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Accentuated Rehabilitation Recovery from Spinal Cord Injury in Rats through Increased Behavioral Activity besides Minocycline Treatment: A Nursing Care Perspective

Mohammad Ahmad[1]*, Ahmad Abo Shaiqah[2], Abdualrahman Saeed Alshehri[1] and Abdulaziz Moadi Alotaibi[3]

[1]*Department of Medical Surgical Nursing, King Saud University, Saudi Arabia*

[2]*Department of Nursing Administration and Education, King Saud University, Saudi Arabia*

[3]*College of Nursing, King Saud University, Riyadh, Saudi Arabia*

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***Corresponding author:** Mohammad Ahmad, Department of Medical Surgical Nursing, College of Nursing, King Saud University, Saudi Arabia, Tel: 966-505195887; Fax: 966-11-4693625; Email: mbadshah@ksu.edu.sa

Abstract

The present study aimed at developing improved rehabilitative intervention which can accentuate known therapeutical treatment for a better functional recovery from spinal cord injury (SCI). Furthermore, this research intends to utilize the passion of nursing care by bringing awareness among nurses for SCI patient's care and opening avenues and interests in nursing research also. Young adult male rats were subjected to spinal injury and were allocated to five groups with eight animals in each, viz. Group 1 as normal uninjured control; group 2 as sham control; group 3 as SCI group with spinal injury; group 4 as SCI treated group A that were same as group 3 but were treated with a daily injection of Minocycline (50mg/kg) for 29 days and subjected to BBB behavioral test every alternate days; group 5 as SCI treated group B that were same as group 4 except that the animals were subjected to a daily enforced extra 5 tasks in same sequence as for exercises in BBB test. Minocycline had an attenuating effect on SCI in both treated groups A and B, however, the recovery in Group-B was observed to be significantly ($p<0.001$) greater than Group-A. It is concluded that enforced behavioral exercises in addition to drug treatment can enhance functional recovery. Furthermore, the present study can encourage the nurses to develop their nursing skills for SCI rehabilitation and their research abilities.

Keywords : Spinal cord injury; Rats; Minocycline; BBB scoring; Rehabilitation; Nursing care

Introduction

Suitable animal models of spinal cord injury (SCI) for experimental studies simulating clinical conditions as observed in humans, are important source to understand the pathophysiology of the disease and to develop research modalities in search of effective treatment. Even till to date, humans with traumatic SCI need satisfactory physiotherapeutically related rehabilitation process and/or drug treatment. The aim of the present study is to understand the behavioral episode that is often an important phase following the initial primary injury, and to develop suitable rehabilitative intervention along with effective pharmacological agent that may enhance sensory and motor functions in an improved manner. Furthermore, the present research design may bring an awareness among the nurse communities working in occupational health set-ups, general wards, and specialized wards, to understand the need to show their passion for SCI patient's care through exploring and learning standardized and improvised rehabilitation methods for managing and practicing effective nursing caring skills. Minocycline, a semi synthetic second-generation tetracycline, has been shown to have robust neuroprotective effects in rodent models of neurodegenerative diseases [1] and provide neuroprotection in experimental models of various neurological diseases including SCI [2-5]. Furthermore, minocycline has been shown to improve functional outcome, to reduce lesion size, to reduce cell death, and to alter cytokine expression after SCI [6-8]. In a murine model of SCI, minocycline treatment was superior to methylprednisolone, in promoting functional improvement [7] and had neuroprotective effects on SCI epicenter [9] and motor neuron recovery and neuropathic pain [10].

Thus, the present study was designed to investigate the neuroprotective effects of Minocycline on behavioral recovery from SCI. Furthermore, from the perspective of educating the nursing community from a rehabilitative awareness point of view and to assess as to if the repetitive enforcement of SCI subjects to extra sequential behavioral activities in addition to pharmacological treatment do accentuate the rehabilitation process for a better functional recovery from SCI or not?

Materials and Methods

Animals

Young adult male Sprague-Dawley rats, weighing 250-280g, bred, reared and housed under controlled conditions (diurnal 12-hour light-dark cycle, temperature 22±1 °C, humidity 50-60%, free access to food and water) in the animal facility of the College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, were used in the present study. All care was taken to minimize animal stress and suffering. Moreover, all animal practices and animal study protocols were approved by the Research and Ethics Committee of King Saud University, Riyadh, Saudi Arabia, for the humane care of animals.

