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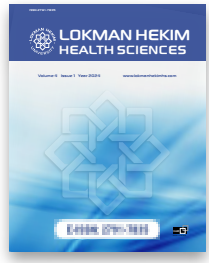

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ORIGINAL ARTICLE

Comparison of Protective Effects of Gelsolin with Methylprednisolone on Traumatic Spinal Cord Injury in an Animal Model

Travmatik Omurilik Yaralanmaları Hayvan Modelinde Gelsolin ile Metilprednizolonun Koruyucu Etkilerinin Karşılaştırılması

Demet Acar[1], Ahmet Ak[2], Ayşegül Bayır[2], Hasan Kara[2], Rabia İstanbulluoğlu[2], Fikret Akyürek[3], Metin Kocacan[4]

[1]Department of Emergency, Konya City Hospital, Konya, Türkiye
[2]Department of Emergency, Selçuk University Faculty of Medicine Hospital, Konya, Türkiye
[3]Department of Biochemistry, Selçuk University Faculty of Medicine Hospital, Konya, Türkiye
[4]Department of Histology and Embryology, Selçuk University Faculty of Medicine Hospital, Konya, Türkiye

Abstract

Introduction: Traumatic spinal cord injury (tSCI) is a highly devastating disease. In this study, we aimed to determine the neuroprotective effects of gelsolin (GSN) as an alternative treatment to methylprednisolone in an animal model of tSCI.

Methods: In this study, adult healthy New Zealand rabbits (n=32) with an average body weight of 2–2.5 kg were utilized. The animals were distributed randomly into four groups (n=8): control, sham, methylprednisolone, and gelsolin groups. Blood and cerebrospinal fluid (CSF) samples were collected on the 0th and 24th hours, and spinal cord samples were obtained on the 24th hour.

Results: In between the 24th-hour results of methylprednisolone and control groups, a statistical significance in terms of CSF GEL (p=0.04), CSF IL-6 (p=0.01), blood CAS-3 (p=0.032), and blood IL-6 (p=0.008) levels was found. In between the 24th-hour results of gelsolin and control groups, in terms of CSF GEL (p=0.042) and CSF CAS-3 (p=0.010) levels, a statistical significance was also found. There was no significant difference between methylprednisolone and gelsolin groups in terms of CSF IL-6, CAS-3, and blood GEL, IL-6, and CAS-3 levels.

Discussion and Conclusion: Given these data, future studies must investigate the physiological mechanisms of gelsolin treatment in traumatic SCI, which may involve higher doses of gelsolin.

Keywords: Gelsolin; Methylprednisolone; Spinal cord injury

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Correspondence: Demet Acar, M.D. Konya Şehir Hastanesi, Acil Servisi, Türkiye
E-mail: dr_demetacar@hotmail.com **Submitted:** 13.01.2024 **Revised:** 21.02.2024 **Accepted:** 27.03.2024

Traumatic spinal cord injury (tSCI) is a distressing condition. Its annual incidence ranges from 12.1 to 57.8 cases per million.[1] Unfortunately, tSCI is associated with permanent disability and reduced life expectancy. This places an enormous burden on the injured person, their family and carers, and society as a whole. Besides the physical and psychosocial trauma, the economic burden is significant, with increased healthcare costs and higher rates of morbidity and premature mortality.[2]

From a pathophysiological perspective, tSCI occurs in two steps: the mechanical insult resulting from the external forces and the secondary degenerative response to this insult. The primary injury results from mechanical damage to the spinal cord, damaging the blood–brain barrier and neuronal tracts, causing disruption of blood flow, edema, hemorrhage, and immediate neuronal death, which are inevitable.[3] After the primary injury, the spinal cord undergoes a series of sequential pathological changes. Pro-inflammatory cytokines, glutamate, and reactive oxygen species are produced in the injured spinal cord tissue, which leads to axonal swelling, myelin breakdown, inflammation, and mitochondrial dysfunction, followed by apoptotic death of neurons and glial cells.[4–6] As potential targets for therapeutic intervention, these secondary injury processes are important.

