Original Article

# Clinical Evaluation of the Effect of Methylprednisolone Sodium Succinate and Meloxicam in Experimental Acute Spinal Cord Injury

**Azin Khodabakhshi Rad[1], Hossein Kazemi Mehrjerdi[1*], Mir Sepehr Pedram[2], Mohammad Azizzadeh[1], Shiva Amanollahi[1]**

*1. Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran*
*2. Department of Surgery & Radiology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran*

Use your device to scan and read the article online

**How to Cite This Article** Khodabakhshi Rad, A., Kazemi Mehrjerdi, H., Pedram,M. S., Azizzadeh, M., & Amanollahi, S. (2023). Clinical Evaluation of the Effect of Methylprednisolone Sodium Succinate and Meloxicam in Experimental Acute Spinal Cord Injury. *Iranian Journal of Veterinary Medicine, 17*(2), 129-138. http://dx.doi.org/10.32598/ijvm.17.2.1005246

http://dx.doi.org/10.32598/ijvm.17.2.1005246



## ABSTRACT

**Background:** Central nervous system (CNS) has limited repair capacity, and any spinal cord injury (SCI) can cause persistent disability in motor, sensory, and autonomic functions. The harmful reactions around the lesion must be stopped to prevent this consequence.

**Objectives:** The present study compares the clinical effects of methylprednisolone sodium succinate (MPSS) and meloxicam in acute spinal cord injury in an animal model of rats.

**Methods:** We randomly divided 24 male Wistar rats into 4 groups: 1) sham, 2) placebo, 3) SCI+MPSS (30 mg/kg, IV), and 4) SCI+meloxicam (1 mg/kg, SC). We used a Fogarty embolectomy catheter to induce a compression injury to the rats' T8-T9 spinal cord segment. The drugs were injected one hour after surgery. Neurological evaluation was performed using BBB (Basso, Beattie, and Bresnahan) test immediately after recovery and then once a week for up to 6 weeks.

**Results:** According to the BBB test results, single-dose administration of MPSS one hour after injury improved motor function significantly compared to placebo. But, there was no significant difference between MPSS and meloxicam groups and between meloxicam and placebo groups ($P>0.01$).

**Conclusion:** In clinical evaluation, single-dose administration of MPSS one hour after injury improved motor function compared to meloxicam.

**Keywords:** BBB (Basso, Beattie, and Bresnahan) test, Meloxicam, Methylprednisolone sodium succinate, Non-steroidal anti-inflammatory drugs (NSAIDs), Spinal cord injury (SCI)

**Article info:**
**Received:** 12 Sep 2022
**Accepted:** 16 Nov 2022
**Publish:** 01 July 2023

*** Corresponding Author:**
*Hossein Kazemi Mehrjerdi, Associate Professor.*
***Address:*** *Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran.*
***Phone:*** *+98 (51) 3880 5611*
***E-mail:*** *h-kazemi@um.ac.ir*

## 1. Introduction

A traumatic spinal cord injury (SCI) is a devastating event that results in disturbances in normal sensory, motor, or voluntary function and ultimately reduces physiological and psychological status and the patient's quality of life (Fehlings et al., 2017; Ulndreaj et al., 2017). This damage includes the primary and secondary phases (Fehlings et al., 2017). Secondary injury of SCI begins within seconds or minutes of the primary injury and lasts for several weeks or months, leading to the affected tissue's expansion (Alizadeh et al., 2019). Fracture or dislocation followed by the first spinal cord trauma results in minor bleeding in the white and gray matter, axonal injury, and damage to the cell membrane. Following initial injury, pathophysiological events disrupt neuronal homeostasis, apoptosis, tissue destruction, and free-radical-induced lipid peroxidation (Wilson et al., 2013). In most mammals, regeneration of the damaged axons in the central nervous system (CNS) is not spontaneous; but the peripheral nervous system axons regenerate after peripheral nerve damage (Vaquie et al., 2019; Silver et al., 2015). Sensory-motor function after SCI depends on the amount of the remained healthy white matter in the damaged site and the enhancement of neural plasticity (Beattie et al., 2000; Zhang et al., 2021). Degeneration of axons' myelin, loss of neurons and glial cells, ischemia, and inflammation cause glial scars and cystic cavities in the spinal cord (Ahuja et al., 2016; Anderson et al., 2016). These changes are progressive in the chronic phase of the injury and, in combination with poor endogenous remyelination, axonal regrowth, and intrinsic recovery potential of SCI, cause permanent neurological deficits (Ahuja et al., 2017; Ahuja & Fehlings, 2016). So, preventing myelin destruction and promoting its production effectively help treat traumatic SCI. Targets of medical therapy in the acute phase of the SCI affect the white matter, prevents secondary injuries, and preserve myelin (Beattie et al., 2000). Various compounds are effective in improving SCI in laboratory animals. These compounds include synthetic corticosteroids, non-steroidal anti-inflammatory drugs, dimethyl sulfoxide, naloxone, thyrotropin-releasing hormone, selenium and vitamin E, systemic hypothermia, Riluzole, Imatinib and magnesium (Kjell and Olson, 2016). In addition, plants like Chassalia curviflora have anti-inflammatory and analgesic effects (Greeshma et al., 2018; Salleh et al., 2021) and recently shown that leaves extract of this plant has the highest neuropharmacological effects (Islam et al., 2022). Also, it has been shown that Manna of Hedysarum ethanolic extract has an antinociceptive effect in mice and possibly acts on opioidergic, nitrergic, histaminergic, and serotonergic systems (Nikjooy et al., 2022). To reduce neuropathic pain as a chronic condition, testosterone has an anti-nociceptive activity, and this effect is mediated by the opioidergic, GABAergic, and dopaminergic receptors (Rezaei et al., 2022).

