgery. Surgery is a stress that causes physiological reactions (endocrine) and psychological stress (fear and anxiety) [1-3]. A patient who enters the hospital can be mildly, moderately, or severely anxious, and by knowing and determining the anxiety level, it is possible to plan for the implementation of his/or her medical and nursing care [4-6]. One of the situations that can cause anxiety is surgery, and its appearance in patients is not only normal but very common. Surgery can be planned or unplanned, small or large, invasive or non-invasive, and involve any part or system of the body, but any type of surgery is considered an anxiety-provoking experience because it poses a threat to it as a threat to the body integrity and sometimes to life [7-9]. The steps before the operation, the day of the operation and worrying about the results all cause anxiety. Worries about not having control, being in an unfamiliar situation, and feeling threatened by death all contribute to this unpleasant phenomenon.

Anxiety before anesthesia and the problems caused by it (severe and excessive changes in hemodynamic parameters, causing arrhythmia, and sometimes dangerous hemodynamic

complications for the patient during anesthesia, restlessness and low pain threshold after surgery, etc.) in the field of surgery and the anesthesiologist is well-known and the need to eliminate it has been the subject of many studies for a long time [10-13]. Giving information before the operation leads to more satisfaction and the healing process progresses. Providing proper information is effective in reducing the anxiety, stress, and pain levels of patients [14].

Concerning that in Iranian hospitals, surgeons usually perform a series of tests and consultations in the pre-operative stage, and also the place of education in ambulatory surgery is not very active compared to inpatient surgery. On the other hand, in the usual method, the anesthesiologist meets the patient in most hospitals in a maximum of 2-3 minutes interview and a quick review of the case, and that too inside the operating room. Therefore, in this short time of the interview, not only sufficient examination is not done, but also the patient's needs are not properly answered. Given that the patient's energy is necessary for healing and tissue repair, providing solutions to reduce the physical and mental symptoms of anxiety, the use of non-pharmacological treatment methods such as informing patients in nursing care are recommended. On the other hand, increased anxiety levels are strongly associated with severe pain after surgery [15-17].

Despite many new techniques and modern analgesic treatments, postoperative pain is still a controversial issue. Orthopedic surgeries are associated with high postoperative pain due to the nature of surgery on joints and bones [18]. The use of intravenous, intramuscular, intraspinal, and epidural narcotics are all pain control methods associated with side effects such as respiratory weakness, itching, nausea and vomiting, and cardio-respiratory arrest. Rarely, adding compounds such as ketamine, fentanyl, prostigmine, and midazolam, clonidine to local anesthetics in spinal anesthesia is one of the researches that have been conducted in this field and all of them have some kind of advantages and disadvantages [19].

Painful stimulation leads to the release of glutamine and aspartate neurotransmitters, which bind to excitatory amino acid receptors such as N-methyl-di-aspartate receptors. The activation of N-methyl-di-aspartate receptors leads to the entry of sodium and calcium into the cell and the exit of potassium out of the cell, causing central sensitization that the use of magnesium as a non-competitive antagonist of N-methyl-di-aspartate receptor prevents this central sensitization [20-22]. This drug exerts pain controlling effects on the spinal axis. Intravenous administration of magnesium sulfate during general anesthesia reduces the need for narcotics during and after surgery. Research has shown that administration of intrathecal magnesium is able to strengthen the analgesic properties of opioids during childbirth and pain control after knee arthroscopy. The above studies have been coordinated with the intrathecal administration of magnesium in animals. The safety of administering intrathecal magnesium has been proven in many studies and this drug has no toxic effects in histopathological analyses [23]. For example, in one study, the effects of intrathecal magnesium sulfate administration in preventing spinal cord ischemia during aortic cross-clamp have been proven and no histopathological damage has been observed. The aim of this systematic review is to investigate the beneficial effects of adding intrathecal magnesium to spinal anesthetic solution in lower limb orthopedic surgeries [24].

2. Methodology

The current study is a systematic review study that was conducted in the first quarter of 2023 at Tabriz University of Medical Sciences. Initially, the basic keywords to search for articles published in all English-language databases were

determined by both authors of this study; These keywords include magnesium, magnesium sulfate, intraspinal, spinal, intrathecal, anesthetic solution, lidocaine, bupivacaine, surgery, orthopedics, lower limb, pain, pain intensity, hemodynamic status, blood pressure, systolic, diastolic, opioid , opioid use, analgesic, analgesia, pain control, pain management, severe pain, and acute and painful pain.

