Original Article

Comparing the Use of Memantine with Dextromethorphan and Placebo to Reduce Pain before Orthopedic Surgery

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Abstract

Background: To compare the use of Memantine with Dextromethorphan and placebo to reduce pain after orthopedic surgery.

Materials and Methods: The present study was a double-blind clinical trial including180 patients undergoing elective orthopedic surgery of the lower limbs. Patients were divided randomly into three groups of 60 patients each. The first group (Group M) received 30 mg Memantine orally, the second group (Group D) received 45 mg of Dextromethorphan and the third group (Group P) received only placebo, two and a half hours before the operation. The intensity of pain (VAS score), sedation score, and nausea and vomiting were recorded postoperatively.

Results: In this study, 60 patients were enrolled in each group. The total VAS (Visual Analogue Scale) score was significantly lower among patients receiving Memantine and the satisfaction was significantly higher compared to the Dextromethorphan and placebo groups (P-value <0.001).

Conclusion: The present study results indicate that Memantine has a relatively better outcome compared to Dextromethorphan or placebo in reducing the post-surgical pain among patients undergoing orthopedic surgeries. It also reduced the need for post-surgical opioid use and improved the patients' satisfaction.

Keywords: Memantine, dextromethorphan, pain, surgery

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Introduction

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (1). Acute post surgical pain is one of the most important complications of any surgical procedure and may increase perioperative mortality rate. Post operative pain has negative effects on various body systems such as respiratory, cardiovascular, gastrointestinal and urinary systems and causes metabolic, neurological, and hormonal changes (2). Methods of reducing acute pain after surgery, including preoperative administration of analgesics as well as central and peripheral nerve blocks, each have their usage in reducing the post operative pain. One of pain management procedures to control acute postoperative pain is the use of medical interventions (3, 4).

N-methyl-D-aspartate (NMDA) is a receptor for glutamate neurotransmitter, which is released

following a painful stimulus. NMDA is in fact one of several important receptors for rapid transmission in central nervous system and plays an important role in the central sensitization phenomenon (5). Activation of NMDA receptors causes hyperalgesia, neuropathic pain and reduction of opioid receptors' activity. Hyperalgesia and neuropathic pain are due to increase in spinal nerves sensitivity causing higher levels of pain. Reduction in activity of opioid receptors is associated with a decline in their sensitivity. The decrease in sensitivity is known as opioid tolerance and means there is a need for a higher dose to achieve the effects of treatment. So NMDA antagonists can have a role in pain control (6,7), and combined use of opioids and NMDA antagonists will increase the efficacy of opioids and decrease the drug resistance (8). There are different sites for NMDA antagonists to bind and the differences in their potency have been attributed to the difference in binding site and the affinity of the receptors (6, 7). Several studies have shown that NMDA receptor antagonists might have a role in somatic as well as acute and chronic visceral pain control (9, 10).

NMDA receptor antagonists include Ketamine, Methadone, Memantine, Amantadine and Dextromethorphan. Ketamine is a strong receptor antagonist for this receptor. The severity and frequency of adverse symptoms depends on the affinity of drug to NMDA receptor and these symptoms manifest mainly in the central nervous system in the form of hallucinations, lightheadedness, fatigue, confusion, nightmares, headaches and sensory changes in adults, which is more severe when using Ketamine (11, 12).

Memantine is another oral NMDA receptor antagonist which has a non-competitive moderate affinity for this receptor with a rapid onset and fewer side effects. Previous studies have shown that this drug, when administered prior to nerve damage, has the ability to reduce the neuropathic pain (13, 14). Memantine was synthesized for the first time in 1960 and after clinical trials in Germany was used in treatment of dementia, brain diseases and Parkinson disease in the late 1980s. Also after receiving approval from Food and Drug Administration in 2003 this drug is widely used in treatment of Alzheimer's disease, but its use in treatment of chronic pain is relatively new. This drug is different from the first-generation NMDA receptor antagonists like Ketamine since it is better tolerated and causes less hallucinogenic side effects. Several differences may explain why these drugs are significantly different when comparing their clinical side effects. The elimination half-life of Memantine is 60-80 hours compared to a half-life of 2.5 hours for oral or intravenous Ketamine. Faster pharmacokinetics of Ketamine may lead to a sharp increase in drug serum levels and possibly psychotomimetic effects (13-17).

Previous studies had indicated that Memantine might be effective in analgesia, so it was first used in patients with post-surgical neuropathic pain. There is a potential benefit for early treatment, since NMDA channels show a post-surgical increase in activity and might cause neuropathic pain (18,19).