Spinal cord injury (SCI)

Rats were anesthetized with chloral hydrate (450mg/kg), and were subjected to spinal trauma by the modified method of Nystrom and Berglund [11]. After shaving the back of the animal, a longitudinal incision was made on the midline of the back, exposing the paravertebral muscles. Laminectomy was performed under surgical operating binocular microscope, at T 7-8 level leaving the dura intact. SCI was produced by placing a metallic rectangular plate (2.5X5.0mm) loaded with a total weight of 35g for 5 minutes, over the exposed extradural area of the spinal cord for compression. The wound was closed in layers through aseptic surgical stitching and animals were allowed to recover from anesthesia by placing them on a warm heating pad maintained at 37±1 °C. All animals were given intramuscular injections of gentamycin at a dose of 3mg/kg for 3 days after surgery. The animals' bladders were manually pressed twice a day to avoid urinary complications until the rats were able to regain normal bladder functioning. Sham injured animals were only subjected to laminectomy with same surgical procedures without any compression.

Experimental groups

Rats were randomly allocated to the following five groups with eight animals in each group:

1. Normal control group; without any laminectomy or compression injury.

2. Sham group; with laminectomy only but no spinal compression injury.

3. SCI control group; with laminectomy surgery and spinal compression injury.

4. SCI treated groups A and B; these were same as SCI control groups except that SCI

(50mg/kg) treatment for the recovery from SCI using behavioral parameter of BBB scoring every alternate day as described below. The dose of this drug was selected on the basis of our pilot screening at low, medium and high doses (25, 50 and 100mg/kg respectively). The best effective drug dose of Minocycline (50mg/kg) was selected based on those pilot studies. The drug was administered orally in the morning session always. The first dose of the drug was administered one hour after SCI and thereafter, daily for three weeks.

Behavioral analysis

The behavioral motor functions in the form of BBB scorings were observed in the evening session and were assessed in a blind manner. The scores of each test were evaluated the next day after injury and every alternate day for 29 days after SCI for each animal. BBB scoring: Hind limb motor function (including hind limb reflexes and coordinated use of hind limbs) was assessed using the Basso-Beatie-Breshnahan (BBB) locomotor rating scores [12]. The method for scoring this BBB rating was modified in a sense that instead of placing the individual rats in an open field for the evaluation of the hind limb motor behavior, the animals were allowed to travel through a "Gait Performance Tunnel" (GPT). This innovative GPT consisted of a narrow tunnel, constructed from a wooden block of size (180X10X5cm) with side-walls made of clear perspex glass (180 X 18cm2), so that the animal movement was clearly visible from the side walls to the blinded observer and the score was assessed carefully for the rehabilitative coordinated movement of the hind limbs and placement of the hind paws. The GPT was placed at a height of 30 cm on the working table. The animal was allowed to enter at one end and travel through up to the other end. Soft bedding was placed under the other end of the GPT to avoid any injury in case of a fall from the GPT. No time was fixed for the walk in the GPT. The observer was able to assess the movements of hind limbs and placement of hind paws by the animals easily, through the Perspex glass sheet of the GPT. Hind limb function was scored from 0 (complete paralysis or paraplegia) to 21 (complete mobility).

SCI treated group-A and group-B were subjected to similar experimental processes to observe the behavioral parameter of BBB scoring every alternate day, except that the animals of group-B were further repeatedly subjected to daily additional 5 times enforced extra walking on the GPT in the same sequential order with an interval of 5 min rest between the walks. Thus, the animals of group-A after completing the BBB test on alternate days, were left in their home cages with no further disturbance. Whereas, animals of group-B, after BBB scorings, were subjected to additional daily enforced five extra walks through the GPT. After completing 5 additional extra walks, the animals were left in their home cages in a manner like group-A.

Statistical Analysis

The data from the experimental SCI group passing the normality test ($p>0.10$) were compared to the SCI uninjured control group, whereas the data of drug-treated groups were compared with the experimental SCI group using ANOVA with post-hoc testing using Tukey-Kramer Multiple Comparison Tests or Student-Newman-Keuls Multiple Comparison Tests. All results were expressed as means±SEM, and significance was defined as $p<0.05$ for the test [13].

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Results

The results indicated that treatment with the drug Minocycline induced recovery from SCI with respect to time. Although the drug had an attenuating effect on SCI in both treated groups A and B as compared to the SCI only control group, the effectiveness of this drug on the behavioral recovery in treated Group-B was significantly ($p<0.001$) greater than in treated Group-A from SCI (Figure 1). The sham group showed minimal alterations in behavioral activities and attained similar scoring levels to the naïve control groups within a few days, indicating no contusion damage in the spinal cord. Although the behavioral recovery from SCI (in the SCI only group) in 29 days was lesser significant [$F(1)=25.27$, $p<0.01$] compared to the naïve control, the drug treated SCI groups A and B showed better and improved recovery in BBB behavioral scorings compared to the SCI only control group, and the drug treated groups A and B were effective in the order of Minocycline-groupB >Minocycline-groupA ($F=10.28$ and $F=5.83$, $df=2$, $p<0.001$ and $p<0.01$, respectively) as shown in Figure 1.