The exclusion criteria include patients aged less than 20 years old and over 50, the American Society of Anesthesiology class higher than 2, local and systemic infection, coagulation disorder, hypovolemia, drug sensitivity, a history of drug abuse, and longer operation time. It was from 90 minutes. It should be noted that the following criteria were considered as inclusion criteria for the study:

1. Clinical trial studies.
2. Studies conducted randomly.
3. Studies conducted as double-blind or triple-blind studies.
4. The intensity of pain has been investigated as the main outcome of these studies.
5. The amount of opioid used after surgery has been checked.
6. All patients have undergone surgery using spinal anesthesia.
7. Surgery has been performed on the lower limbs of the patients.
8. Patients without systemic infections.
9. The method of evaluating pain intensity in all patients should be with the help of VAS tool.
10. The minimum sample size in all studies should be equal to 60 people.

All patients after receiving 10 ml/kg of an intravenous crystalloid solution for the initial loading dose, by an anesthesiologist who knew the type of drugs used in the syringe so that he/ or she could take the necessary measures in case of problems, in a sitting position on the surface of the seal 3rd and the 4th lumbar or at the levels of the 4th and the 5th lumbar vertebrae have been subjected to spinal anesthesia with needle number 25. In the patients of the intervention group, spinal anesthesia was a combination of 100 mg of lidocaine and 100 mg of magnesium sulfate, and in the control group, normal saline was used instead of magnesium sulfate.

The patient and the anesthesia resident who performed the evaluation and recorded the information were unaware of the injected drugs. After spinal anesthesia, patients were given oxygen by mask at the rate of 4 liters per minute. To monitor the patients, a monitoring device was used, which was able to record the rhythm of the electrical waves of the heart and measure pulse oximetry, as well as equipped with non-invasive blood pressure measurement. The anesthesia resident, who was unaware of the injected drug, performed all post-injection evaluations. Vital signs including blood pressure and heart rate were recorded every 5 minutes to 30 minutes and then every 15 minutes until the end of the procedure. In case of pressure drop (systolic pressure less than 90 mm Hg or pressure drop of more than 20% from the baseline), 250 ml of normal saline was injected as a bolus and in case of no response, 10 mg of ephedrine was injected. In case of decreased heart rate (less than 50 beats per minute), 0.6 mg of atropine was injected. The analgesia duration from the time of intrathecal injection of the drug until the patient's request for pain relief was recorded, and if the patient needed pain relief, 0.5 mg/kg of intravenous pethidine was prescribed. During this period, motor activity was checked by Bromage scoring system. After the end of operation, the analgesia duration until the need for painkillers, the patients' pain based on the visual pain scale, the amount of pethidine consumed, motor activity, blood pressure, heart rate, and respiratory depression were evaluated and complications were reported.

3. Results

As can be seen from the results seen in Figure 1, variables such as age, gender, and underlying

diseases were introduced as effective factors on pain intensity after surgery (Figure 1).