Dextromethorphan and its metabolites are non-competitive NMDA receptor antagonists with low afinity (20). Dextromethorphan is a synthetic derivative of narcotics, but with no narcotic effect (21). Dextromethorphan has a long history of safe use, and it seems that if used in the period immediately before surgery, it reduces the need for analgesic drugs in the post surgical period (22, 23).

In recent years the use of preemptive analgesia has increased worldwide and with substantial progress in understanding pain mechanisms, new therapeutic concepts have emerged. Studies have shown that sensitization of neurons in the dorsal horn of spinal cord after tissue damage, leads to hyperalgesia or allodynia and this process plays a key role in development of chronic pain after a painful stimulation. Thereby reducing the over-stimulation of neurons in the dorsal horn of the spinal cord, with starting the analgesic treatment before tissue damage such as surgical incision, is necessary to reduce the up regulation of central nervous system which is the concept of preemptive analgesia (24).

Numerous studies about the benefits of preemptive analgesia, especially in the last 10 years, have been conducted and all of them have confirmed its benefit. These studies suggest that preemptive analgesia has three objectives: a) reduce the pain caused by the activation of inflammation mechanisms following surgical incision, b) prevent the call memory of the central nervous system to pain, and c) ensure

adequate control of postoperative pain to avoid the spread of chronic pain (24).

Preemptive analgesia is an intervention performed before the surgical incision to reduce the establishment of central sensitization and consequently reduces the inflammatory and incisional damage during and after the surgery. The preemptive analgesia can hypothetically prevent the hyperalgesia as well as acute and chronic postoperative pain by reducing the sensitization of central nervous system (24).

The main objective of the present study was to compare the effect of Memantine with Dextromethorphan and placebo in reducing pain after elective orthopedic surgery.

Methods

In this prospective study, 180 patients undergoing elective orthopedic surgery of the lower limbs (calf fracture) aged 18-65 years and physical health status of ASA 1 or 2 were selected and randomly divided into three groups of 60 people each. All patients were visited before and after surgery by an anesthesiologist and entered the study after giving written informed consent. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (sbmu.rec.1393.552). The study was also registered in Iranian Registry of Clinical Trials (IRCT2017062413364N4).

Group (M) received 30 mg oral Memantine group (D) received 45 mg Dextromethorphan and the group (P) was given placebo, about two and a half hours before the start of operation. Only the physician responsible for treatment knew the drug each patient received. The patient and another physician tasked with documenting the post-surgical pain score, the need for analgesics and the patients' satisfaction, were blinded to the drug received by the patient.

The exclusion criteria were ASA physical health status of 3 or 4, diseases of the respiratory system, heart, brain and endocrine glands, any drug consumption in one week prior to surgery, sensitivity to drugs used in the study, a history of mental illness, MAOIs or SSRIs during 4 weeks before the surgery, pregnancy, a history of stroke and finally type 1 and 2 diabetes mellitus. Also all patients developing compartment syndrome were excluded from the study.

All patients went under spinal anesthesia using a number 25 spinal needle and Bupivacaine 0.5 percent. Patients were transferred to recovery after the conclusion of surgery and their VAS score was documented after the return of lower limbs sensation. At this time intravenous PCA pump containing morphine at a concentration of 2.0 mg per ml and transfer rate of 4 ml per hour and a bolus dose of 5.0 ml every 15 minutes was used to control patients' pain. If the patient had a VAS (Visual Analogue Scale) score of over 4 in the recovery or anytime till 48 hours after the surgery, they would receive a 4mg dose of Morphine and the total dose of Morphine was documented. Also at the end of 48 hours the total amount of drugs consumed through intravenous PCA pump was recorded for each patient. The intensity of pain (VAS), sedation score, and nausea and vomiting were recorded 6, 12, 24, 36 and 48 hours after the surgery.

The pain score was assessed on the basis of VAS score, by displaying a scaled ruler to the patient, so that zero equaled no pain and 10 equaled the maximum imaginable pain for patients.

Sedation scores were classified as follow: 0 for restless, 1 for quiet, 2 for sleepy, 3 for confused but with respond to verbal commands, 4 for no response to verbal commands, and 5 for no response to painful stimulus.

Measurement of nausea and vomiting were as follow: 0 for no nausea and vomiting, 1 for mild nausea without the need for medication, 2 for nausea needing medication, 3 for nausea and lack of response to anti-nausea drugs.

At the end of 48 hours post operation patient satisfaction during this period was evaluated based on the following criteria: 0 for absolutely no pain, 1 for sometimes moderate pain, 2 for always moderate pain, 3 for sometimes severe pain, 4 for always moderate pain and sometimes severe pain, and ۵ for always severe pain.

