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Memantine as a Potential Therapy in Subacute Herpetic Neuralgia: A Randomized Clinical Trial

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ABSTRACT

Background: Varicella-Zoster virus (VZV) is the causative agent of herpes zoster, or "shingles." Most cases of acute herpes zoster are self-limiting, although the pain can cause significant suffering, and experience postherpetic neuralgia (PHN), particularly in older adults. Early treatment of herpetic neuralgia in the subacute phase may prevent PHN progression. This study aimed to evaluate the efficacy of memantine in the treatment of subacute neuropathic herpes zoster.

Methods: This randomized clinical trial was performed on sixteen patients aged 18-75 years with subacute herpetic neuralgia. Patients were randomly assigned to the intervention or control group according to the inclusion and exclusion criteria (8 in each group). The duration of the study was eight weeks. Patients in the memantine group received Gabapentin 300 mg per day and memantine 5 mg twice a day. Then, after one week, the memantine dose was tapered up to 10 mg twice a day. In the control group, patients received only Gabapentin from the first week to the end of the study. DN4 questionnaire is used to measure the severity of nerve pain. The patients of both control and intervention groups completed the questionnaire before starting the treatment and it was done again after the end of the treatment period (8 weeks).

Results: The results showed improvement in pain in patients who received Memantine along with Gabapentin in comparison with Gabapentin alone (P =0.001). Moreover, the DN4 questionnaire score evaluation indicated a significant difference only for the intervention group's Q1 variable in within-group analysis (P =0.031).

Conclusion: Co-administration of memantine with Gabapentin reduced the severity of subacute neuropathic herpes. In addition, memantine is expected to be a viable option for treating and relieving subacute and chronic nerve pain in patients.

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Introduction

The varicella-zoster virus remains latent in the posterior nerve root ganglion (DRG) or cranial nerve ganglia approximately one year after the primary infection (chickenpox) has healed (1, 2). The prevalence of herpes zoster is about 1,000,000 people in the US each year,

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representing approximately 1 case per 100 populations with 60 years of age and older (3). There are three stages of herpes zoster (4, 5). The acute phase refers to pain within the skin manifestations of the disease, which usually lasts up to 30 days from the onset. The subacute phase is usually within four months of onset and is defined as a pain that remains beyond the acute phase but resolves before PHN is diagnosed. The PHN phase also refers to persistent pain that occurs four months after the initial onset of skin manifestations.

Studies show that antidepressants, antiepileptics, opioids, glucocorticoids, anticonvulsants, and NSAIDs effectively relieve neuropathic pain (6-10). In addition, some studies indicated the relationship between N-Methyl-D-aspartate receptor (NMDA) medications and their anti-hyperalgesic effects in controlling PHN (11, 12). Memantine (1-Amino-3-hydroxy-5, 7-dimethyladamantane) is a non-competitive NMDA receptor antagonist that has been approved to treat moderate to severe forms of Alzheimer's disease (AD) (13). It is a type of insurmountable antagonist that blocks NMDA receptors in pathological cases (higher levels of glutamate than normal and physiological) and maintains the normal function of NMDA receptors under physiological conditions (14). Moreover, this medication inhibits the entry of excess calcium by blocking the channels and, therefore, reduces glutamate's neurotoxicity effect (15).

Studies on memantine demonstrated that use of this medication can be effective in postherpetic neuralgia, diabetic neuropathic pain, postoperative pain, complex regional pain syndrome, chronic phantom limb pain, drug-resistant pain, and fibromyalgia (16). However, due to the paucity of relevant experimental studies and small samples, more studies are needed.

Due to the minimal adverse effect of memantine and particularly its mechanism of action, it is considered a valuable option for preventing and treating NP (17, 18). This study is conducted to evaluate whether memantine could improve the subacute neuralgic pain in patients with herpes zoster.

Methods

This randomized clinical trial was performed on subacute herpetic neuralgia patients whom were diagnosed by dermatologist in the dermatology clinic of Sina Hospital in Tabriz University of Medical Science, Tabriz, Iran. The local Ethics Committee approved the protocol of this study of Tabriz University of Medical Sciences, Tabriz, Iran) IR.TBZMED.REC.1398.135(. Also, the trial was registered at the Iranian Registry of Clinical Trials (IRCT20180404039187N6). In this study, all criteria for working with human samples were observed following the rules approved by the ethics committee in medical research. All patients were informed about the study and gave written informed consent before initiating the study.

This study included sixteen patients aged between 18 to 75 years from April 2019 to August 2020. All patients with a history of diabetic neuropathy, uncontrolled blood pressure, acute heart failure, seizures, hepatic impairment (Child-c), chronic kidney disease, and pregnant or lactating women were excluded from the study. Moreover, patients with a medication history of tricyclic antidepressants (TCAs), Selective serotonin reuptake inhibitors (SSRI), Serotonin and norepinephrine reuptake inhibitors (SNRI), NMDA antagonist, antiepileptic drugs, anticholinergics, barbiturates, Monoamine oxidase inhibitors (MAOIs), antispasmodics, antiarrhythmic medications were excluded from the study.