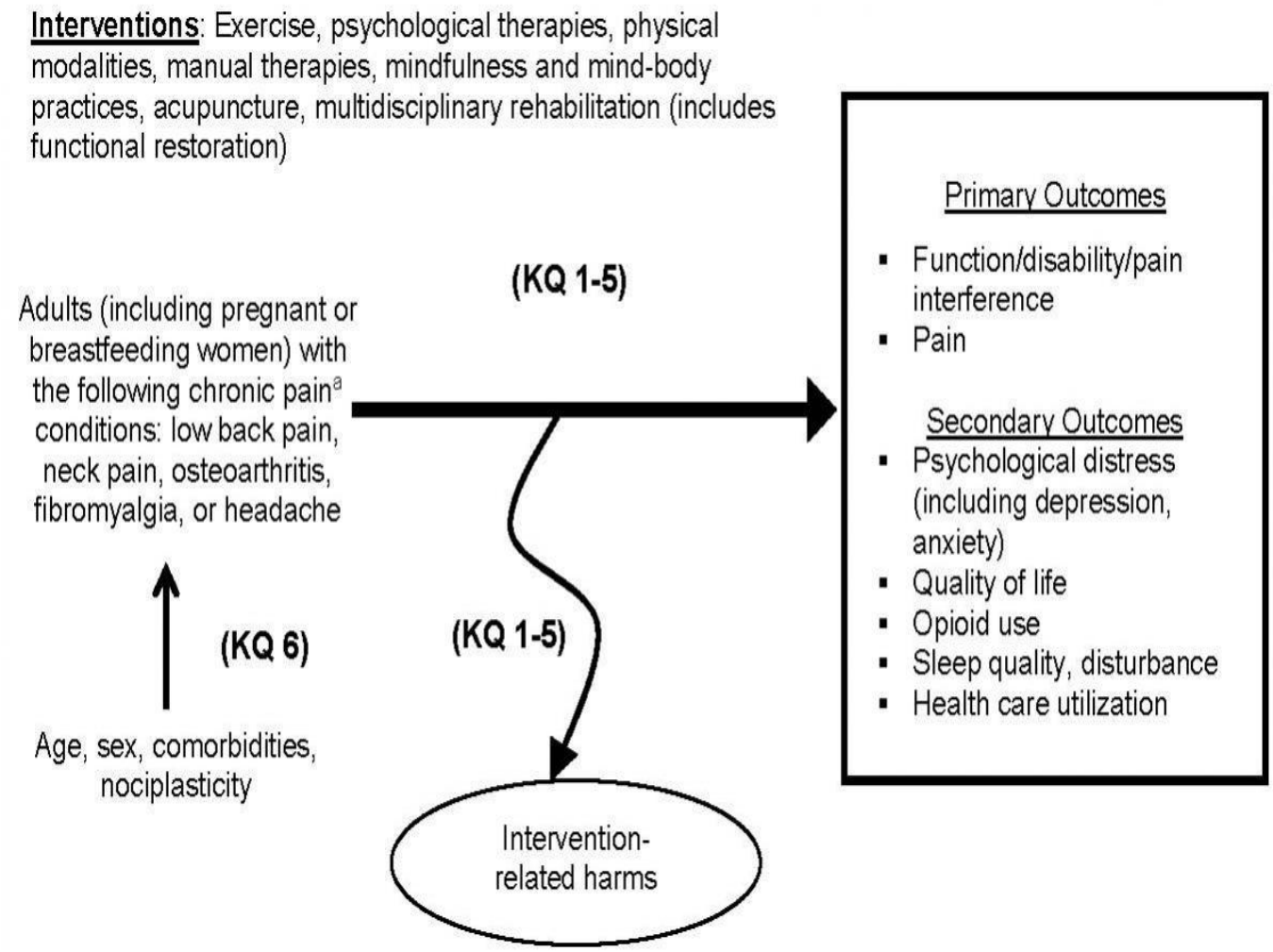


Fig. 1. Risk factors of pain after surgery

The results indicated that the addition of intrathecal magnesium leads to a significant reduction in pain intensity after lower limb orthopedic surgeries. This means that whenever magnesium sulfate is injected into the spinal cord following the injection of intrathecal anesthetic, the intensity of pain after surgery is significantly reduced, and the use of intrathecal magnesium leads to optimal and useful pain management (Figure 2). Also, the results showed that the intensity of pain decreases with time in the group receiving magnesium in a significant way compared to the control group (Figure 3). The results indicate that the activation of N-methyl-di-aspartate receptors leads to the entry of sodium and calcium into the cell and the exit of potassium out of the cell and causes central sensitization (Figures 4 and 5).