Results

In the present study, 60 patients were enrolled in each group. There was not a significant difference between three groups regarding age and sex (Table 1). Also the type of surgery had no meaningful difference

Table 1: Demographic findings among the three groups of patients entering the study.

Variable	D n=60	M n=60	P n=60	P-value
Age	45.13±11.75	45.68±11.65	42.38±11.64	0.259
Gender				0.914
Female	28 (46.7%)	26 (43.3%)	28 (46.7%)	
Male	32 (53.3%)	34 (56.7%)	32 (53.3%)	
Type of surgery				0.573
Interlock surgery	27 (45.0%)	32 (53.3%)	27 (45.0%)	
Plate surgery	33 (55.0%)	28 (46.7%)	33 (55.0%)	

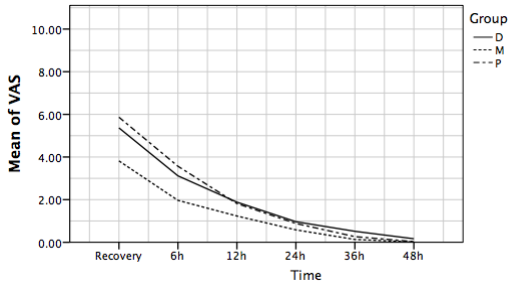

Figure 1. VAS changes in the first 48 hours after the surgery in three groups of patients entering the study.

among the three groups.

The mean VAS score was significantly different among the three groups of patients and was significantly lower in group M compared to group D and group P (P-value <0.001). But this difference was not significant between groups D and P.

The following chart shows changes in VAS score within 48 hours after the surgery. As it can be observed the pain was lower in Memantine group compared to the other two groups.

Table 2 shows the percentage of quiet and restless patients in the three groups. As it can be observed at 6, 12 and 24 hours after the surgery the percent of restless patients was significantly lower in group M compared to group D, but this difference

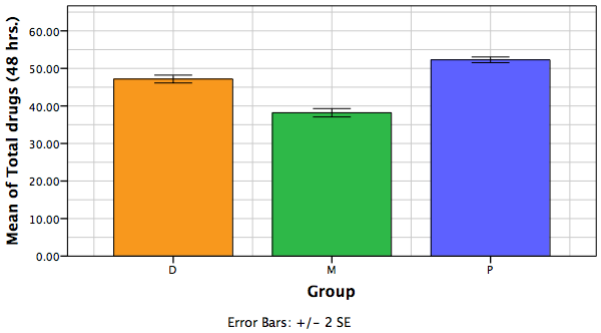

Figure 3. The total use of opioid during 48 hours post-surgery in three groups of patients entering the study.

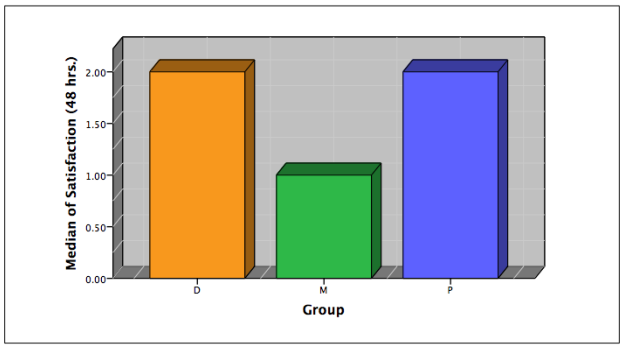

Figure 2. Satisfaction among patients at the end of 48 hours post-surgery.

was not statistically significant 36 and 48 hours after the surgery.

In 6 and 12 hours post-surgery the number of patients with nausea was lower in group M compared to group D and P, but this difference was not significant in other post-surgical intervals. When comparing the overall satisfaction among patients at the end of 48 hours post-surgery the overall satisfaction was significantly higher in group M compared to groups D and P. There was no significant difference in overall satisfaction between D and P groups (Table 3, Figure 2).

Also the total use of opioid during 48 hours post-surgery was lower in group M compared to group D and P (Table 4, Figure 3).

Discussion

The present study showed that the rate of post-operative pain in group M was lower than group D. Interestingly in group M the pain within 48 hours was significantly lower than Group D, but the difference was more significant during the first 24 hours. This might be due to the half-life of the drugs which makes them less effective after 24 hours.

It should be noted that Memantine as a NMDA

Table 2: The percentage of quiet and restless patients in the three groups entering the study.

