

ORIGINAL RESEARCH

The Effect of Intrathecal Administration of Muscimol on Modulation of Neuropathic Pain Symptoms Resulting from Spinal Cord Injury; an Experimental Study

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Abstract

Introduction: Neuropathic pain can be very difficult to treat and it is one of the important medical challenging about pain treatments. Muscimol as a new agonist of gamma-Aminobutyric acid receptor type A (GABA_A) have been introduced for pain management. Thus, the present study was performed to evaluate the pain alleviating effect of intrathecal injection of different doses of muscimol as GABA_A receptor agonist in spinal cord injury (SCI) model of neuropathic pain. **Methods:** In the present experimental study, male Wistar rats were treated by muscimol 0.01, 0.1 or 1 µg/10ul, intrathecally (i.t.) three weeks after induction of spinal cord injury using compression injury model. Neuropathic pain symptoms were assessed at before treatment, 15 minutes, one hour and three hours after muscimol administration. The time of peak effect and optimum dosage was assessed by repeated measures analysis of variance and analysis of covariance, respectively. **Results:** Muscimol with the dose of 0.01 µg in 15 minutes caused to improve the thermal hyperalgesia (df: 24, 5; F= 6.6; p<0.001), mechanical hyperalgesia (df: 24, 5; F= 7.8; p<0.001), cold allodynia (df: 24, 5; F= 6.96; p<0.001), and mechanical allodynia (df: 24, 5; F= 15.7; p<0.001). The effect of doses of 0.1 µg and 1 µg were also significant. In addition, the efficacy of different doses of muscimol did not have difference on thermal hyperalgesia (df: 24, 5; F= 1.52; p= 0.24), mechanical hyperalgesia (df: 24, 5; F= 0.3; p= -0.75), cold allodynia (df: 24, 5; F= 0.8; p= -0.56), and mechanical allodynia (df: 24, 5; F= 1.75; p= 0.86). **Conclusion:** The finding of the present study revealed that using muscimol with doses of 0.01µg, 0.1µg, and 1 µg reduces the symptoms of neuropathic pain. In addition, the effect of GABA_A agonist is short term and its effectiveness gradually decreases by time.

Key words: Neuropathic pain; GABA_A receptor agonists; muscimol; pain management

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Introduction:

Today neuropathic pain, which happens following the injury or dysfunction of peripheral or central nervous system, turns to one of the important medical challenging about pain. In most of these situations, neuropathic pain involve the at-level of injury but gradually extend and can occurred above or below the level of injury. These changes lead to decrease life quality, functional loss and physical dependence, and undermine mental health and social relations (1). The most annoying symptoms of these patients are hyperalgesia (hypersensitivity to painful stimulus) and allodynia (pain due to a stimulus which does not normally aggravate priorities weather in acute or in chronic cases (2). However, eliminating of these symptoms is one

of the current treatment strategies have less efficiency and lead only to decrease 30-40% of pain in less than half of patients (3). Medications in this situation align with some problems such as not responding to drugs and their side effects. For example, weight gain and constipation are common symptoms of patients with spinal cord injuries (SCI) treated with tricyclic antidepressants (2). Because of drug resistance, using narcotic drugs is not acceptable and long-term use of anti-epileptic drugs, gabapentin, and topiramate has a low effectiveness (4-6). In patients with SCI even narcotic drugs, which are one of the best sedative agents, have a poor or moderate responses (6). Alternatively, intrathecal (i.t) pumps are one of the new common cures (7, 8). Intrathecal baclofen has remarkable effects on reducing the symptoms of SCI-related pain due. But applying this medication in some patients causes to worsen the neuropathic pain symptoms (9). Intrathecal clonidine has also been suggested in some studies (8).

