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

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Abstract

BACKGROUND: CNS has confined repair capacity and any spinal cord injury (SCI) can to cause persistent disability in motor, sensory and autonomic functions. To prevent this consequence, chains of harmful reactions developing around the lesion must be blocked.

OBJECTIVES: In the present study, the clinical effects of Methylprednisolone Sodium Succinate (MPSS) and Meloxicam in acute spinal cord injury in an animal model of rats has compared.

METHODS: We randomly divided 24 male Wistar rats into 4 groups, including: 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 for inducing a compression injury to the T8-T9 segment of the spinal cord of rats. 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 was effective in improving motor function than Placebo, and was statistically significant. But, statistically, there was no significant difference between MPSS and Meloxicam

groups (groups 3 and 4 respectively), as well as between Meloxicam (group 4) and placebo. (P>0.01).

CONCLUSIONS: In clinical evaluation, single dose administration of MPSS, one hour after injury was effective in improving motor function than Meloxicam.

KEYWORDS: BBB test, Meloxicam, Methylprednisolone Sodium Succinate, NSAIDs, Spinal cord injury

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 and leading to the expansion of the affected tissue (Alizadeh *et al*., 2019). Fracture or dislocation followed by the first trauma to the spinal cord, 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 CNS is not spontaneously; but axons of the PNS, regenerate after peripheral nerve damage (Vaquie *et al.,* 2019; Silver *et al*., 2015). Sensory-motor function after SCI depends on the amount of the rest 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 development of glial scar and cystic cavities in the structural of the spinal cord (Ahuja *et al*., 2016; Anderson *et al*., 2016). This changes are progressive in the chronic phase of the injury and in combination with poor endogenous remyelination and axonal regrowth and poor intrinsic recovery potential of SCI cause permanent neurological deficits (Ahuja *et al*., 2017; Ahuja and Fehlings, 2016). So, preventing myelin destruction and promoting its production are very effective in treatment of traumatic SCI. Targets of medical therapy in the acute phase of the SCI are effect on the white matter, prevents secondary injuries, and preserves myelin (Beattie *et al*., 2000). A variety of compounds are effective in improving of SCI in the laboratory animals. These include synthetic corticosteroid, Non-Steroidal Anti-Inflammatory, 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 has 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).

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 plays an effective role in preventing the loss of spinal cord neurofilament proteins, inducing impulse conduction, improving blood flow and enhancing Na+, K+ ATPase activity. It also protects the

spinal cord structure by decreasing lipid peroxidation and preventing ischemia-induced tissue damage (Hall, and Braughler, 1982; Braughler and Hall, 1984). Although MPSS has been proposed as first-line treatment for acute SCI, the discussion has continued because of the over the optimal dose, timing, efficacy and side effects of this drug in recent decades. If this drug administered within 8 hours of injury, has small but clinically significant recovery in neurological function (Ulndreaj *et al.,* 2017; Fehlings *et al*., 2017).

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 reported in some studies (Hayta and Elden, 2018).

Meloxicam is a long-acting preferential cyclo-oxygenase-2 (COX-2) inhibitor with analgesic, antipyretic, and anti-inflammatory properties (Maseda and Ricciotti, 2020) and the therapeutic index of Meloxicam is higher than that of other NSAIDs. Oral Meloxicam is not indicated for the management of acute pain (Pedram *et al.,* 2018; Singla *et al.,* 2018). COX-2 inhibitors are neuroprotective and reducing 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 effects of MPSS as the first line of treatment for acute SCI, but because of its complication, it is still controversial. The objective of our study is to compare MPSS and Meloxicam in development of 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.

Material and methods

Experimental groups

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

Surgical procedure

After intra muscular 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 exposed. These muscles

were dissected. With small scissor, spinous process of T10/T11 was removed. Then by a micro-motor, a small two millimeter hole was created in the dorsal lamina of T10/T11 vertebrae to put and guide the catheter into the spinal cord canal. A 2-French Fogarty catheter (Penrose Medical, Ivry Le Temple, France) that filled with normal saline and connected to an airtight 50µl Hamilton syringe (Hamilton Co; Reno, NV, USA) was placed into the epidural space and advanced 1 cm until the balloon of the catheter to rest at the T8-T9 spinal cord level (Figure 1). Balloon was filled with 20 µl normal saline and then the balloon after 5 min, was deflated and removed (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 24hr, 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 observer. So that, locomotor rating scale from 0 (complete paralysis) to 21 (normal gate) was given (Hall and Braughler, 1982; Braughler and Hall, 1984). It was performed after recovery (one day after surgery), and then continued once a week for up to six weeks. Manual expression of bladder was performed before giving locomotion scoring. For performing this test, we used a circular plate that was 90 cm in diameter

and its height was 21 cm. The rats placed on this plate and for 2 min their function was observed and recorded by video camera and scored (Pedram *et al.,* 2018).