Methylprednisolone sodium succinate (MPSS) is a synthetic corticosteroid with intense anti-inflammatory effects and neuroprotection potential in acute traumatic SCI (Ulndreaj et al., 2017; Fehlings et al., 2017). This drug effectively prevents the loss of spinal cord neurofilament proteins, inducing impulse conduction, improving blood flow, and enhancing $Na^+$ and $K^+$ ATPase activity. It also protects the spinal cord structure by decreasing lipid peroxidation and preventing ischemia-induced tissue damage (Hall & Braughler, 1982 a, b). Although MPSS has been proposed as the first-line treatment for acute SCI, the debate remains because of this drug's extra dose, timing, efficacy, and side effects reported in recent decades. If administered within 8 hours of injury, this drug produces a small but clinically significant recovery in neurological function (Ulndreaj et al., 2017; Fehlings et al., 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory and neuroprotective effects (Kopp et al., 2012). These drugs are oligodendrogenesis and promote myelin production (Fu et al., 2007; Xing et al., 2011; Cheli et al., 2015; Fan et al., 2015; Preisner et al., 2015). Limiting secondary injury, fiber, and axonal regeneration and enhancing functional recovery are the effects of NSAIDs on animal models of SCI that have been reported in some studies (Hayta & Elden, 2018).

Meloxicam is a long-acting preferential cyclo-oxygenase-2 (COX-2) inhibitor with analgesic, antipyretic, and anti-inflammatory properties (Maseda & Ricciotti, 2020) and the therapeutic index of meloxicam is higher than that of other NSAIDs. Oral meloxicam is not indicated for managing acute pain (Pedram et al., 2018; Singla et al., 2018). COX-2 inhibitors are neuroprotective and reduce prostanoid and free radical synthesis. Also, it was previously shown that meloxicam has neuroprotective effects in experimental brain injury due to trauma (Hakan et al., 2010).

There are many reports of MPSS administration as the first line of treatment for acute SCI, but its use is still controversial because of its complications. Our study aims to compare MPSS and meloxicam in clinical improvement and functional effect of the spinal cord following acute compression injury in rats and whether meloxicam is a suitable alternative to MPSS in reducing acute spinal cord injury.

## 2. Materials and Methods

### Experimental groups

Twenty-four adult male Wistar rats, 16-20 weeks old, weighing 300-350 g, were used for this study. They had minimal variations in the spinal canal diameter. Animals before and after surgery were housed in separate cages with food pellets and water in a ventilated, humidity (65%-70%) and temperature (21ºC±2ºC) controlled room with a 12:12 h cycle of light and dark. The rats were randomly divided into four groups. In group 1, skin and muscle incisions were made without causing spinal cord injury. Group 2 underwent spinal cord injury and received distilled water subcutaneously. Group 3, one hour after SCI, received MPSS (Pfizer company) in a single dose (30 mg/kg) intravenously (lateral coccygeal vein). Group 4, one hour after SCI, received meloxicam 2% (Razak Company, Iran, Tehran) subcutaneously in a single dose (1 mg/kg). Our study followed the guidelines of the Iran Animal Care Committee.

### Surgical procedure

After intramuscular anesthesia, induced with an anesthetic cocktail composed of ketamine 10% (75 mg/kg, Bremer Pharma GMBH, Germany) plus xylazine 2% (10 mg/kg, Alfasan, Netherlands), animals were maintained with isoflurane (Isoflurane®, United Kingdom) via face mask throughout the operation. The back of animals was shaved, scrubbed, and under sterile condition, a 2 cm longitudinal midline incision was made over spinous processes of T10-L1 vertebrae. The soft tissue was removed until the paravertebral muscles were exposed. These muscles were dissected. The spinous process of T10/T11 was removed with a small scissor. Then a micro-motor created a small 2 mm hole in the dorsal lamina of T10/T11 vertebrae to put and guide the catheter into the spinal cord canal. A Fogarty catheter (2 French) (Penrose Medical, Ivry Le Temple, France) that was filled with normal saline and connected to an air-tight 50 µL Hamilton syringe (Hamilton Co; Reno, NV, USA) was placed into the epidural space and advanced 1 cm until the balloon of the catheter rest at the T8-T9 spinal cord level (Figure 1). The balloon was filled with 20 µL normal saline, then deflated and removed after 5 min (Pedram et al., 2010). Eventually, soft tissues and skin were sutured (Pedram et al., 2018; Vanický et al., 2001).

After the rats recovered from anesthesia, they were placed in separate cages, and the bladder was emptied daily by hand until the bladder voluntary reflex returned. Antibiotic therapy with diluted enrofloxacin 10% (10 mg/kg, q 24 h, Rooyan Darou, Iran, Tehran) was carried out for 1 week (Pedram et al., 2018; Vanický et al., 2001). After surgery, 2 mL of Ringer serum was injected subcutaneously to compensate for lost blood volume during surgery and to provide glycemia.

### Behavioral analysis

The first behavioral analysis with Basso-Beattie-Bresnahan (BBB) was performed immediately after the rats recovered from anesthesia by two blinded observers. So, the locomotor rating scale from 0 (complete paralysis) to 21 (normal gate) was rated (Hall & Braughler, 1982 a, b). It was performed after recovery (one day after surgery) and then continued once a week for up to 6 weeks. Manual expression of the bladder was performed before giving locomotion scoring. For this test, we used a circular plate that was 90 cm in diameter, and its height was 21 cm. The rats were placed on this plate for 2 min, and their function was observed, recorded by video camera, and scored (Pedram et al., 2018).