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Epidural and intrathecal use of sedative drugs has been widely applied and there are strong evidences for their helpfulness in acute and chronic situation. Most trials and a meta-analysis have shown that preoperative, intraoperative and postoperative epidural anaesthesia /analgesia reduces the incidence of phantom pain significantly (10, 11). Opioids, local anesthetics, α_2 -agonists, and baclofen are the most significant drugs of this group. Along with these agents, newest drug compounds like sodium channel blockers, trophic factors, and new agonist of gamma-Aminobutyric acid (GABA) receptors have also been introduced (12-14). One of the type A of GABA (GABA_A) receptor agonists is muscimol which is extracted as a psychotropic drug from a mushroom named *Amanita muscaria* and used as a local anesthetic drug (15, 16). Efficacy of muscimol on reducing the neuropathic pain symptoms has been shown in some studies, while in most of them the peripheral model of neuropathic pain has been used (15, 17). Since the main cause of neuropathic pains is direct injury of spinal cord, evaluating the effectiveness of intrathecal pumps of muscimol in reducing the neuropathic pain arisen from SCI has not yet been cleared. Thus, the present study was performed to evaluate the pain alleviating effect of intrathecal injection of different doses of muscimol as GABA_A receptor agonist in spinal cord injury (SCI) model of neuropathic pain.

Methods:

Study design and setting:

The present experimental study was conducted in accordance with guidelines of ethics for the evaluation of pain in conscious animals (18) and approved by the ethic committee of Iran University of medical sciences, Tehran, Iran. The length of trials was kept short as much as possible and the number of animals taken to a minimum with all efforts made to minimize animal suffering.

Animals and drugs:

Thirty male Wistar rats (10 rats in each group) weighing 140-160 g were used. Animals were maintained under controlled laboratory conditions (temperature: 21 ± 1 C; 12 hour light/dark cycle; 4 rats per cage) and had free access to water and food. All tests were performed between 10:00 am and 02:00 pm, in a sound-proof and air-regulated room. Muscimol (Sigma chemical company, St, Louis, USA) was dissolved in saline and the animals received 0.01, 0.1 or 1 μ g/10 μ l, intrathecally (i.t.). Before muscimol administration and 15 minutes, one hour and three hours after on, behavioral tests were evaluated.

Animal preparation

A compression injury model was used to induce SCI. This method was previously described by Hama and Sagen (19). Briefly, after anesthesia [by a combination of ketamine (80 mg/kg) and Xylazin (10 mg/kg)], dor-

sal laminectomy was performed at T6–T8 to expose the spinal cord. The lower blade of the micro-vascular clip (Harvard Apparatus, MA) was placed on the exposed cord with avoidance of damage to the adjacent nerve roots. After 60 seconds, the clip was removed, muscles sutured shut, and skin closed. Three weeks following compression, a PE10 cannula was placed intrathecally at L5-L6 level of Spinal cord during deep anesthesia based on the method introduced by Xu et al (20). For this purpose, a longitudinal skin incision was made over L4-L5 location and a 6 cm long PE10 cannula implanted into the subarachnoid space and passed 1 cm rostrally.

Behavioral tests

A) Mechanical allodynia

The threshold of mechanical allodynia, as a behavioral measure of neuropathic pain, was measured by assessing hind paw sensitivity to innocuous mechanical stimulation to third metatarsal bone area of the both hind paw. The 50% paw withdrawal thresholds were evaluated with a set of specific Von Frey filaments using the up-down paradigm (21). Lifting, shaking, or licking the paw and running away were considered as positive responses. The 50% paw withdrawal thresholds were assessed before and 15 minutes, 1 hour, and three hours after muscimol administration. Only robust and immediate withdrawal responses including lifting, shaking or licking the paw and running away were considered as positive.

B) Mechanical hyperalgesia

Increasing mechanical pressure (48 g/s) was applied to the hind paw by the Randall–Selitto mechanical hyperalgesia test for the assessment of mechanical hyperalgesia. It can detect neuropathic pain in both fore paws and hind paws (22). The mechanical force was applied to the plantar surface of both hind paws (two trials per each paw) until a withdrawal response observed. The maximum applied pressure was 1000 g to evade damage. The average score of two trials was used in analysis.