Statistical analysis

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

Result

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

Based on our results, locomotion scorings between some groups was significant ($P< 0.01$). Also, MPSS and Meloxicam had no side effects at the given dose. On calculation of the mean recovery index, it was observed that MPSS produced better clinical recovery as compared to Meloxicam that given after 1 hr following SCI but this result was not statistically significant ($P> 0.01$). Also locomotion score in the Meloxicam group was not significantly different from Placebo group in any of the study weeks ($P> 0.01$) but in terms of clinical improvement was better. The locomotion score in the Placebo group was significantly lower in weeks 1 to 6 than MPSS group (P value was 0.004 in all weeks). Bar charts and box plots showing the distribution of movement score in the different groups during the 6 weeks (Figure 2). These graphs showed that the rate of recovery in MPSS group was better than Meloxicam.

Discussion

MPSS has been recommended as first-line treatment for acute spinal cord injury. However, its clinical use is controversial due to its moderate benefits and high side effects (Sámano *et al.,* 2016). Due to the side effects of steroid drugs, it is nowadays trying to find alternative therapies. Therefore, many studies have compared the effects of MPSS with other drugs and therapies method on acute spinal cord injury. NSAIDs such as Meloxicam have been shown to increase axonal growth and improve locomotion score following SCI. This drugs prevent the inflammation and damage of oligodendrocytes and produce myelin (Pedram *et al.,* 2018). Since no comparison was made between Methylprednisolone sodium succinate and Meloxicam on the improvement of locomotion function, 1 hr after acute SCI, we decided to perform this study.

The present study showed that a single dose of MPSS (30 mg/kg) is effective in improving postoperative locomotion function and did not had side effects from repeated and high doses including hemorrhage of stomach, septicemia, lung infection, myopathy, and wound infection. Different results showed that this beneficial effect is observed only at 30 mg/kg (Bracken *et al.,* 1992). In the study of Saien *et al.* (2013), was shown 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 model of SCI. Methylprednisolone (single dose, 30 mg/kg, intraperitoneally) administered at the time of injury. They showed that combined therapy of MPSS and Dextromethorphan did not show benefit effect to 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 and their results was 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 hrs was injected subcutaneously. They indicated that MPSS inhibited apoptosis and autophagy and have neuroprotective effects in the SCI (Seo *et al.,* 2015). Means *et al*. (1981) indicated that administration of MPSS (15 mg/kg, IV) one hour after injury, and then divided doses MPSS (15 mg/kg/day, IM) for a total of 9 days causes promoting recovery, preserving spinal cord tissue and enhancing microvascular perfusion in feline SCI (Means *et al.,* 1981).

The time of administration MPSS after SCI is one of certain variables in the experimental studies. The present study showed that administration of MPSS, 1 h after induction of SCI caused improvement of clinical recovery and locomotion score. The therapeutic intervention time is within the first 4 hours, before hemorrhagic necrosis and tissue edema become 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 hrs after SCI showed in gray matter, while the changes in mean white matter blood flow are less dramatic. Within 2 hrs, 4 hrs and 6 hrs 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 MPSS, dantrolene sodium, or combination of these drugs 3 h after laminectomy did not prevent neuronal, glial loss and apoptosis, and did not 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 minutes after injury and then with dosing of 5.4 mg/kg/h for 23 hours, at improved locomotor function after injury is ineffective. The results of this study indicated that using of this dosage of MPSS following acute spinal cord contusion had no effect on neurological recovery after 7 weeks than with vehicle group (Pereira *et al.,* 2009).

NSAIDs in secondary injuries prevents of different axonal growth inhibitors, injury expansion and cellular death, they have a considerable effect on healing of the SCI and improves motor function (Fu *et al.,* 2007; Xing *et al.,* 2011; Zhou *et al.*, 2003). In mammals, NSAIDs affects on axonal patency and are one of the definitive treatment methods of CNS injuries (Xing *et al.,* 2011). NSAIDs can prevent destruction of oligodendrocytes, deficient axonal and myelin regeneration following SCI in the CNS (Wu and Ren, 2009). NSAIDs inhibits RhoA molecule and increases regeneration and neuroprotection effects, and causes functional recovery following SCI (Kopp *et al.,* 2012*)*. Meloxicam by reducing the oxidative reactions, can protect spinal cord against biochemical and histopathological changes and prevents leucocyte migration to the injured area and limits inflammation following SCI and causes improvement functional recovery (Hakan *et al.*, 2011).