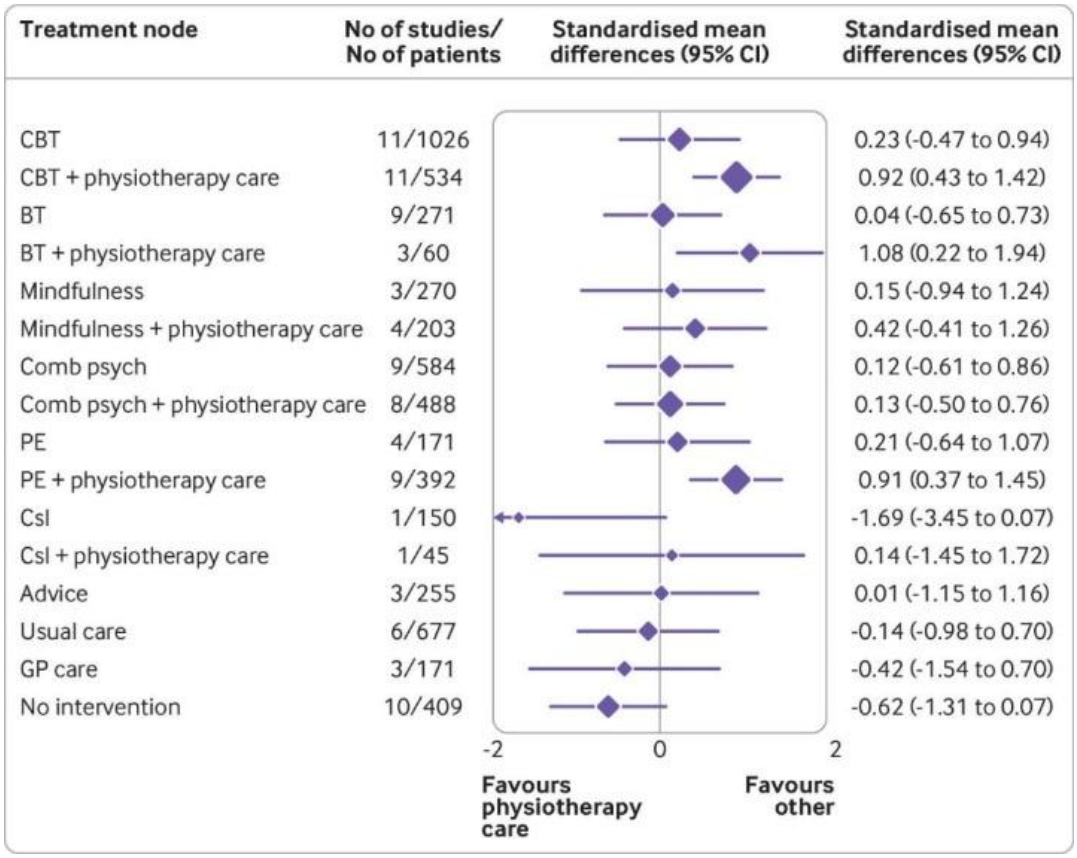


Fig. 2. Results of pain intensity after surgery based on receiving or not receiving intrathecal magnesium