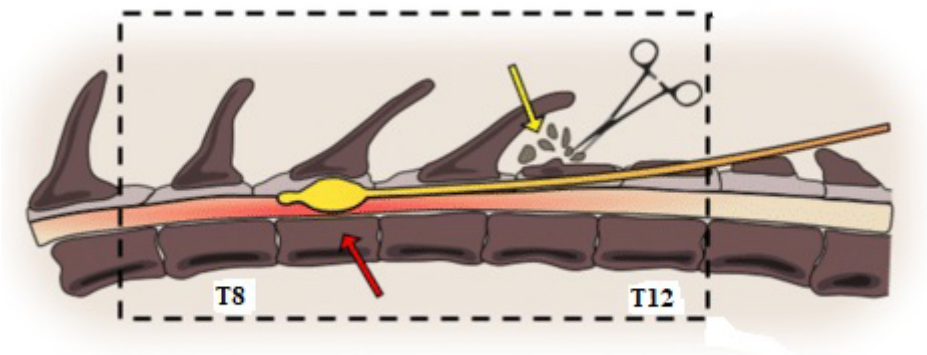


**Figure 1.** Schematic drawing showing the induction of spinal cord injury (Murgoci et al., 2020)

### Statistical analysis

The behavioral function scorings were compared across the experimental groups using the Kruskal-Wallis and Mann-Whitney U tests to determine significant pairwise differences between groups. Due to multiple pairwise comparisons, a significant level was set at $P<0.01$. All tests were performed by SPSS software, version 21 (SPSS Inc., Chicago, IL).

## 3. Results

All experimental rats had no movement and muscle tone in the hindlimbs after SCI, and urine retention was seen in the paraplegic animals.

Our results showed that locomotion scorings between some groups were significant ($P<0.01$). Also, MPSS and meloxicam had no side effects at the given dose. On the calculation of the mean recovery index, it was observed that MPSS produced better clinical recovery than meloxicam after 1 h following SCI. Still, this effect was not significant ($P>0.01$). Also, the locomotion score in the meloxicam group was not significantly different from the placebo group in any of the study weeks ($P>0.01$). Still, in terms of clinical improvement, it was better. The locomotion score in the placebo group was significantly lower in weeks 1 to 6 than in the MPSS group ($P=0.004$ in all weeks). Bar charts and box plots show the movement score distribution in the groups during the 6 weeks (Figure 2). These graphs showed that the recovery rate in the MPSS group was better than that in the meloxicam group.

## 4. Discussion

MPSS has been recommended as the first-line treatment for acute spinal cord injury. However, its clinical use is controversial due to its moderate benefits but serious side effects (Sámano et al., 2016). Due to the side effects of steroid drugs, alternative therapies are trying nowadays. Therefore, many studies have compared the effects of MPSS with other drugs and therapeutic methods on acute spinal cord injury. NSAIDs such as meloxicam have been shown to increase axonal growth and improve locomotion scores following SCI. These drugs prevent the inflammation and damage of oligodendrocytes and produce myelin (Pedram et al., 2018). Since no comparison was made between MPSS and meloxicam on improving locomotion function 1 h after acute SCI, we decided to perform this study.

The present study showed that a single dose of MPSS (30 mg/kg) effectively improved postoperative locomotion function and did not have side effects from repeated and high doses, side effects, such as stomach bleeding, septicemia, lung infection, myopathy, and wound infection. Different results showed that this beneficial effect is