Treatment with corticosteroids has been studied to control inflammation by reducing the levels of pro-inflammatory cytokines and reducing the severity of the initial injury following tSCI.[7] Administration of methylprednisolone (MP) within 8 h of injury is the current standard of care for tSCI.[8] Indeed, by inhibiting lipid peroxidation, calcium influx, and inflammation, MP reduces the secondary response of tSCI. However, there remains some uncertainty in the literature regarding the effectiveness of this treatment.[9] In a detailed review, the differences between the final motor and sensory scores of patients in the MP group were found to be nonsignificant and minimal in relation to the maximum possible normal score. This does not suggest a clinical benefit[10] Additionally, this treatment is controversial because of its high incidence of serious complications including gastrointestinal bleeding, blood glucose elevation, myopathy, and infection.[11]

Gelsolin (GSN) is a ubiquitous actin nucleation protein of eukaryotes that severs and caps actin filament.[12,13] Gelsolin exists in both intracellular (cytoplasmic protein, cGSN) and extracellular (a secreted protein or plasma gelsolin, pGSN) forms and pGSN also exists in human cerebrospinal fluid (CSF).[14] Although the exact role of GSN is still uncertain, pGSN has a high affinity for filamentous actin (F-actin), and its physiological functions are related to this affinity. This actin-binding protein is suggested to scavenge actin leaked from injured tissue and limit subsequent damage instigated by extracellular F-actin.[15] Reportedly, GSN can form complexes with phosphatidylinositol 4, 5-bisphosphate and inhibit capase-3 and capase-9 activities, playing an important role in the regulation of inflammation.[16] In a mouse model of endotoxemic sepsis, repletion of pGSN led to solubilization of circulating actin aggregates and significantly reduced mortality in mice.[17] Interestingly, gelsolin knockout mice neurons are vulnerable to glucose/oxygen deprivation, whereas gelsolin-overexpressing transgenic mice have been demonstrated to show neuroprotection against experimental stroke.[18] Nevertheless, to the best of our knowledge, the effects of GSN in tSCI have not been examined before.

To test the hypothesis that the administration of GSN can antagonize the pathology of tSCI, we evaluated the levels of gelsolin, interleukin-6 (IL-6), and caspase-3 in blood and CSF together with the histopathological evaluation of the spinal cord in a model of tSCI induced in rabbits treated with gelsolin or MP. In this study, we aimed to determine the neuroprotective effects of GSN as an alternative treatment to MP in tSCI.

Materials and Methods

Experimental Protocol

The Ethics Committee of the Necmettin Erbakan University Experimental Medicine Research and Application Centre was approved the study protocol (date: 30.01.2013, number: 2013-004). All procedures were in accordance with the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85–23, revised 1996). In this study, we did not use any artificial intelligence-assisted technologies (such as large language models [LLMs], chatbots, or image creators) in the production of submitted work. The study was carried out according to the Declaration of Helsinki.

Adult 2- or 2.5-year-old healthy New Zealand rabbits (n=32) with an average body weight of 2–2.5 kg were used in this study. The rabbit model of tSCI was established according to modified Allen's method.[19] The animals were distributed randomly into four groups (n=8); in the control group, no tSCI was performed on the rabbits; in the sham group, tSCI was performed, but no treatment was given; in the MP group, tSCI was performed, and then, the rabbits were immediately treated with 30-mg/kg MP via their dorsal ear vein; in the gelsolin group, tSCI was performed,

Table 1. Mean ranks of biochemical results of groups at different time intervals

	CSF GSN (ng/ml)	CSF Cas-3 (ng/ml)	CSF IL-6 (ng/ml)	Plasma GSN (ng/ml)	Plasma Cas-3 (ng/ml)	Plasma IL-6 (ng/ml)
Control group 0th h (n=6)	21.00	14.67	18.17	50.07	53.00	46.75
Control group 24th h (n=6)	12.17	14.17	11.13	41.17	24.83	11.00
Sham group 0th h (n=8)	28.75	31.38	32.50	67.06	56.00	58.75
Sham group 24th h (n=8)	29.75	26.88	32. 13	40.25	43.25	41.63
Methylprednisolone group 0th h (n=7)	32.43	29.50	21.38	36.38	54.63	41.13
Methylprednisolone group 24th h (n=7)	46.00	30.43	30.86	31.29	53.43	48.71
Gelsolin group 0th h (n=7)	25.00	39.00	45.86	28.13	28.63	40.25
Gelsolin group 24th h (n=7)	29.29	41.71	35.86	21.57	45.86	30.86

CSF: Cerebrospinal fluid; GSN: Gelsolin; IL-6: Interleukin-6; Cas-3: Caspase-3.

and then, the rabbits were immediately treated with 20-mcgr/kg recombinant human gelsolin via their dorsal ear vein. From all living rabbits, blood and CSF samples were collected on the 0th and 24th hours, and spinal cord samples were obtained on the 24th hour. Some of the rabbits died.