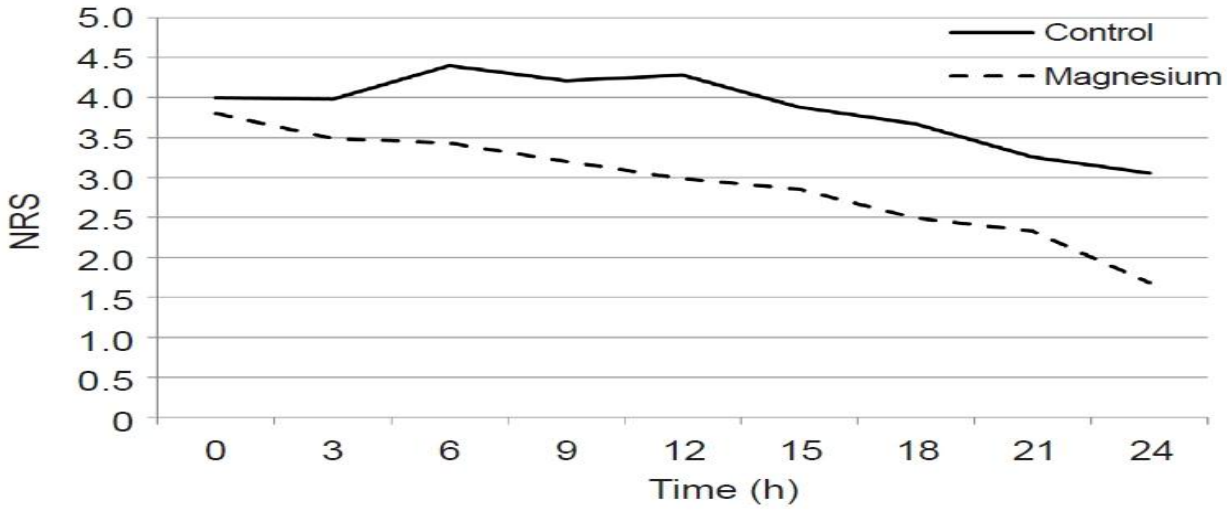


Fig. 3. Changes in pain intensity over time

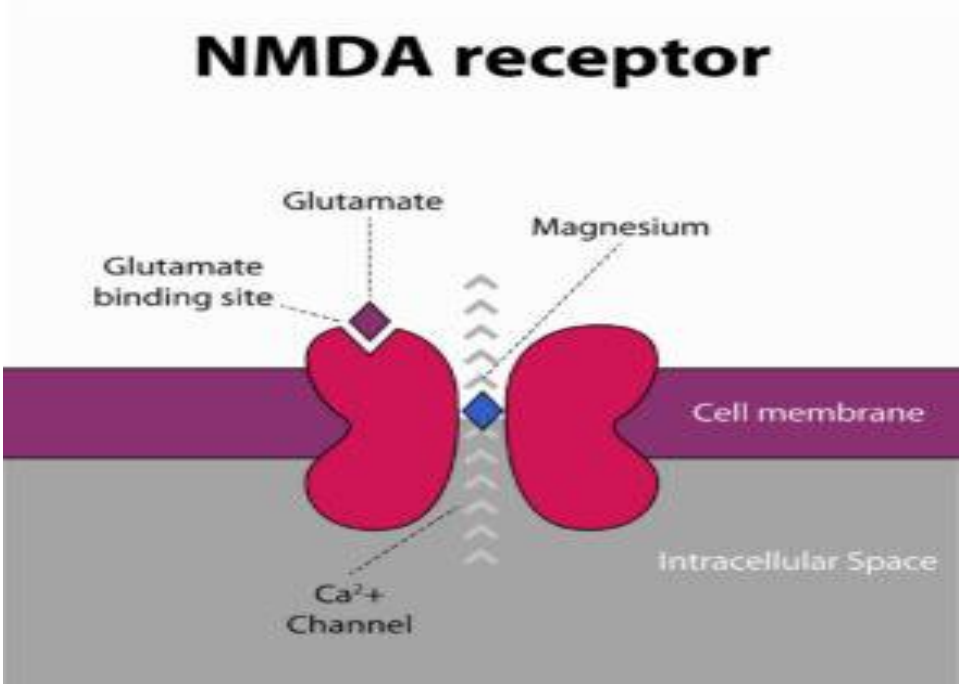


Fig. 4. How NMDA receptors enter the cell

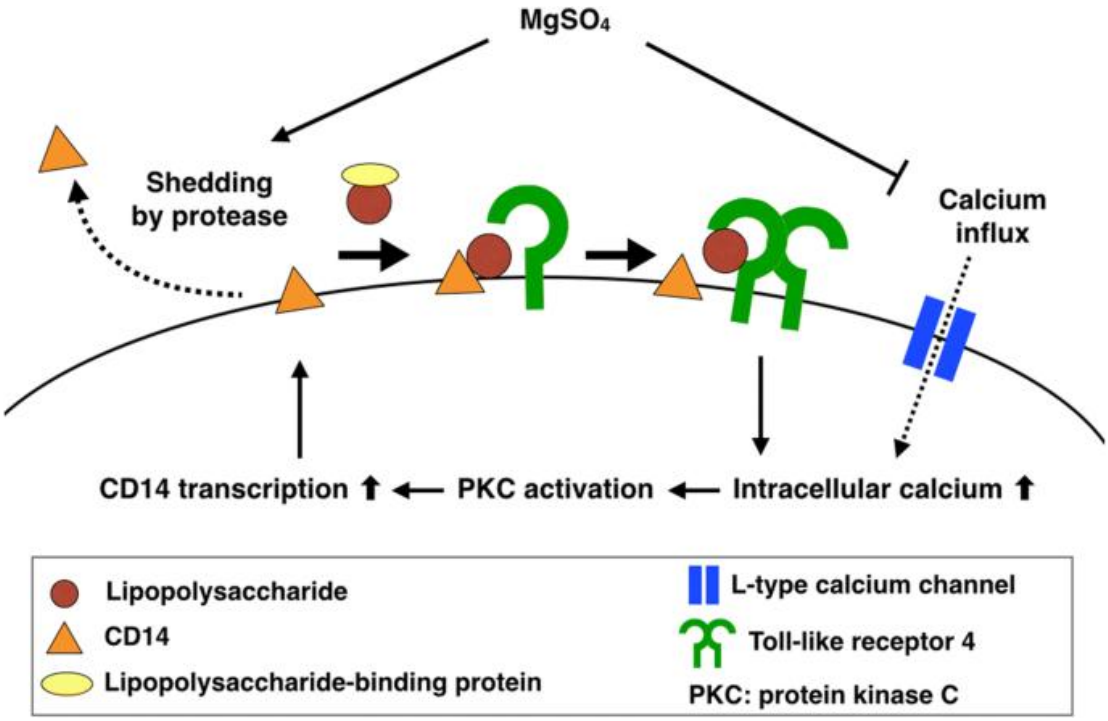


Fig. 5. How NMDA receptors enter the cell after using magnesium sulfate

4. Discussion

The present study shows interesting results about the role of magnesium sulfate in postoperative analgesia. In some ways, this study has more power than similar studies, because the two studied groups did not differ significantly in terms of demographic factors. Therefore, these

factors did not have a disturbing effect on the results of the study [25-27]. The safety of intrathecal magnesium sulfate has been proven in many animal and human studies. In this study, a dose of 100 mg of intrathecal magnesium sulfate was used, which, in a study by Lee *et al.* [2007] prolonged the analgesia duration without side effects. However, in a study conducted in 2013 by two researchers on mice, neurodegenerative changes were observed by intrathecal magnesium sulfate. However, a similar study that can show the neurotoxic effect of magnesium sulfate with a dose of 50-100 mg has not been done in humans [28-30]. Therefore, it seems that intraspinal magnesium sulfate is a good and safe drug, which is also well shown in our study, which did not cause any side effects with this drug. Likewise, in our study, there was no significant difference in terms of hemodynamic changes in the two groups [31-33].

Based on the results of the study, the analgesia duration was significantly longer in the magnesium sulfate group than in the control group. In this study, the analgesia duration was analyzed in two groups according to gender, and the research results showed that the duration of analgesia in both men and women in the treatment group was significantly longer than the control group. In a study conducted in 2014 by several researchers to investigate the effect of intravenous magnesium sulfate to sufentanil in controlling pain after orthopedic surgery, it has been shown that magnesium sulfate is effective in controlling the pain of these patients [34-36].

In addition, several researchers investigated the effect of adding magnesium sulfate to bupivacaine and fentanyl in spinal anesthesia in knee arthroscopy [37]. The results of the study showed that the consumption of painkillers during 24 hours in the group that used magnesium sulfate was not different from the control group. The duration of the first analgesic request was significantly longer in the magnesium sulfate group, which is similar to our study [38-40].