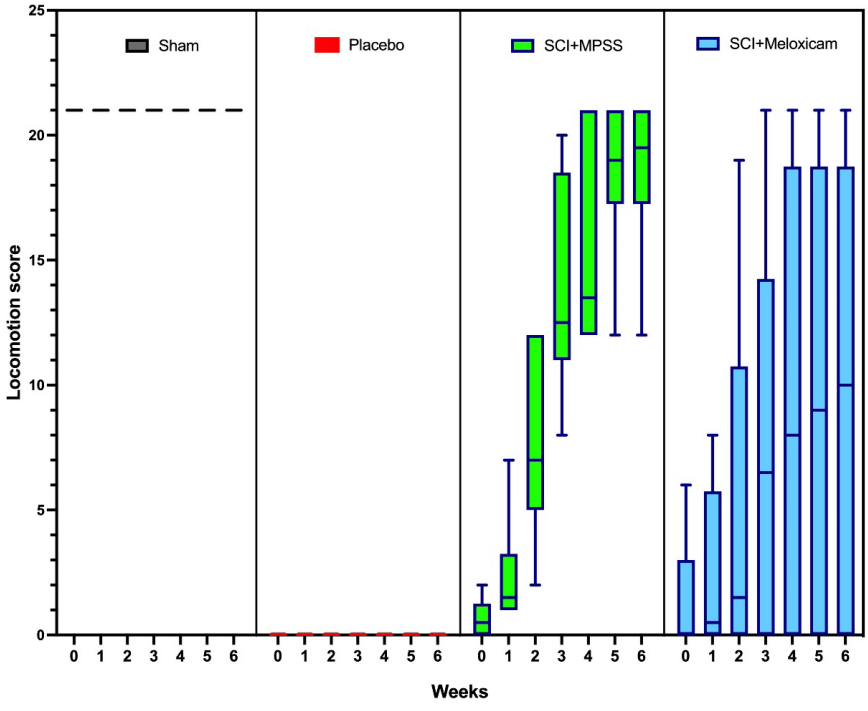


**Figure 2.** Representation of locomotion score as a function of time with bar charts and box plots

observed only at 30 mg/kg (Bracken et al., 1992). Saien et al. study (2013) show that alpha lipoic acid is as effective as MPSS (single dose of MPSS, 30 mg/kg, intraperitoneally, immediately after trauma) in neuroprotection after SCI (Sayin et al., 2013). Topsakal et al. (2002) reported the effects of methylprednisolone and dextromethorphan on lipid peroxidation in rat animal models of SCI. Methylprednisolone (single dose, 30 mg/kg, intraperitoneally) was administered at the time of injury. They showed that combined therapy of MPSS and dextromethorphan did not benefit MPSS/dextromethorphan single therapies (Topsakal et al., 2002). Other studies also have shown that repeated or divided, and reduced doses of MPSS can improve locomotion function. Their results were similar to ours with single-dose administration of MPSS. In the report of Seo et al. (2015), MPSS (30 mg/kg) was administered intraperitoneally after surgery, then after 1 hour, 5.4 mg/kg/h×23 h was injected subcutaneously. They indicated that MPSS inhibited apoptosis and autophagy and had neuroprotective effects in the SCI (Seo et al., 2015). Means et al. (1981) suggested that administration of MPSS (15 mg/kg, IV) one hour after injury and then divided doses of MPSS (15 mg/kg/d, IM) for a total of 9 days would promote recovery, preserve spinal cord tissue and enhance microvascular perfusion in feline SCI (Means et al., 1981).

The time of administration of MPSS after SCI is one of the particular variables in the experimental studies. The present study showed that administration of MPSS one hour after induction of SCI improved clinical recovery and locomotion score. The therapeutic intervention time is within the first 4 hours before hemorrhagic necrosis and tissue edema becomes significant. Steroids should be given up to 1 hour after the onset of ischemia to be effective (Means et al., 1981). Progressive reduction in blood flow within 1-2 h after SCI showed in gray matter, while the changes in mean white matter blood flow are less dramatic. Within 2, 4, and 6 h, neuronal and axonal degeneration occurs with accompanying edema, ischemia, and advanced structural degeneration (Sharma et al., 2004). Rosado et al. (2014) evaluated the effect of MPSS (30 mg/kg, intravenously in the lateral coccygeal vein, 3 h after laminectomy), alone or in association with dantrolene sodium on experimental spinal cord injury in rats. They concluded that administration of MPSS, dantrolene sodium, or a combination of these drugs 3 h after laminectomy did not prevent neuronal, glial loss, and apoptosis or promote functional recovery (Rosado et al., 2014). This study confirms the effectiveness of early administration of methylprednisolone immediately after spinal cord injury.

Contrary to reported studies, Pereira et al. (2009) showed that administration of methylprednisolone (30 mg/kg) intraperitoneal bolus 10 min after injury and then with dosing of 5.4 mg/kg/h for 23 hours was ineffective in improving locomotor function after an injury. The results of this study indicated that using this dosage of MPSS following acute spinal cord contusion did not affect neurological recovery after 7 weeks than with the vehicle group (Pereira et al., 2009).

NSAIDs in secondary injuries prevent different axonal growth inhibitors, injury expansion, and cellular death; they considerably affect the healing of the SCI and improve motor function (Fu et al., 2007; Xing et al., 2011; Zhou et al., 2003). NSAIDs affect axonal patency in mammals and are a definitive treatment method for CNS injuries (Xing et al., 2011). NSAIDs can prevent the destruction of oligodendrocytes and deficient axonal and myelin regeneration following SCI in the CNS (Wu & Ren, 2009). NSAIDs inhibit the RhoA molecule, increase regeneration and neuroprotection effects, and cause functional recovery following SCI (Kopp et al., 2012). By reducing oxidative reactions, meloxicam can protect the spinal cord against biochemical and histopathological changes, prevents leucocyte migration to the injured area, limits inflammation following SCI, and causes improvement in functional recovery (Hakan et al., 2011).

Scoring observations of this study showed that, although there was a clinically significant improvement in locomotion score in the meloxicam treatment group than in the placebo group, the difference was not statistically significant. Also, the recovery rate in the MPSS group was greater than in the meloxicam group.

Pedram et al. (2018) reported that the combination therapy of photobiomodulation and meloxicam had an important role in treating acute experimental SCI. In this study, meloxicam was injected subcutaneously in the first week (1.0 mg/kg/d) and in the second week (0.5 mg/kg/d). They concluded that the administration of meloxicam alone and with photobiomodulation improved motor function compared to the control group, but it was not statistically significant between treatment groups (Pedram et al., 2018). The difference between the results of this report and the present study may be due to differences in the timing and numbers of administration of meloxicam as well as in the pharmaceutical company produced.

The effects of inhibitory and neuroprotective meloxicam in rats' diffuse brain injury models were shown (Hakan et al., 2010). In a study, 30–60 min after induction of SCI, meloxicam (2 mg/kg/d) intraperitoneally was injected, and then it lasted for a week. It was finally determined that meloxicam improved histological and neurological conditions and had a neuroprotection effect on spinal cord trauma in rats. Meloxicam inhibited free radicals produced by lipid peroxidation, neutrophil infiltration, and DNA damage in SCI and had anti-inflammatory properties. Similar to our study, in the report of Hakan, locomotion scores were better in the meloxicam-treated group, probably due to repeated prescriptions, but it was not statistically significant compared to the control group (Hakan et al., 2010).