Patients were randomized by block randomization. The size of the blocks was 4. They were given a block size of 4, and six possible ways to equally assign participants to a block. Allocation was performed by randomly selecting one of the orderings and assigning the next block of participants to study groups by the physician according to the specified sequence.

Eligible patients were randomly divided into either intervention or control groups (8 in each group). The duration of the study was eight weeks. Patients in the intervention memantine (Tasnim company) group received Gabapentin 300 mg and memantine 5 mg twice a day. Patients didn't take corticosteroids or antiviral agents. Then, after one week, the dose of memantine was tapered up to 10 mg twice a day. In the control group, patients received only fixed dose of Gabapentin 300 mg from the first week to the end of the study. In both groups pain reduction was the primary outcome.

Douleur Neuropathique en 4 (DN4) is a clinical tool for neuropathic pain diagnosis. This questionnaire has four questions that are divided into ten related items. In current Study Reliability and Validity of DN4 questionnaire for subacute herpetic neuralgia was done before beginning of the data collection. These items included yes or no answers, and points one and zero are considered for the answers, respectively. A score of one is given to each positive item and a score of zero to each negative item. The total score is calculated as the sum of the ten items, and the cut-off value for the diagnosis of neuropathic pain is a total score of 4/10. 22 The patients of both control and intervention groups completed the questionnaire before starting the treatment and it was done again after the end of the treatment period (8 weeks). Patients in the memantine group who did not adhere to the use of medication for eight weeks were excluded from the study. Moreover, patients

were followed up weekly by a phone call to preserve good compliance and follow up on the possible adverse events.

Statistical Analysis

In order to between groups comparisons, considering the difference of 3 points for the average pain score in the two groups as an important and clinically meaningful difference, and considering the standard deviation obtained from the data and the available sample size, the power of the independent t-test, performed for comparison intervention and control groups, for the baseline pain score was 0.94 and for the pain score after the intervention was 0.95. Therefore, the available sample size (8 patients in each group) is enough to detect such an effect size. Regarding the within-group comparison of the pain score, according to the information obtained from the data for the correlation coefficient and standard deviation and the available sample size, the power of the test for the desired difference between the before and after values of the pain score (3 points) was 0.96. (Power analysis was calculated with Gpower 3.1.2 software.

Continuous variables were described as mean and standard deviation (SD). The Kolmogorov-Smirnov test was used to assess normality. Shapiro-Wilk test was used for distribution assessment. They were compared between intervention groups using independent samples t-test or Mann-Whitney U-test. Categorical variables were expressed as frequency and percentage, and a comparison between the intervention and control group in pain parameters was made by chi-square or Fisher's exact test. P values less than or equal to 0.05 were considered statistically significant.

Results

In this study, 30 patients diagnosed with subacute neuropathic zoster were evaluated for eligibility to enter the study. Two patients did not meet the inclusion criteria. As a result, 28 patients were divided into intervention or control groups (each group=14). Due to nonadherence, six patients in the control group withdrew from the study during the follow-up. Conversely, six patients did not continue taking memantine in the intervention group due to side effects, dizziness, and concerns about side effects. As a result, eight patients in the memantine group completed the study. The data of the DN4 questionnaire score have a normal distribution (Table 1). The most common underlying disease in the study participants was hyperlipidemia, of which three cases were observed in the control group and four cases in the intervention group. There was no noteworthy difference between other medications taken by patients. Comparing age, weight, height, sex, smoking, and baseline DN4 score did not show remarkable differences between the control and intervention groups. Still, the results of the final DN4 score assessment indicated a significant difference between the control and intervention groups (P <0.001) (Table 2). Within-group analysis of the baseline DN4 score and final DN4 score showed no statistically significant difference between the baseline and final score of the DN4 questionnaire in the control group, whereas it was significant in the intervention group (P =0.001) (Table2).

Table 1. Demographic and baseline characteristic of the study participants

Variable	Control group(n=8)	Intervention group(n=8)	P-Value
Age (years)	53.75±15.71	61±7.27	0.255
Sex-male (%)	6 (75%)	4 (50%)	0.6
Weight (kg)	76.8±9.9	78.12±13.1	0.833
Height (cm)	180±5.4	176±4.2	0.105
Smoking-yes (%)	6 (75%)	3 (37.5%)	0.6
Baseline DN4 Score	6.25±1.9	7±1.51	0.398

Values are mean± standard deviations or number (%)

Table2. Comparison of Pain score (DN4 score)

Variable	Control group	Intervention group	P-Value [2]
Baseline DN4 score	6.25±1.9	7.00±1.5	0.398
Final DN4 score	6.5±1.7	2.7±1.2	0.001
P-Value [1]	0.7	0.001	

Values are mean± standard deviations
1 Denotes the significance of within-group changes (Paired samples t -test)
2 Denotes the significance of between-group changes (Independent t -test)

Discussion

Neuropathic pain is a significant factor in the disease that burdens communities (19). The prevalence of NP is reported between 6.9 and 10% of the general population (20). Several causes of environmental and central disorders lead to NP (20). Studies have recently suggested the role of the NMDA receptor and the phenomenon of central sensitization, which can affect the severity and quality of pain and neuropathic pain in herpetic neuralgia (21, 22). This study aimed to evaluate the efficacy of memantine as a non-competitive NMDA receptor antagonist in reducing the severity of subacute neuropathic pain in patients with herpes zoster.

