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Original Article

Riluzole Can Improve Sensory and Motor Function in Patients with Acute Spinal Cord Injury

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Abstract

Background: Spinal cord injury (SCI) causes sensory, motor function and consists of a large proportion of patients that referred to trauma centers. Riluzole blocks the sodium channels and has possible supportive effects on the central nervous system. The aim of this study was to investigate the effect of riluzole on sensory and motor improvement and pain level in patients with acute SCI. **Materials and Methods:** In this clinical trial, sixty patients with acute SCI with A to C Frankel grade selected and randomly divided into two groups (each group included thirty patients). The two groups carefully matched in terms of age, sex, and Frankel class. Case group, in addition to conventional treatment, received riluzole and was evaluated after 6-week, 3-month, and 6-month periods in terms of sensory and motor status and compared with control group. **Results:** There were sixty patients divided into case and control groups. In the 6-week follow-up period and 3-month follow-up period, there was no significant difference between the two groups based on sensory and motor function (P = 0.053). In 6-month follow-up period, the difference was significant in case group (P = 0.001). **Conclusion:** The compressions between two groups demonstrated a significant difference in sensory and motor improvement and reduce pain level in patients with SCI.

Keywords: *Pain, riluzole, sensory and motor function, spinal cord injury, trauma*

Introduction

Spinal cord injury (SCI) is one of the most important sensory, motor dysfunction, and spinal nerve roots lesions.[1-3] SCI may occur as complete or incomplete lesions.[4,5] Complete lesions show the severity of SCI. The term complete injury means no existence of sensory and/or motor function more than three segments below the injury area. Incomplete injury means existence of some sensory and motor function below the injury area and not removed completely.[6,7] SCI have two stages: Primary injury due to physical injury and the secondary injury due to severe inflammatory response, vascular changes, glutamate excitotoxicity, ischemia-reperfusion injury, ionic homeostasis changes, and oxidative cell injury.[8,9] The primary changes open voltage-dependent ion channels (Ca^{++}, Na^{+}, K^{+}) that release neurotransmitters such as glutamate which open glutamate receptor-operated channels such as N-Methyl-D-aspartate receptor and α-ami no-3-hydroxy-5-methyl-4-isoxazolepropion ic acid receptor.[10] Classically, conservative treatment and surgical intervention was common for management of these patients.[11] Recently, neuroprotective treatments created more attractions for managing the SCI.[1] Riluzole blocks sodium channels and used for patients with amyotrophic lateral sclerosis (ALS) with Food and Drug Administration (FDA) approval.[12,13] Lang-Lazdunski *et al*. used riluzole in a pilot study for the treatment of SCI in rabbits.[14] Riluzole blocks voltage-activated sodium and calcium ion channels, inhibits glutamate releasing, and also activates potassium ion channels.[15,16] The blockage of Na+ channel causes neuroprotective activity in primary and early acute injury phase of SCI, and this effect could inhibit accumulation of intracellular Na+. This mechanism may protect neurons.[17] In some other studies, the advantages of riluzole demonstrated in SCIs and traumatic injuries,[18-21] but there are a few studies that investigate neuroprotective effect of riluzole in patients with sensory and motor dysfunction after SCI. Hence, the aim of this study is to investigate the effect of riluzole on sensory and motor function in patients with SCI.

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Materials and Methods

This is a clinical trial study which includes all patients with acute SCI referred to Imam Reza Hospital of Tabriz University of Medical Sciences during 1 year in 2014–2015. This clinical trial study registered in Iranian Registration of Clinical Trial Center: 201403183497. In this study, sixty patients enrolled by Professor Ali Meshkini with acute SCI and classified in A to C category based on Frankel grade. The patients randomly divided into two groups (each group included thirty members). To prevent the effects of gender on the study, men and women were equal in both groups. All patients underwent surgery. Case groups received riluzole at admission and control group did not. Inclusion criteria were as follows: acute SCI with Frankel grade A to C, age 18–70, and fracture of vertebra L2 to C4. Exclusion criteria were as follows: kidney and liver diseases, penetrating trauma, traumatic brain injuries, pregnancy or breastfeeding situation, recent consumption of alcohol, neurological diseases or mental disorders, life-threatening injuries, and oral medication disabilities. During this study, patients were investigated in four periods, at admission, 6 weeks, 3 months, and 6 months later. Riluzole was prescribed each 12 h for 8 weeks by dose of 50 mg per os for the case groups. At the end of follow-up periods, motor and sensory function and level of the pain were assessed by neurosurgeons. Level of pain in this study was assessed based on visual analog scale (VAS) system. Terms of recovery and nonrecovery were also investigated. Recovery states considered obtaining full sensory and motor function.