At the beginning of the study, after each rabbit was anesthetized with an intramuscular injection of a mixture of xylazine hydrochloride and ketamine, an intravenous line was achieved from the dorsal ear vein of all rabbits. At the 0th and 24th hours, 5-ml blood was obtained from all rabbits, and 0.9% sodium chloride was given back instead. The obtained blood was centrifuged and stored at -80 °C. After the blood was gained, the back of the rabbits was shaved and cleaned with 10% povidiniodin. With the posterior longitudinal excision at thoracic 8–10 levels, total laminectomy was performed at thoracic 10 level. After the elevation of ligamentum flavum, we reached the spinal cord. At the 0th and 24th hours, 1-ml BOS was attained, and 0.9% sodium chloride was given back again instead. The obtained BOS was centrifuged and stored at -80 °C. After the procedure, the spinal cord was closed with paravertebral muscles and sutured. Spinal cord biopsy has also been obtained during this procedure for histopathological evaluations, and these biopsy materials were fixed with 10% formaldehyde. After the procedure, all rabbits were sacrificed with high-dose ketamine.

Plasma and CSF IL-6, caspase-3, and gelsolin levels were measured using a rabbit IL-6, caspase-3, and gelsolin enzyme-linked immunosorbent assay kit.

Histological Assessments

All medulla spinalis specimens were fixed in 10% formalin. Samples were embedded in paraffin and cut with a knife blade along the coronal plane. Sections (thickness of 4–6 μm) were obtained using a standard rotator microtome and stained with hematoxylin and eosin and toluidine blue. Histopathological changes, including general structural integrity, the condition of meninx, hemorrhage in the dura, structural integrity and presence of hematoma of white and gray matters, presence of inflammatory cells, the structure of neuron and glia, the conditions of the central canal with axon and myelin, presence of pyknotic cells, and necrotic areas were evaluated using a trinocular microscope. All slices were evaluated by two different double-blind pathologists, and each parameter was scored as Grade 0 (no change), 1 (slight alteration), 2 (moderate change), 3 (marked change), or 4 (very severe change). All scores are evaluated separately and then totally for each rabbit.

Statistical Analysis

All data were analyzed via SPSS17.0 (SPSS Inc., Chicago, IL, USA). Since the number of cases was below 30 in all groups, non-parametric tests were employed in the study. For the distribution of data frequency analysis, and in comparison of groups, the McNemar test, Mann–Whitney U-test, and Wilcoxon signed rank test were utilized; $p<0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the plasma and CSF values of gelsolin, IL-6, and CAS-3.

The statistically significant differences between groups were as follows:

- The plasma IL-6 levels in the control group in the 0th and 24th hours (p=0.025);
- The CSF IL-6 levels in the sham group in 0th and 24th hours (p=0.02);
- The 24th-hour CSF gelsolin (p=0.04), CSF IL-6 (p=0.010), plasma CAS 3 (p=0.032), and plasma IL-6 (p=0.008) levels in the control and MP groups;

Table 2. Mean ranks of histopathological scores of groups

	Control group (n=8)	Sham group (n=8)	Met. group (n=7)	Gelsolin group (n=7)
General structure	9.58	19.56	14.14	13.00
Meninx	7.42	19.50	15.50	14.00
White matter	4.33	18.13	12.93	20.64
Gray matter	6.67	19.44	15.71	14.36
Dura hemorrhage	4.00	19.50	12.57	19.71
Hematoma	4.92	16.69	14.50	20.21
Inflammation	7.00	15.00	19.93	14.93
Neuron	4.33	19.88	11.64	19.93
Axon	4.53	19.31	18.07	13.93
Myelin	4.58	16.50	12.93	22.29
Vasculature	4.50	13.25	21.21	17.79
Necrosis	4.75	17.81	16.71	16.86
Cyst formation	5.83	17.56	18.71	14.21
Glia	6.00	21.38	13.57	14.86
Apoptosis/pyknosis	5.00	17.00	19.43	14.86
Cavitation	11.50	13.38	15.21	17.64
Central canal	14.33	17.00	15.29	11.00

Met.: Methylprednisolone.