C) Cold allodynia

The application of a drop (0.1 ml) of acetone to the center of plantar surface of hind paw was performed to measure cold allodynia (23). Rats were located on a mesh floor cages and acetone pushed to center of plantar surface of hind paw. This test was repeated five times per foot (3–5 min between each test) and withdrawal responses calculated as the percentage response frequency using following formula:

$$\frac{\text{number of paw withdrawals}}{\text{number of trials}} \times 100$$

D) Heat hyperalgesia

Responses to noxious heat (Hargreaves method) were evaluated using a radiant heat source (24). Animals



Table 1: Effectiveness of muscimol prescription on neuropathic pains in different times [↑](#)

Type of test	Before administration	After 15 minutes	The first hour	The third hour
Thermal hyperalgesia (second)				
0.01µg	10.4 (0.12)	12.8 (0.4)*	10.2 (0.4)	10.1 (0.4)
0.1µg	10.5 (0.3)	13.04 (0.5)*	9.6 (0.35)	10.4 (0.55)
1µg	10.2 (0.4)	12.9 (0.8)*	10.1 (0.5)	10.2 (0.4)
Mechanical hyperalgesia (gram)				
0.01µg	5.2 (0.2)	6.9 (0.2)*	5.8 (0.25)#	5.7 (0.2)#
0.1µg	5.1 (0.1)	6.6 (0.3)*	5.8 (0.2)#	5.9 (0.1)#
1µg	5.2 (0.3)	6.8 (0.2)#	5.7 (0.2)*	5.9 (0.1)#
Cold allodynia (%)				
0.01µg	87.5 (13.9)	52.5 (10.3)#	65.0 (13.9)#	72.5 (5.9)
0.1µg	97.5 (10.3)	62.5 (7.0)#	68.8 (10.8)#	76.3 (1.8)#
1µg	96.3 (5.9)	62.5 (11.5)#	71.3 (5.8)#	77.5 (4.9)#
Mechanical allodynia (gram)				
0.01µg	8.8 (0.55)	14.75 (0.25)*	13.4 (1.1)#	12.2 (1.8)#
0.1µg	9.3 (0.7)	14.6 (0.3)*	14.3 (0.4)#	13.1 (1.4)#
1µg	8.5 (0.8)	14.9 (0.1)*	14.4 (0.5)#	13.0 (0.2)#

*have a significant difference in $p < 0.001$ with before administration time; #shows a significant difference in $p < 0.05$ with before administration time. The findings was extracted in terms of repeated measures ANOVA test.

were placed in a transparent Plexiglas box and allowed to adapt within 20 minutes. Time to initiating the thermal stimulation to paw withdrawal response was defined as withdrawal latency. A cut-off time was set at 25 seconds to prevent tissue damage. Each hind paw was tested Three times. Finally, the average of three trials was used for statistical analysis.

Statistical analysis

Data were entered to SPSS version 20 and expressed as Mean \pm SEM (standard error of mean). One-way analysis of variance (one-way ANOVA) was used to compare the difference among three groups before administration of muscimol. Repeated measures ANOVA was carried out to change the pain over time among before, 15 minutes, 60 minutes, and 180 minutes after treatment to clear the time of peak effect. For assessment of dosage effect, analysis of covariance (ANCOA) adjusted for mean pain score before muscimol administration was performed. Because the maximum effect was observed at 15 minutes, two-way ANOVA was performed to evaluate the significant difference among three doses of muscimol in this time. $P < 0.05$ was defined as the significance level.

Results:

Muscimol administration causes to reduce the symptoms of neuropathic pain, noticeably. As shown in [Table 1](#), thermal hyperalgesia, mechanical hyperalgesia, cold allodynia, and mechanical allodynia decreased after 15 minutes. Except thermal hyperalgesia (df: 24, 5; $F=1.1$; $p=0.12$), other neuropathic pain symptoms had significant improvement after one hour and three hours of

muscimol administration.

Using muscimol with the dose of 0.01 µg/kg in 15 minutes caused to improve the thermal hyperalgesia (df: 24, 5; $F= 6.6$; $p < 0.001$), mechanical hyperalgesia (df: 24, 5; $F= 7.8$; $p < 0.001$), cold allodynia (df: 24, 5; $F= 6.96$; $p < 0.001$), and mechanical allodynia (df: 24, 5; $F= 15.7$; $p < 0.001$). Muscimol with a dose of 0.1 µg/kg also led to improve the thermal hyperalgesia (df: 24, 5; $F= 5.9$; $p < 0.001$), mechanical hyperalgesia (df: 24, 5; $F= 7.2$; $p < 0.001$), cold allodynia (df: 24, 5; $F= 7.03$; $p < 0.001$), and mechanical allodynia (df: 24, 5; $F= 13.4$; $p < 0.001$) after 15 minutes of administration. The significant effect was also seen with a dose of 1 µg/kg ([Figure 1](#)). The analysis of covariance showed that the efficiency of various muscimol doses was similar in reducing the symptoms of pain in different times. Based on this result, the efficacy of different doses of muscimol did not have difference on thermal hyperalgesia (df: 24, 5; $F= 1.52$; $p= 0.24$), mechanical hyperalgesia (df: 24, 5; $F= 0.3$; $p= -0.75$), cold allodynia (df: 24, 5; $F= 0.8$; $p= -0.56$), and mechanical allodynia (df: 24, 5; $F= 1.75$; $p= 0.86$) ([Figure 2](#)).