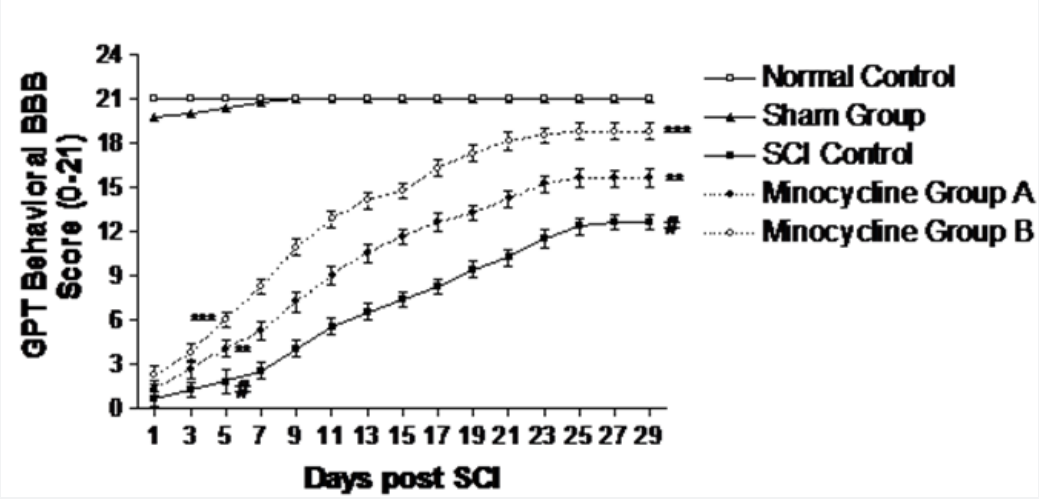

Figure 1: Effect of Minocycline on gait performance tunnel (GPT) behavioral motor performance activities (BBB Score) of hind limbs of rats subjected to spinal cord injury (SCI). The graph shows the comparative functional recovery from SCI over a period of 29 days. Animals were treated with the drugs daily after SCI for 3 weeks. Minocycline Group A is (50 mg/kg with no enforced walk) and Minocycline Group B is (50 mg/kg with daily enforced extra walk). The groups are effective in the order Group B > Group A. # shows the SCI group significantly ($p<0.001$) different from the SCI uninjured control group. ** and *** represent the SCI FK506 treated groups A and B significantly different at $p<0.01$ and $p<0.001$, respectively, compared to the SCI group by ANOVA with post-hoc testing using Tukey-Kramer or Student-Newman-Keuls Multiple Comparison Tests.

Discussion

Results of scoring from behavioral parameters of BBB for assessing the recovery from SCI in all experimental groups (Figure 1) showed that SCI group exhibited severe deficits in hind limb function and moved using only the forelimbs, dragging the paraplegic hind limbs throughout the observation period. However, treatment with Minocycline in treated groups A and B when administered systematically after SCI, resulted in significantly recovery of functional deficits starting at 1-week post injury (p. i.) as compared to the SCI group. Because the functional recovery of both treated groups A and B differentiated significantly from the SCI controls from the earliest time point studied (3 days), the mechanism of the drug under study is likely due to neuroprotection rather than tissue regeneration, as suggested earlier [13]. The treated groups recovered hind limb reflexes more rapidly, and a higher percentage of these rats regained responses comparable with those of injured untreated control rats. The treated rats also achieved a faster and greater degree of recovery of coordinated use of their hind limbs in maintaining their body position from 14 to 28 days (Figure 1).

However, between treated groups A and B the better and more significant functional recovery was observed in group B than group A. In group B the SCI animals were treated with Minocycline and additionally, were subjected to daily enforced 5 extra walks on the GPT as compared to group A. Thus, although the treated groups A and B showed improved recoveries in their BBB behavioral activities scorings, group B was comparatively better accentuated than group A and the recovery could easily be observed in the order of Minocycline group B >Minocycline group A. The only possible reason for such significant difference in the movement behavior between the two groups could be because in addition to the therapeutic effects of Minomycin, the daily enforced extra walks in group B apparently worked as a potential factor in accentuating the animal's behavioral activities resulting into a rehabilitative exercise that ultimately helped them to recover significantly at a faster pace than the animals of group A.

Conclusion

It is evidently concluded from this study that such interventions with enhanced physiotherapeutically related rehabilitation process can possibly be helpful to attenuate the

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repair in the traumatically injured spinal cord in humans as well. From the perspective of nursing care, the present study aims at serving as a model research activity for the general nurses and/or the specialized nurses working in the field of rehabilitative services to the SCI patients in particular and in general to all other fields as well, working for improved mobilization of patients for better healthcare and wellbeing. Furthermore, nowadays, emphasis is laid on the increased clinical research leading to a need of innovated, improved and standardized education on research opportunities provided to nurses also. Thus, the present study can be a source of inspiration for the inextricable link for bringing change in the delivery of nursing care by the healthcare nurses and showing their compassionate abilities in clinical nursing practices. However, further detailed studies are required to confirm this presumption.

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