Aiello et al. (2015) evaluated the effects of prednisone and meloxicam in treating rats that underwent acute SCI. MPSS and meloxicam treatment groups received MPSS and meloxicam with a dosage of 2 mg/kg, IP, every 24 h for 72 h. The beginning of administering two drugs was 60 minutes after the surgical procedure in all the groups. They showed that meloxicam and MPSS could exhibit antioxidant effects and neuroprotective action, but the necrosis and Wallerian degeneration did not stop in rats that underwent acute SCI compared to the control group. Also, they reported that meloxicam had an antioxidant activity that was more prolonged than the group treated with MPSS, mainly due to decreased catalase activity (Aiello et al., 2015). Similar to our study, they administered meloxicam and MPSS one hour after the spinal cord injury. Meloxicam inhibits COX-2 and prevents membrane damage by initiating peroxidation and hydrolysis of lipids. They expressed that because of these features, meloxicam has fewer side effects and better clinical recovery than MPSS. Perhaps the reason for the difference between this study and the present study was the increase and repetition of the meloxicam dosage in this study. In our study, and based on other studies (Bracken et al.,1992), it has been shown that MPSS should be administered at 30 mg/kg within one hour after injury to be effective. The reduced dose of methylprednisolone (2 mg/kg) in the study of Aiello et al. (2015) is a clear reason for the reduced effect of methylprednisolone compared to meloxicam.

Also, Hayta & Elden (2018), in a study, stated that the administration of different NSAIDs in animal models of SCI is not significantly associated with an improvement in locomotor function (Hayta & Elden, 2018).

## 5. Conclusion

Our experimental study showed that administration of MPSS and meloxicam one hour after contusion could have beneficial effects on clinical improvement followed by acute SCI in rat animal models compared to the placebo group. However, the results in the meloxicam group were not statistically significant compared to the placebo group. Moreover, results revealed that the onset of MPSS effects, clinical recovery, and locomotion score is way faster than that in the meloxicam group. Histopathological evaluation methods are helpful in accurate conclusions and should be considered in future studies.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles are considered in this article and the project was approved by the Research Council of the Faculty of Veterinary Medicine of Ferdowsi University of Mashhad: No.: 49019).

### Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

### Authors' contributions

Conceptualization, methodology and validation: Hossein Kazemi Mehrjerdi and Mir Sepehr Pedram; Formal analysis: Mohammad Azizzadeh; Investigation, resources and data curation: Azin Khodabakhshi Rad and Shiva Amanollahi Writing original draft, review & editing, visualization and supervision: Shiva Amanollahi, Hossien Kazemi Mehrjerdi and Azin Khodabakhshi Rad; Project adminestration and funding acquisition: Hossien Kazemi Mehrjerdi.

### Conflict of interest

The authors declared no conflict of interest.

### Acknowledgments

We thank the staff of the Faculty of Veterinary Medicine Teaching Hospital of the Ferdowsi University of Mashhad for their cooperation.

## References


Aiello, G., Mazzanti, A., Beckmann, D. V., Santos, R. P. D., Andrades, A. O. D., & Palma, H. E., et al. (2015). [Prednisona e meloxicam no tratamento de ratos submetidos ao trauma agudo da medula espinhal (Portuguese)]. *Ciência Rural*, *45*, 124-130. [DOI:10.1590/0103-8478cr20131102]

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M., Druschel, C., & Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews Disease Primers*, *3*(1), 1-21. [DOI:10.1038/nrdp.2017.18] [PMID]

Ahuja, C. S., & Fehlings, M. (2016). Concise review: Bridging the gap: Novel neuroregenerative and neuroprotective strategies in spinal cord injury. *Stem Cells Translational Medicine*, *5*(7), 914-924. [DOI:10.5966/sctm.2015-0381] [PMID] [PMCID]

Ahuja, C. S., Martin, A. R., & Fehlings, M. (2016). Recent advances in managing a spinal cord injury secondary to trauma. *F1000Research*, *5*. F1000 Faculty Rev-1017. [DOI:10.12688/f1000research.7586.1] [PMID] [PMCID]

Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms. *Frontiers in Neurology*, *10*, 282. [DOI:10.3389/fneur.2019.00282] [PMID] [PMCID]

Anderson, M. A., Burda, J. E., Ren, Y., Ao, Y., O'Shea, T. M., & Kawaguchi, R., et al. (2016). Astrocyte scar formation aids central nervous system axon regeneration. *Nature*, *532*(7598), 195–200. [DOI:10.1038/nature17623] [PMID] [PMCID]

Beattie, M. S., Farooqui, A. A., & Bresnahan, J. C. (2000). Review of current evidence for apoptosis after spinal cord injury. *Journal of Neurotrauma, 17*(10), 915-925. [DOI:10.1089/neu.2000.17.915] [PMID]

Bracken, M. B., Shepard, M. J., Collins, W. F., Jr, Holford, T. R., Baskin, D. S., & Eisenberg, H. M., et al. (1992). Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second national acute spinal cord injury study. *Journal of Neurosurgery*, *76*(1), 23–31. [DOI:10.3171/jns.1992.76.1.0023] [PMID]

Braughler, J. M., & Hall, E. D. (1984). Effects of multi-dose methylprednisolone sodium succinate administration on injured cat spinal cord neurofilament degradation and energy metabolism. *Journal of Neurosurgery*, *61*(2), 290-295. [DOI:10.3171/jns.1984.61.2.0290] [PMID]

Cheli, V. T., González, D. S., Spreuer, V., & Paez, P. M. (2015). Voltage-gated $Ca^{++}$ entry promotes oligodendrocyte progenitor cell maturation and myelination in vitro. *Experimental Neurology*, *265*, 69-83. [DOI:10.1016/j.expneurol.2014.12.012] [PMID] [PMCID]

Fan, L. W., Bhatt, A., Tien, L. T., Zheng, B., Simpson, K. L., & Lin, R. C., et al. (2015). Exposure to serotonin adversely affects oligodendrocyte development and myelination in vitro. *Journal of Neurochemistry*, *133*(4), 532-543. [DOI:10.1111/jnc.12988] [PMID] [PMCID]