Discussion:

The findings of the present study showed that using muscimol in each of three evaluated doses leads to reduce the acute neuropathic pain. Peak alleviating effect, was observed within 15 minutes and gradually decreases in three hours. However, except heat hyperalgesia, intrathecal administration of muscimol could remarkably relief the other symptoms. This effect has persisted until three hours after administration. It



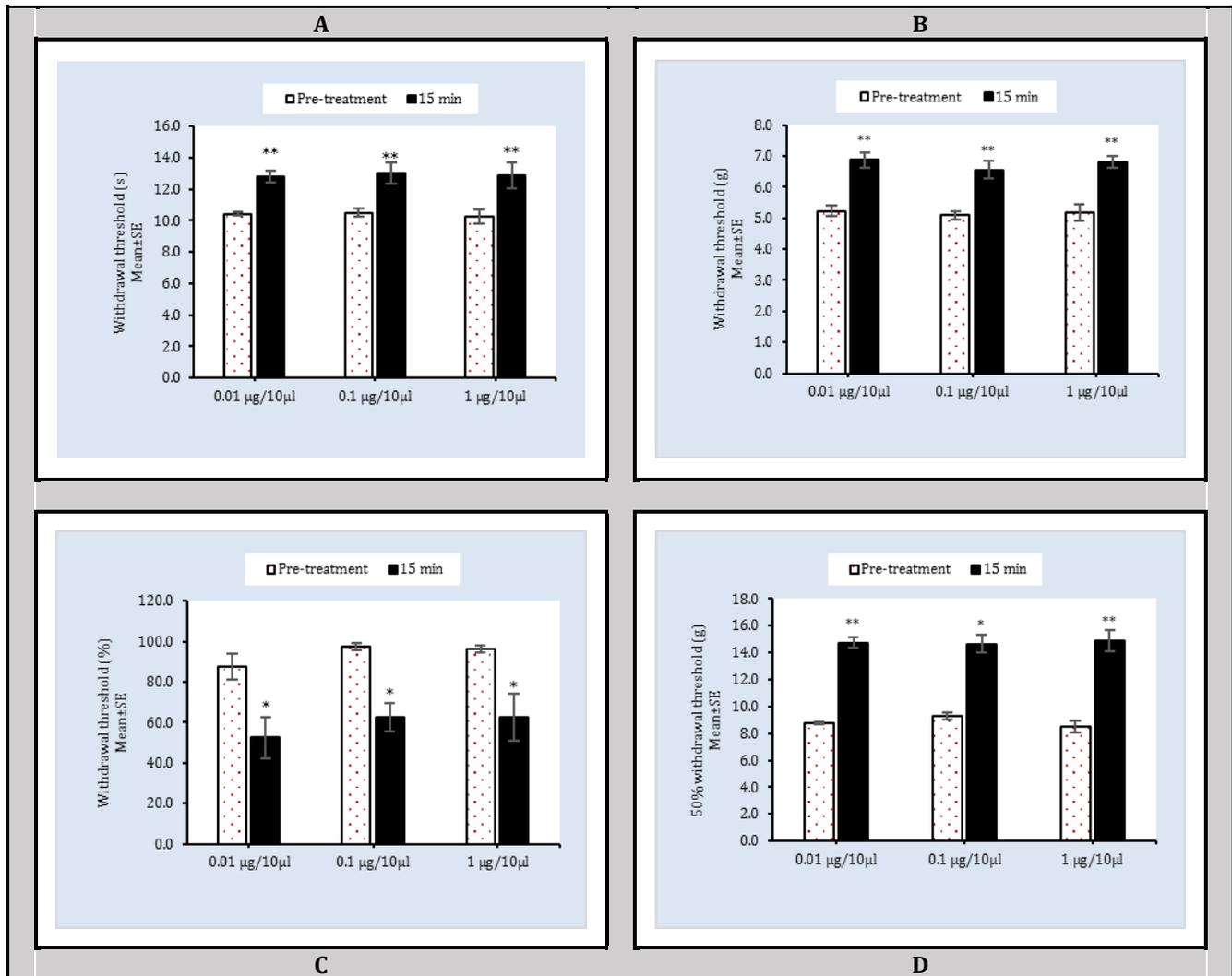


Figure 1: Effectiveness of different muscimol dose administration on reducing the neuropathic pain. Data are presented as Mean±SEM. A: heat hyperalgesia; B: mechanical hyperalgesia; C: cold allodynia; D: mechanical allodynia. **have a significant difference in $p < 0.001$ with before administration time; *shows a significant difference in $p < 0.01$ with before administration time. The significance level was defined in terms of Two-way ANOVA test. [↑](#)

should be noted that mechanical allodynia (tactile allodynia) is one of the annoying pain which always SCI patients complain of (25, 26). Therefore, Muscimol administration could be able to control mechanical allodynia. Neuropathic pain in human has presented in the first days, especially in mechanical allodynia and those of SCI which have an incomplete injury (27). Although mechanisms responsible for neuropathic pain are not fully understood, but it seems that increase in glutamate and decrease in GABA content have critical role in excitotoxicity, cell death and inflammation, neuronal plasticity and hyperstimulation (28-34). Therefore, using GABA_A agonists like muscimol could reduce these pains. The findings obtained in the present study confirmed it. Intrathecal administration of medications in SCI patients could decrease their systematic effects. Consequently, in recent years some methods like in-

trathecal pumps have been used (7, 9, 13). In this regard, the present project was evaluated the effect of intrathecal injection of muscimol on pain symptoms in a central neuropathic pain model. This method, which has favorable outcomes, has been used in controlling the acute and chronic pains. However, there are some risks aligned with using intrathecal therapy such as catheter or pumps dysfunction, catheter removal, causing inflammatory reactions, and etc (35, 36). Therefore, the investigation on this issue is still on. There are just few studies, which have evaluated the effect of muscimol administration in reducing the neuropathic pain. Among these studies, Naik et al. revealed that using muscimol in dorsal horn of the spinal cord avoid hyperalgesia. This animal study used a peripheral injury model showed that muscimol causes to improve nerve regeneration in addition to decreasing the acute