In a study conducted in 2012 by several researchers to evaluate the effect of intrathecal magnesium sulfate on post-hysterectomy analgesia, it showed that the duration of post-operative analgesia was longer in the magnesium sulfate group and the need for post-operative painkillers was clearly reduced. The results of the previous two studies are comparable to our study, and in our study, the first time of needing to receive painkillers is longer, and the amount of narcotics consumed is clearly lower in the magnesium sulfate group than in the control group [41-43].

Our study was superior to the other similar studies in terms of sample size and dose of intrathecal drug prescribed because the sample size of the current study was larger. However, one of the limitations of our study was the use of pethidine as a postoperative analgesic because in many countries of the world, pethidine is no longer used to control postoperative pain. However, many developed countries still use pethidine for postoperative analgesia. Hence, in a study conducted in South Africa, it showed that pethidine is the most common drug used after cesarean section [44-46]. Also, it is better to avoid using pethidine in the following cases, which include cancer patients, patients with anemic tuberculosis, autosomal dominant polycystic kidney disease (absolute prohibition), dialysis patients, and as an analgesic after surgery [47-49]. Therefore, it is better not to use pethidine in future studies to control the pain of patients and to use alternative drugs for this purpose [50]. It is also recommended for future research that this study be conducted in surgeries other than orthopedics with higher doses and compared to other drugs that are able

to increase the duration of the nerve block, and then the analgesia [51].

5. Conclusion

Our study showed that adding 100 mg of magnesium sulfate to spinal anesthesia can prolong the duration of analgesia without side effects after orthopedic procedures. Likewise, the safety of higher intrathecal dose of magnesium sulfate was shown in this study. As the results of our study and other studies conducted in the world have shown, the consumption of magnesium sulfate is very effective in reducing the amount of pain and its use can be very useful in-patient comfort and patient satisfaction with anesthesia.

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