Fehlings, M. G., Tetreault, L. A., Wilson, J. R., Kwon, B. K., Burns, A. S., & Martin, A. R., et al. (2017). A clinical practice guideline for the management of acute spinal cord injury: Introduction, rationale, and scope. *Global Spine Journal, 7*(3_suppl), 84S-94S. [DOI:10.1177/2192568217703387] [PMID] [PMCID]

Fehlings, M. G., Wilson, J. R., Harrop, J. S., Kwon, B. K., Tetreault, L. A., & Arnold, P. M., et al. (2017). Efficacy and safety of methylprednisolone sodium succinate in acute spinal cord injury: A systematic review. *Global Spine Journal*, *7*(3_suppl), 116S-137S. [DOI: 10.1177/2192568217706366] [PMID] [PMCID]

Fu, Q., Hue, J., & Li, S. (2007). Nonsteroidal anti-inflammatory drugs promote axon regeneration via RhoA inhibition. *Journal of Neuroscience*, *27*(15), 4154-4164. [DOI:10.1523/JNEUROSCI.4353-06.2007] [PMID] [PMCID]

Greeshma, K. C., Kumar, N. M., & Krishna, J. G. (2018). Preliminary pharmacognostical and phytochemical analysis of chassalia curviflora (wall.) thwaites roots. *Journal of Pharmacognosy and Phytochemistry*, *7*(6), 1043-1048. [Link]

Hakan, T., Toklu, H. Z., Biber, N., Ozevren, H., Solakoglu, S., & Demirturk, P., et al. (2010). Effect of COX-2 inhibitor meloxicam against traumatic brain injury-induced biochemical, histopathological changes and blood-brain barrier permeability. *Neurological Research*, *32*(6), 629-635. [DOI:10.1179/016164109X12464612122731] [PMID]

Hakan, T., Toklu, H. Z., Biber, N., Celik, H., Erzik, C., & Oğünç, A. V., et al. (2011). Meloxicam exerts neuroprotection on spinal cord trauma in rats. *International Journal of Neuroscience, 121*(3), 142-148. [DOI:10.3109/00207454.2010.537415] [PMID]

Hall, E. D., & Braughler, J. M. (1982). Glucocorticoid mechanisms in acute spinal cord injury: A review and therapeutic rationale. *Surgical Neurology*, *18*(5), 320-327. [DOI:10.1016/0090-3019(82)90140-9] [PMID]

Hall, E. D., & Braughler, J. M. (1982). Effects of intravenous methylprednisolone on spinal cord lipid peroxidation and (Na++ K+)-ATPase activity: Dose-response analysis during 1st hour after contusion injury in the cat. *Journal of Neurosurgery*, *57*(2), 247-253. [DOI:10.3171/jns.1982.57.2.0247] [PMID]

Hayta, E., & Elden, H. (2018). Acute spinal cord injury: A review of pathophysiology and potential of non-steroidal anti-inflammatory drugs for pharmacological intervention. *Journal of Chemical Neuroanatomy, 87*, 25-31. [DOI:10.1016/j.jchemneu.2017.08.001] [PMID]

Islam, F., Akter, A., Mimi, A. A., Urmee, H., Islam, M. R., & Rahaman, M. S et al. (2022). Neuropharmacological effects of chassalia curviflora (rubiaceae) leaves in Swiss albino mice model. *Archives of Razi Institute*, *77*(2), 881-890. [DOI:10.22092/ARI.2021.356880.1937] [PMID] [PMCID]

Kjell, J., & Olson, L. (2016). Rat models of spinal cord injury: From pathology to potential therapies. *Disease Models & Mechanisms, 9*(10), 1125-1137. [DOI:10.1242/dmm.025833] [PMID] [PMCID]

Kopp, M. A., Liebscher, T., Niedeggen, A., Laufer, S., Brommer, B., & Jungehulsing, G. J., et al. (2012). Small-molecule-induced rho-inhibition: NSAIDs after spinal cord injury. *Cell and Tissue Research*, *349*(1), 119-132. [DOI:10.1007/s00441-012-1334-7] [PMID] [PMCID]

Maseda, D., & Ricciotti, E. (2020). NSAID-gut microbiota interactions. *Frontiers in Pharmacology*, *11*, 1153. [DOI:10.3389/fphar.2020.01153] [PMID] [PMCID]

Means, E. D., Anderson, D. K., Waters, T. R., & Kalaf, L. (1981). Effect of Methylprednisolone in compression trauma to the feline spinal cord. *Journal of Neurosurgery*, *55*(2), 200-208. [DOI:10.3171/jns.1981.55.2.0200] [PMID]

Murgoci, A. N., Baciak, L., Cubinkova, V., Smolek, T., Tvrdik, T., & Juranek, I., et al. (2020). Diffusion tensor imaging: Tool for tracking injured spinal cord fibres in rat. *Neurochemical Research*, *45*(1), 180-187. [DOI:10.1007/s11064-019-02801-9] [PMID]

Nikjooy, N., Asghari, A., Hassanpour, S., & Arfaee, F. (2022). Study of anti-nociceptive role of the manna of hedysarum and the neurotransmitter systems involved in mice. *Iranian Journal of Veterinary Medicine*, *16*(3), 265-273. [DOI:10.22059/IJVM.2022.332803.1005202]

Pedram, M. S., Dehghan, M. M., Shojaee, M., Fekrazad, R., Sharifi, D., & Farzan, A., et al. (2018). Therapeutic effects of simultaneous photobiomodulation therapy (PBMT) and meloxicam administration on experimental acute spinal cord injury: Rat animal model. *Journal of Photochemistry and Photobiology B: Biology*, *189*, 49-54. [DOI:10.1016/j.jphotobiol.2018.09.022] [PMID]