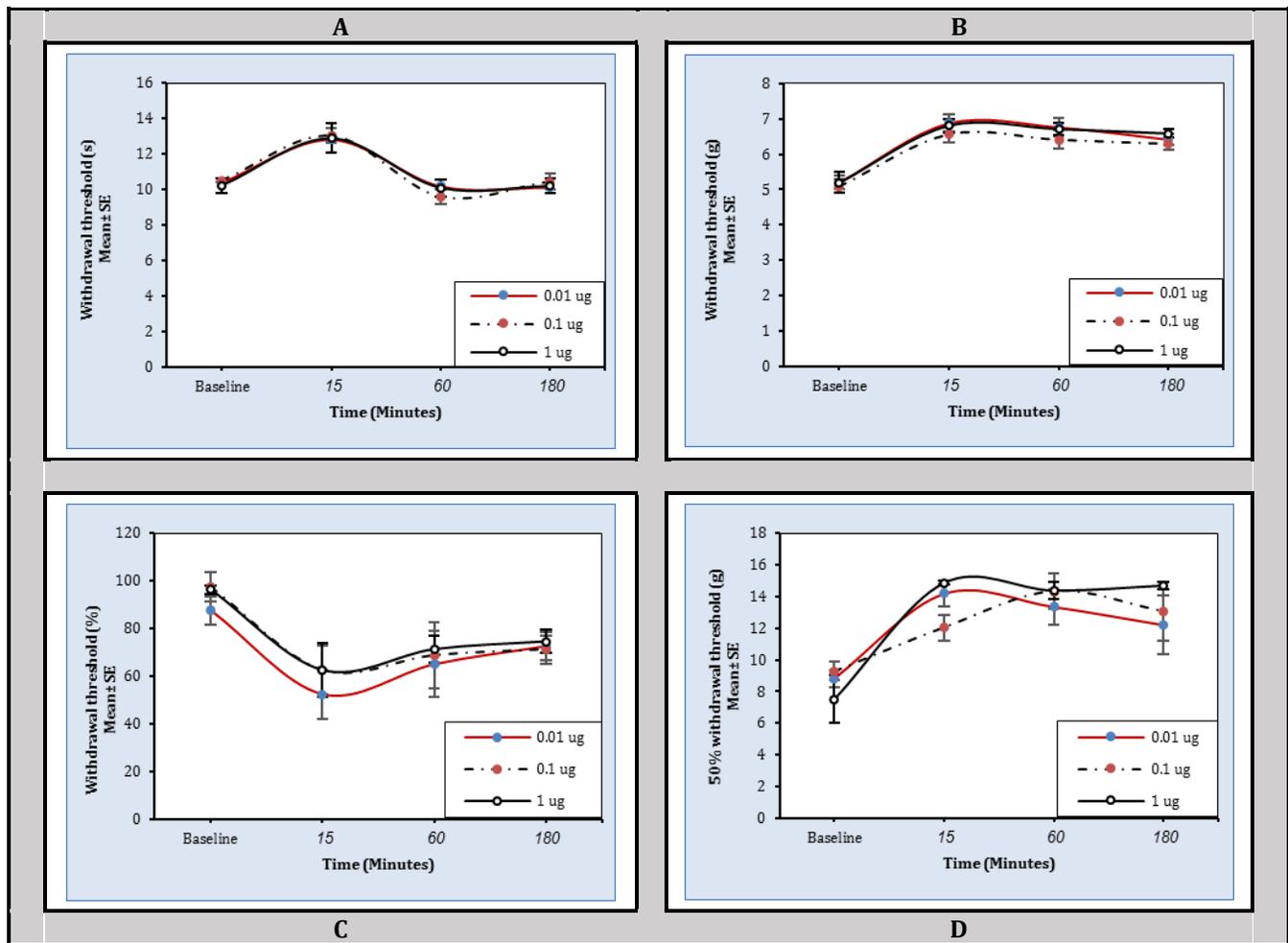


Figure 2: Effectiveness of various muscimol doses on reducing the neuropathic pain symptoms in corresponding times. A: heat hyperalgesia; B: mechanical hyperalgesia; C: cold allodynia; D: mechanical allodynia. The significance level was evaluated based on ANCOVA test. No significant difference was seen among various doses in evaluated times to reduce the neuropathic pain symptoms [↑](#)

hyperalgesia (37). These researchers also displayed in another study that muscimol causes to reduce the thermal and mechanical hyperalgesia (38). In addition, Baba et al showed that using muscimol leads to decrease irritability the A and C sensory fibers (39). These results support the present findings. Some studies evaluated the effectiveness of this drug on chronic models. For instance, Miletic et al revealed that muscimol can improve the nerve plasticity in posterior horn of the spinal cord (40). Such effects aligned with sedative role of muscimol, causes to reduce the acute neuropathic pain with neuronal growth and synaptic connections, too. The outcomes of these changes lead to improve the sensory motor function. Finally, it was found that using muscimol causes to decrease the neuropathic pain. Moreover, the efficiency of this drug progressively reduces after 15 minutes for thermal hyperalgesia. As a result, it may be possible to use muscimol combined with a long-acting drug, endomorphine, or clonidine in

treatment of neuropathic pains. Of course, more studies are needed to determine the efficiency and effectiveness of this combination therapy.

Conclusion:

The finding of the present study revealed that using muscimol with doses of 0.01 μ g, 0.1 μ g, and 1 μ g causes to reduce the symptoms of neuropathic pain. Nevertheless, its effectiveness gradually decreased after 15 minutes. Thus, combination therapies could be an appropriate option for compensation of this limitation. However, further studies are required to confirm this hypothesis.

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Conflict of interest:

None

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Authors' contributions:

FN designed the study and MY analyzed data and developed first draft of the manuscript. MH and ZK induced the animal model of SCI. AJ and ZH contributed in were assessed behavioral tests. All authors contributed substantially to its revision and take responsibility for the paper as a whole.

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