Ethical consideration

Written consent obtained from patients before the beginning of the study. It should be noted that all of the patient's records kept secret entirely. The study design was approved by the Ethics Committee of Tabriz University of Medical Science.

Method of data analysis

T-test for quantitative variables and Chi-square test for qualitative variables were used. Data were analyzed by SPSS™ 16. In this study, *P* value was significant <0.05 ($P < 0.05$) in terms of statistics.

Results

Finally, sixty patients (thirty patients in each group) were finished the study. There were 19 men and 11 women in case and control groups. The mean age in case group was 37.67 ± 1.8 (minimum = 23, maximum = 62) and in the control group was 36.93 ± 2.04 (minimum = 22, maximum = 64) [Table 1]. The severity of spinal cord based on Frankel grade was shown in Table 2. In 6-week follow-up period and 3-month follow-up period, patients had no significant sensory and motor improvement, but in 6-month follow-up period, the comparison between case and control group demonstrated a significant improvement in sensory and motor function improvement ($P = 0.043$). Comparisons of patient's pain based on VAS system in two groups of patients were shown in Table 3. Comparison of patient's pain degree based on VAS system after surgery demonstrated that riluzole had no significant effect on pain level in 6 weeks and 3 months. In 6-month follow-up

Table 1: The results matched in two groups at admission

	Case group, *n* (%)	Control group, *n* (%)	*P*
Sex			
Male	19 (63.3)	19 (63.3)	0.87
Female	11 (36.7)	11 (36.7)	
Age	37.67±1.8	36.93±2.04	0.25

Table 2: The severity of spinal cord injuries based on Frankel grade at admission, 6 weeks, 3 months, and 6 months later

Frankel classification	Case group, *n* (%)	Control group, *n* (%)	*P*
At admission			
A	11 (36.7)	12 (40)	0.92
B	9 (30)	9 (30)	
C	10 (33.3)	9 (30)	
D	0	0	
E	0	0	
6 weeks			
A	10 (33.3)	12 (40)	0.18
B	7 (23.3)	8 (26.8)	
C	7 (23.3)	7 (23.3)	
D	5 (16.7)	3 (10)	
E	1 (3.3)	0	
3 months			
A	10 (33.3)	11 (36.7)	0.46
B	6 (20)	7 (23.3)	
C	7 (23.3)	7 (23.3)	
E	5 (16.7)	4 (13.3)	
F	2 (6.7)	1 (3.3)	
6 months			
A	7 (23.3)	11 (36.7)	0.043
B	4 (13.3)	7 (23.3)	
C	8 (26.8)	7 (23.3)	
E	6 (20)	4 (13.3)	
F	3 (10)	1 (3.3)	

Data analyzed by *t*-test

Table 3: Comparison of patient's pain degree based on visual analog scale system after surgery

	Case group	Control group	*P*
At admission	8.78±0.69	8.68±0.68	0.66
6 weeks	6.17±1.26	6.79±0.96	0.65
3 months	4.03±1.7	4.28±1.8	0.053
6 months	3.11±0.82	3.8±0.53	0.001

Data provided for mean±SD. The data analyzed by *t*-test,
SD – Standard deviation

period, riluzole reduced pain in case group (P = 0.001). Investigation of recovery or nonrecovery states in two groups of patients was shown in Tables 4-6. Investigation of recovery and nonrecovery states in patients with SCI demonstrated that riluzole had no significant effect in different period of time.