Sedation	D n=60	M n=60	P n=60	P-value
6h				<0.001
Restless	58 (96.7%)	37 (61.7%)	59 (98.3%)	
Quiet	2 (3.3%)	23 (38.3%)	1 (1.7%)	
12h				0.001
Restless	33 (55.0%)	14 (23.3%)	17 (28.3%)	
Quiet	27 (45.0%)	46 (76.7%)	43 (71.7%)	
24h				<0.001
Restless	13 (21.7%)	2 (3.3%)	2 (3.3%)	
Quiet	47 (78.3%)	58 (96.7%)	58 (96.7%)	
36h				0.129
Restless	4 (6.7%)	1 (1.7%)	0 (0.0%)	
Quiet	56 (93.3%)	59 (98.3%)	60 (100.0%)	
48h				>0.999
Restless	0 (0.0%)	1 (1.7%)	1 (1.7%)	
Quiet	6 (100.00%)	59 (98.3%)	59 (98.3%)	
Total				<0.001

antagonist has been used in treatment of many neuropathic pains, but its use in the treatment of acute postoperative pain is not widespread. Oral Memantine has a bioavailability of about 40% and it takes 24 hours to reach a constant plasma level. After a single oral dose the drug reaches Cmax within 6 hours and it has a half-life of 60 to 100 hours. If used as a skin patch it has greater bioavailability of approximately 60% and provides adequate plasma levels for several days (25).

NMDA receptors increase the plasticity of synapses. Only synapses with active NMDA can create plasticity and neuronal pain memory in response to entrance of Ca after unblocking of Mg ++ (26).

Memantine has been indicated to reduce the post-surgical pain in several studies (27). In our study Memantine showed a good potency to reduce the pain during the 48 hours after the surgery, which was significantly better than Dextromethorphan. In fact, Dextromethorphan did not significantly reduce the postoperative pain. Dextromethorphan is a non-competitive antagonist of NMDA receptor with low affinity to these receptors while Memantine has a higher affinity for NMDA receptors, so the difference in analgesic effect of these two drugs is likely to be due to their different affinity for NMDA receptors.
Numerous studies have indicated that Memantine administered after surgery can reduce the chance of chronic post-surgical pain and also prevent phantom

Table 3: Satisfaction among patients at the end of 48 hours post-surgery.

Satisfaction	D n=60	M n=60	P n=60	P-value	P_1*	P_2	P_3
Median (IQR)	2 (1-2)	1 (0-1)	2 (2-2)	<0.001	<0.001	0.699	<0.001
0: Absolutely no pain	0 (0.0%)	17 (28.3%)	0 (0.0%)				
Sometimes moderate pain	17 (28.3%)	37 (61.7%)	12 (20.0%)				
2- Always moderate pain	34 (56.7%)	5 (8.3%)	42 (70.0%)				
3- Sometimes severe pain	9 (15.0%)	1 (1.7%)	6 (10.0%)				
4: Always moderate pain and sometimes severe pain	0 (0.0%)	0 (0.0%)	0 (0.0%)				
5: Always severe pain	0 (0.0%)	0 (0.0%)	0 (0.0%)				

* P_1= P-value for difference between Group D and M
P_2= P-value for difference between Group D and P
P_3= P-value for difference between Group M and P

Table 4: The total use of opioid during 48 hours post-surgery in three groups of patients entering the study.

Opioid	D n=60	M n=60	P n=60	P-value	P_1*	P_2	P_3
The total use of opioid in 48 hours post-surgery	47.17±4.05	38.18±4.30	52.28±2.94	<0.001	<0.001	<0.001	<0.001

* P_1= P-value for difference between Group D and M
P_2= P-value for difference between Group D and P
P_3= P-value for difference between Group M and P

pain after amputation (28-31).

A previous study has indicated that the use of Dextromethorphan syrup 2 to 3 hours before the knee arthroscopic surgery reduces the pain and the need for opioids in first 8 post-surgical hours (8), which is similar to our findings, but the present study indicated that Memantine had a better outcome in reducing the post-surgical pain compared to Dextromethorphan.

In this study, postoperative nausea and vomiting was significantly lower in Memantine group compared to Dextromethorphan group in the first 12 hours after surgery.We also found that after using Memantine the first patient's request for opioid is delayed and also the total post-surgical opioid usage is lower compared to Dextromethorphan or placebo, which can explain the lower incidence of opioid side effects like nausea and vomiting.

It should be noted that in the present study Memantine resulted in significantly higher patient satisfaction, lower post-surgical pain scores and less need for post-surgical opioid use compared to placebo, but there was no difference between placebo and Dextromethorphan. Also the overall satisfaction was higher when comparing Memantine and Dextromethorphan.

Conclusion

The present study results indicate that Memantine has a relatively better outcome compared to Dextromethorphan or placebo in reducing the pain among patients undergoing orthopedic surgeries. It also reduced the need for post-surgical opioid use and improved the patients' satisfaction.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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