In scoring observations of this study showed that, although there was a clinically significant improvement in locomotion score in the Meloxicam treatment group than to the Placebo group, but the difference was not statistically significant. Also, the rate of recovery in the MPSS group was greater than the Meloxicam group

Pedram *et al*. (2018) reported, the combination therapy of Photobiomodulation (PBMT) and Meloxicam have an important role in treatment of experimental acute SCI. In this study, Meloxicam was injected subcutaneously in first week (1.0 mg/kg/day) and in second week (0.5 mg/kg/day). They concluded that administration of Meloxicam alone and with PBMT, improved motor function in comparison to control group, but it was not statistically significant between treatment groups (Pedram *et al.,* 2018). The difference between the results of this report and 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 of Meloxicam in the diffuse brain injury model in rats was shown (Hakan *et al*., 2010). In a study, 30–60 min after induction of SCI, Meloxicam (2 mg/kg/day) intraperitoneally was injected and then it lasted for a week. It was finally determined that Meloxicam improved histological and neurological condition and had 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 significantly in comparison to the control group (Hakan *et al*., 2011).

Aiello., *et al*. (2015), was evaluated the effects of Prednisone and Meloxicam in the treatment of rats underwent to acute SCI. MPSS and Meloxicam treatment groups were received MPSS and Meloxicam with dosage 2mg/kg, IP, every 24 hrs for 72 hrs. The beginning of the administration of two drugs were 60 minutes after surgical procedure in all the groups. They showed that Meloxicam and MPSS can exhibit antioxidant effect and neuroprotective action, but the necrosis

and Wallerian degeneration were not stop in rats underwent to acute SCI in comparison to control group. Also, they reported that, Meloxicam had antioxidant activity which was more prolonged than the group treated with MPSS, mainly due to a decrease in catalase activity (Aiello *et al.,* 2015). Similar to our study, they also administered Meloxicam and MPSS within one hour after spinal cord injury. Meloxicam inhibits COX-2 and prevents membrane damage through the initiation of peroxidation and hydrolysis of lipids. They expressed that because of these features, Meloxicam has fewer side effect and better clinical recovery in comparison to MPSS. Perhaps the reason for the difference between this study and the present study was the increase and repetition of dosage of Meloxicam 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 a dose of 30 mg/kg within one hour after injury to be effective. The reduced dose of Methylprednisolone (2 mg/kg) in the study of Aiello (Aiello *et al.,* 2015) is a clear reason for the reduced effect of Methylprednisolone compared to Meloxicam.

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

Conclusion

Our experimental study showed that administration of MPSS and Meloxicam one hour after contusion, can have usefulness effects on clinical improvement followed by acute SCI in rat animal model in comparison to Placebo group, although the Meloxicam group was not statistically significant comparison to Placebo group. Moreover, results revealed that the onset of MPSS effects, clinical recovery and locomotion score are way faster than Meloxicam.

Histopathological evaluation methods are very helpful in accurate conclusions and should be considered in future studies.

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Conflict of interest

The authors declare they have no conflicts of interest.

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

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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: 24 رت نر ویستار را به طور تصادفی به 4 گروه شامل: گروه شم، گروه دارونما، گروه متیل پردنیزولون سدیم سوکسینات (30 میلی‌گرم به ازای هر کیلوگرم از وزن بدن، وریدی) با آسیب نخاعی و گروه ملوکسیکام (1 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-T9 نخاع 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 6 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 3 و 4) و همچنین بین ملوکسیکام (گروه 4) و دارونما تفاوت معنی داری وجود نداشت ($P>0.01$).

نتیجه گیری 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.

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

Figure 1. Schematic drawing showing the induction of SCI (Murgoci et al., 2020).

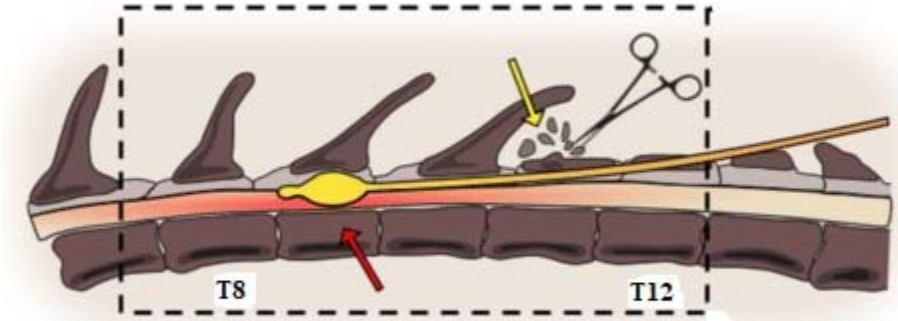

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Figure 2. Representation of locomotion score as a function of time with bar charts and box plots.