Our data showed a significant improvement in pain scores in patients who received memantine (P =0.001), which could be the reason for memantine's positive efficacy and effectiveness in reducing subacute neuropathic pain caused by shingles.

As far as we know, this study is a pioneering study to evaluate the effect of memantine on the subacute phase of herpes neuralgia. Several studies have different results on the effectiveness and efficiency of NMDA receptor antagonists in reducing the severity of nerve pain caused by nerve damage. Studies show that the efficacy of memantine in reducing pain intensity depends on the type of NP (23).

A survey of the use of memantine before surgery in animals showed that the administration of memantine prevents the increase of allodynia stress in the animal NP model (24). Subsequently, in a study by Morel et al., in adult male Sprague-Dawley rats candidates for L5 spinal nerve ligation (SNL). The results showed that prophylactic memantine a few days before surgery of the spinal nerve diminished the development of pain (25). In a laboratory study in mice, intrathecal injection of NMDA antagonists such as memantine appeared to be significantly more effective in relieving chemically facilitated pain and tactile allodynia caused by nerve damage than dextromethorphan and ketamine (26). Another study in 2010 was conducted to evaluate the antinociceptive effect of memantine and morphine on vincristine-induced peripheral neuropathy in rats. This study showed that memantine improves mechanical sensitivity and increases the paw removal threshold in rats (27).

In a double-blind clinical study in nine patients with acute traumatic amputation, the use of memantine significantly reduced the prevalence and severity of phantom lip pain in postoperative orthopedic surgery (28). Other studies indicated the affirmative effect of memantine in the reduction of chronic pain in complex regional pain syndrome (29, 30), phantom limb pain (31), and get a benefit for quality of life in patients with fibromyalgia (32). Clinical studies on pain prevention following mastectomy and FM have limitations and strengths. These studies reported positive results, but both studies had a small sample size. However, in these studies, a high benefit-to-risk ratio was reported, and there were no specific side effects reported in either study. This point is significant in the treatment and management of pain because one of the main reasons for discontinuing the medication in therapy is the onset of side effects of the medication (33). In a randomized clinical trial study on 40 women with non-metastatic breast cancer, memantine as a prophylactic medication at the dose of 20 mg/day has been effective in preventing severity and incidence of docetaxel induced neuropathy (34). Similar results of memantine efficacy have been reported in a study by Chen et al. on the effects of neramaxan and memantine administration in a diabetic model of diabetic neuropathic pain (35).

Treatment of NP due to patients' chronic condition and central sensitization phenomenon is difficult. However, memantine studies have shown discrepant results regarding methodological differences between randomized clinical trials. Moreover, there are differences in the duration of treatment (interval between 3 to 7 weeks), the prescribed dose, how the pain is assessed, and how the placebo is controlled; the main factor may affect the result of studies and the sample size. A placebo-controlled clinical trial conducted by Eisenberg et al., (36) in 1998 showed that memantine did not have significant efficacy in reducing pain intensity in patients with PHN compared with placebo. The number of patients participating in this study was 24 who were randomly divided into two groups of 12. The duration of the study was five weeks, and for the first week, patients received memantine at a dose of 10 mg daily and four weeks at a dose of 20 mg daily. Moreover, In this study, the Neuropathy Pain Scale (NPS), McGill pain questionnaire (MPQ), and quantitative thermal testing (QTT) criteria were used to evaluate the quality of patients' pain. Studies have shown that once memories of pain in the cerebral cortex are involved in the development and pre durability of persistent pain. Regard the role of NMDA receptors and the phenomenon of central sensitization, and the increased activity of these receptors in various neuropathic pains, and it is expected that NMDA receptors can be effective in reducing the severity of pain due to nerve damage.

This study was a randomized clinical trial. Patients did not receive any placebo; therefore placebo-controlled double-blind studies are recommended. In addition small sample size and high rate of drop out in both groups of the study

could influence the results. Future clinical trials with large sample sizes, long-term intervention, and various doses of memantine are recommended.

According to the results of this study, co-administration of memantine with gabapentin reduced the severity of subacute neuropathic herpes. In addition, memantine is expected to be a viable option for treating and relieving subacute and chronic nerve pain in patients.

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