Pedram, M. S., Dehghan, M. M., Soleimani, M., Sharifi, D., Marjanmehr, S. H., & Nasiri, Z. (2010). Transplantation of a combination of autologous neural differentiated and undifferentiated mesenchymal stem cells into injured spinal cord of rats. *Spinal Cord*, *48*(6), 457-463. [DOI:10.1038/sc.2009.153] [PMID]

Preisner, A., Albrecht, S., Cui, Q. L., Hucke, S., Ghelman, J., & Hartmann, C., et al. (2015). Non-steroidal anti-inflammatory drug indometacin enhances endogenous remyelination. *Acta Neuropathologica*, *130*(2), 247-261. [DOI:10.1007/s00401-015-1426-z] [PMID]

Pereira, J. E., Costa, L. M., Cabrita, A. M., Couto, P. A., Filipe, V. M., & Magalhães, L. G., et al. (2009). Methylprednisolone fails to improve functional and histological outcome following spinal cord injury in rats. *Experimental Neurology*, *220*(1), 71-81. [DOI:10.1016/j.expneurol.2009.07.030] [PMID]

Rezaei, S., Asghari, A., Hassanpour, S., & Arfaei, F. (2022). Anti-nociceptive mechanisms of testosterone in unilateral sciatic nerve ligated male rat. *Iranian Journal of Veterinary Medicine*, *16*(1), 36-45. [DOI:10.22059/IJVM.2021.314813.1005143]

Rosado, I. R., Lavor, M. S. L., Alves, E. G., Fukushima, F. B., Oliveira, K. M., & Silva, C. M. O., et al. (2014). Effects of methylprednisolone, dantrolene, and their combination on experimental spinal cord injury. *International Journal of Clinical and Experimental Pathology*, *7*(8), 4617. [PMID] [PMCID]

Salleh, W. M. N. H. W., Nafiah, M. A., & Khamis, S. (2021). Chemical composition and acetylcholinesterase inhibitory activity of chassalia curviflora (wall.) thwaites essential oil. *Rivista Italiana Delle Sostanze Grasse*, *98*(2), 139-143. [Link]

Sámano, C., Kaur, J., & Nistri, A. (2016). A study of methylprednisolone neuroprotection against acute injury to the rat spinal cord in vitro. *Neuroscience*, *315*, 136-149. [DOI:10.1016/j.neuroscience.2015.12.003] [PMID]

Sayin, M., Temiz, P., Var, A., & Temiz, C. (2013). The dose-dependent neuroprotective effect of alpha-lipoic acid in experimental spinal cord injury. *Neurologia i Neurochirurgia Polska*, *47*(4), 345-351. [DOI:10.5114/ninp.2013.36207] [PMID]

Seo, J. Y., Kim, Y. H., Kim, J. W., Kim, S. I., & Ha, K. Y. (2015). Effects of therapeutic hypothermia on apoptosis and autophagy after spinal cord injury in rats. *Spine*, 40(12), 883-890. [DOI:10.1097/BRS.0000000000000845] [PMID]

Sharma, A., Tiwari, R., Badhe, P., & Sharma, G. (2004). Comparison of methylprednisolone with dexamethasone in treatment of acute spinal injury in rats. *Indian Journal of Experimental Biology*, *42*(5), 476–480. [PMID]

Silver, J., Schwab, M. E., & Popovich, P. G. (2015). Central nervous system regenerative failure: Role of oligodendrocytes, astrocytes, and microglia. *Cold Spring Harbor Perspectives in Biology*, *7*(3), a020602. [DOI:10.1101/cshperspect.a020602] [PMID] [PMCID]

Singla, N., Bindewald, M., Singla, S., Leiman, D., Minkowitz, H., & McCallum, S. W., et al. (2018). Efficacy and safety of intravenous meloxicam in subjects with moderate-to-severe pain following abdominoplasty. *Plastic and Reconstructive Surgery Global Open*, *6*(6). [DOI:10.1097/GOX.0000000000001846] [PMID] [PMCID]

Topsakal, C., Erol, F. S., Ozveren, F. M., Yilmaz, N., & Ilhan, N. (2002). Effects of methylprednisolone and dextromethorphan on lipid peroxidation in an experimental model of spinal cord injury. *Neurosurgical Review*, *25*(4), 258-266. [DOI:10.1007/s101430100183] [PMID]

Ulndreaj, A., Badner, A., & Fehlings, M. G. (2017). Promising neuroprotective strategies for traumatic spinal cord injury with a focus on the differential effects among anatomical levels of injury. *F1000Research*, 6. [DOI:10.12688/f1000research.11633.1] [PMID] [PMCID]

Vanický, I., Urdzíková, L., Saganová, K., Čízková, D., & Gálik, J. (2001). A simple and reproducible model of spinal cord injury induced by epidural balloon inflation in the rat. *Journal of Neurotrauma*, *18*(12), 1399-1407. [DOI:10.1089/08977150152725687] [PMID]

Vaquie, A., Sauvain, A., Duman, M., Nocera, G., Egger, B., & Meyenhofer, F., et al. (2019). Injured axons instruct schwann cells to build constricting actin spheres to accelerate axonal disintegration. *Cell Reports*, *27*(11), 3152-3166. [DOI:10.1016/j.celrep.2019.05.060] [PMID]

Wilson, J. R., Forgione, N., & Fehlings, M. G. (2013). Emerging therapies for acute traumatic spinal cord injury. *CMAJ*, *185*(6), 485-492. [DOI:10.1503/cmaj.121206] [PMID] [PMCID]