Discussion

This study on sixty patients with SCI demonstrated that riluzole can improve sensory and motor function and pain in 6-month period. Riluzole as a sodium channel blocker and anti-glutamate drug was already introduced for treatment of ALS patients with FDA approval in the late 90s.[22] The effects of riluzole on ALS are moderate just for the first 6 months.[23] Treatment with riluzole showed functional, histological, and molecular improvement in rats with cervical injury 1–3 h after injury,[24] positive effect shown by the same authors in first 4 h after ischemia/reperfusion injury.[25] Riluzole was well tolerated in a prospective phase 1 study on safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic SCI.[26] Some studies were shown that riluzole has a complicated mechanism such as direct action, noncompetitive receptor blocking, preventing of presynaptic glutamate secretion, inactivating sodium calcium voltage-dependent channel, and stimulation of signal transition dependent to G-protein.[15,27] In a study by Lang-Lazdunski *et al*., 17 New Zealand albino rabbits were under 8 mg/kg of riluzole treatment. It also noted that there was no side effect and morphologic changes and neuronal cells necrosis in gray matter in animals were under riluzole treatment. They reported that riluzole had important role in the prevention of paraplegias in SCI.[14] Grossman *et al*. demonstrated that significant improvements in motor function of patients were treated with riluzole compare with control group.[26] Satkunendrarajah *et al*. demonstrated the positive effects of riluzole in early use of it for 1 week to improve motor function in rats with SCI.[28] Wu *et al*. improved these results previously but by administrating of riluzole 1–3 h after SCI twice a day for 1 week.[24,25] Schwartz and Fehlings confirmed the neurological recovery effect of riluzole; they used riluzole 15 min after injury in rats.[29] Lips *et al*. demonstrated better neurological outcome in rabbits which received riluzole.[30] Stutzmann *et al*. conclude the same positive result for SCI treatment with riluzole.[31] Doble noted that riluzole has a potential effect in central nervous system, including sedative, antiepileptic, and anesthetic effects.[15] In this study in statistical analysis in 6-week period at first and 3-month period, there was no significant difference. It can be seen significant advance in case group based on Frankel grade, but this improvement after 6 weeks was more prominent. In spite of these changes in the clinical findings of patients, differences between two groups did not make sense unlike Lang-Lazdunski study's results. On the other hand, sensory and motor improvement was significant in 6 months. The amount of pain according to VAS system was metered. At the beginning of the study, it was 8.6 ± 1.16 and 8.43 ± 1.47 in case and control groups. Finally, analysis demonstrated a significant reduction in 6-month period (P = 0.001), while after 6-week and 3-month period, it was not. This issue approved by Doble in rats.[15] Investigation of recovery and nonrecovery states in patients with SCI demonstrated that riluzole had no significant effect to recover complete or incomplete lesions. However, 4 patients with complete lesions and 16 patients with incomplete lesions recovered with riluzole treatment. The follow-up period of this study was short for certain conclusion and more studies needed with long-term follow-up to confirm significant effect of riluzole in patients with acute SCI.

Table 4: Investigation of recovery and nonrecovery state in patients with spinal cord injury after 6 weeks

Spinal cord injury	Case group, *n* (%)	Control group, *n* (%)	*P*
Complete lesion			
Recovery	1.(9.09)	0	0.28
Nonrecovery	10.(90.91)	12 (100)	
Incomplete lesion			
Recovery	5.(26.31)	3.(16.66)	0.47
Nonrecovery	14.(73.69)	15.(83.34)	

Data analyzed by Chi-square test

Table 5: Investigation of recovery and nonrecovery state in patients with spinal cord injury after 3 months

Spinal cord injury	Case group, *n* (%)	Control group, *n* (%)	*P*
Complete lesion			
Recovery	1 (9.09)	1 (8.83)	0.94
Nonrecovery	10 (90.91)	11 (91.67)	
Incomplete lesion			
Recovery	6 (31.57)	4 (22.22)	0.52
Nonrecovery	13 (68.43)	14 (77.78)	

Data analyzed by Chi-square test

Table 6: Investigation of recovery and nonrecovery states in patients with spinal cord injury after 6 months

Spinal cord injury	Case group, *n* (%)	Control group, *n* (%)	*P*
Complete lesion			
Recovery	2 (18.18)	1 (8.33)	0.48
Nonrecovery	9 (81.82)	11 (91.67)	
Incomplete lesion			
Recovery	8 (42.11)	5 (27.78)	0.36
Nonrecovery	11 (57.89)	13 (72.22)	

Data analyzed by Chi-square test

Conclusion

We discovered a significant improvement of sensory and motor function and significant pain reduction in riluzole-treated patients in 6-month period. However, using

of riluzole for complete and incomplete spinal cord lesions was not suggestive in recovery and nonrecovery status.

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Conflicts of interest

There are no conflicts of interest.

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