Wu, B., & Ren, X. (2009). Promoting axonal myelination for improving neurological recovery in spinal cord injury. *Journal of Neurotrauma*, *26*(10), 1847-1856. [DOI:10.1089/neu.2008.0551] [PMID]

Xing, B., Li, H., Wang, H., Mukhopadhyay, D., Fisher, D., & Gilpin, C. J., et al. (2011). RhoA-inhibiting NSAIDs promote axonal myelination after spinal cord injury. *Experimental Neurology*, *231*(2), 247-260. [DOI:10.1016/j.expneurol.2011.06.018] [PMID] [PMCID]

Zhang, H., Liu, Y., Zhou, K., Wei, W., & Liu, Y. (2021). Restoring sensorimotor function through neuromodulation after spinal cord injury: Progress and remaining challenges. *Frontiers in Neuroscience*, *15*. [DOI:10.3389/fnins.2021.749465] [PMID] [PMCID]

Zhou, Y., Su, Y., Li, B., Liu, F., Ryder, J. W., &Wu, X., et al. (2003). Nonsteroidal anti-inflammatory drugs can lower amyloidogenic Aß42 by inhibiting Rho. *Science*, *302*(5648), 1215-1217. [DOI:10.1126/science.1090154] [PMID]

مقاله پژوهشی

# ارزیابی بالینی اثر متیل پردنیزولون سدیم سوکسینات و ملوکسیکام در آسیب حاد نخاعی تجربی

آذین خدابخشی راد[1]، *حسین کاظمی مهرجردی[1]، میر سپهر پدرام[2]، محمد عزیززاده[1]، شیوا امان الهی[1]

۱. گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه فردوسی مشهد، مشهد، ایران.
۲. گروه جراحی و رادیولوژی، دانشکده دامپزشکی، دانشگاه تهران، تهران، ایران.

Use your device to scan and read the article online

**How to Cite This Article** Khodabakhshi Rad, A., Kazemi Mehrjerdi, H., Pedram,M. S., Azizzadeh, M., & Amanollahi, S. (2023). Clinical Evaluation of the Effect of Methylprednisolone Sodium Succinate and Meloxicam in Experimental Acute Spinal Cord Injury. *Iranian Journal of Veterinary Medicine, 17*(2), 129-138. http://dx.doi.org/10.32598/ijvm.17.2.1005246

doi: http://dx.doi.org/10.32598/ijvm.17.2.1005246

## چکیده

**زمینه مطالعه:** سیستم عصبی مرکزی ظرفیت ترمیمی محدودی دارد و هرگونه آسیب نخاعی می‌تواند باعث ناتوانی مداوم در عملکردهای حرکتی، حسی و خودمختار شود. برای جلوگیری از این پیامد، زنجیره‌ای از واکنش‌های مضر ایجاد شده در اطراف ضایعه باید مسدود شود.

**هدف:** در مطالعه حاضر، اثرات بالینی متیل پردنیزولون سدیم سوکسینات و ملوکسیکام بر آسیب حاد نخاعی در مدل حیوانی رت مقایسه شده است.

**روش کار:** ۲۴ رت نر ویستار را به طور تصادفی به ۴ گروه شامل: گروه شم، گروه دارونما، گروه متیل پردنیزولون سدیم سوکسینات (۳۰ میلی‌گرم به ازای هر کیلوگرم از وزن بدن، وریدی) با آسیب نخاعی و گروه ملوکسیکام (۱ میلی‌گرم به ازای هر کیلوگرم از وزن بدن، زیرجلدی) با آسیب نخاعی، تقسیم کردیم. از یک کاتتر آمبولکتومی فوگارتی برای ایجاد آسیب فشاری به قطعه T8-T9نخاع موش‌ها استفاده کردیم. داروها یک ساعت پس از جراحی تزریق شدند. ارزیابی عصبی با استفاده از آزمون بازو –بتی –برسنان، بلافاصله پس از بهبودی و سپس یک بار در هفته تا ۶ هفته انجام شد.

**نتایج:** طبق نتایج آزمون بازو –بتی –برسنان، تجویز تک دوز MPSS، یک ساعت پس از آسیب در بهبود عملکرد حرکتی نسبت به گروه دارونما موثر بود و از نظر آماری معنی‌دار بود. اما از نظر آماری بین گروه MPSS و ملوکسیکام (به ترتیب گروه های ۳ و ۴) و همچنین بین ملوکسیکام (گروه ۴) و دارونما تفاوت معنی داری وجود نداشت ( P>۰/۰۱).

**نتیجه‌گیری نهایی:** در ارزیابی بالینی، تجویز تک دوز متیل پردنیزولون سدیم سوکسینات، یک ساعت پس از آسیب، نسبت به ملوکسیکام در بهبود عملکرد حرکتی موثر بود.

**کلیدواژه‌ها:** آسیب نخاعی، داروهای ضد التهابی غیر استروئیدی، متیل پردنیزولون سدیم سوکسینات، آزمون بازو –بتی –برسنان، ملوکسیکام

تاریخ دریافت: ۲۱ شهریور ۱۴۰۱
تاریخ پذیرش: ۲۵ آبان ۱۴۰۱
تاریخ انتشار: ۱۲ فروردین ۱۴۰۲

* **نویسنده مسئول:**
حسین کاظمی مهرجردی
**نشانی:** مشهد، دانشگاه فردوسی مشهد، دانشکده دامپزشکی، گروه علوم درمانگاهی.
**تلفن:** ۳۸۸۰۳۷۰۱ (۵۱) ۹۸+
**رایانامه:** h-kazemi@um.ac.ir

**This Page Intentionally Left Blank**