- The 24th-hour CSF gelsolin (p=0.042) and CSF CAS-3 (p=0.010) levels in the control and gelsolin groups;
- The 24th-hour CSF gelsolin (p=0.025) levels in the MP and gelsolin groups.

Table 2 analyzes and summarizes the histopathological data of all groups.

In the evaluation of histopathological data, a statistically significant difference was observed between the sham and MP groups in terms of general structure (p=0.034), condition of neuron (p=0.024), vasculature (p=0.027), and glia (p=0.038). Conversely, a statistically significant difference was found between the sham and gelsolin groups in terms of general structure (p=0.04), assembly of meninx (p=0.04), and glia (p=0.046). Moreover; in histopathological evaluation, no statistically significant difference was found in any criteria between the MP and gelsolin groups.

DISCUSSION

The current study is the first to report the use of GSN as a protein drug for the reduction of damage after traumatic spinal cord injury. Although no statistically significant difference was found in the inflammation and apoptosis markers IL-6 and CAS-3 in CSF and blood between the sham and gelsolin groups, no significant difference was also found in these markers between the MP and gelsolin groups. In fact, gelsolin was used at a very low dose (20 mcgr/kg) in this study. The finding of similar levels of inflammatory mediators between the MP and gelsolin groups at these low doses is hopeful. Additionally, histopathological evaluations showed significant improvements in overall structure, meninx assembly, and glial structure at these very low doses. A bimodal profile for the dose–response curve of gelsolin has been suggested by Milhalko et al.[20] In light of all these data, we believe that this new treatment regimen should be explored in larger studies with its pathophysiological mechanisms, possibly with higher doses, as an alternative treatment to MP in tSCI.

Gelsolin is an actin-binding protein. It has multiple actin-regulatory activities, including cytoskeletal remodeling and ion channel regulation.[21] In any tissue injury caused by glucose/oxygen deprivation, large amounts of actin are released from damaged cells into the extracellular space. Polymerization of this actin can potentially increase blood viscosity, leading to further disturbances in blood flow. In contrast, pGSN breaks extracellular F-actin into short filaments. By capping the barbed ends, pGSN prevents polymerization and promotes monomer release. In this respect, pGSN limits inflammation and the viscosity of the blood.[17] In this study, we found that the administration of pGSN can reduce neuropathological changes due to traumatic spinal cord injury. However, the mechanisms of this function are not clear. Actin depolymerization and inflammation modulation are the most commonly proposed functions. Endres et al.[18] found that the enhancement or mimicry of the activity of gelsolin could be neuroprotective during a stroke in an animal model. Subsequently, histone deacetylase inhibitor-mediated neuroprotection has been linked to the upregulation of GSN in response to MCA occlusion in GSN knockout mice.[22] Gelsolin is regulated by phosphatidylinositol 4, 5-bisphosphate (PIP2) and contains a lipid signaling binding domain. This domain has been shown to bind to many bioactive lipids including lysophosphatidic acid, lipoteichoic acid, and lipopolysaccharide, which in turn may serve to modulate the inflammatory response thereby protecting against the inflammation related neurodegeneration following spinal cord injury.[23] In an animal model of middle cerebral artery occlusion (MCAO), the infarct volume of the pGSN treatment group was determined to be significantly reduced in comparison with the untreated MCAO rats. In light of these data, gelsolin is suggested to be a promising drug for protection against neurodegeneration following ischemic stroke.[24] In a recent study, gelsolin has been shown to have an effective role against oxidative stress in wound healing of fibroblast cells.[25] In another study, treatment of rats with

gelsolin prevented hyperoxia-induced changes in tissue structure and increased antioxidant enzyme activities.[26]

Unfortunately, traumatic spinal cord injury remains a major health problem. It has a high incidence and morbidity rate. Furthermore, clinicians are under additional pressure due to the lack of an effective treatment modality after tSCI. The primary reaction after tSCI is acute and cannot be avoided. However, hours after the initial insult, the secondary phase begins. This is characterized by a series of cellular and molecular changes in and around the injured area. Secondary processes in tSCI result from increased oxidative stress, calcium mobilization, glutamate excitotoxicity, and inflammatory factors. These ultimately lead to neuronal dysfunction and cell death.[27] Increased levels of free radicals set off chain reactions that lead to cell damage and even the lysis of cell membranes.[28] Following tSCI, there is a rapid increase in intracellular free Ca^{2+} levels. This activates Ca^{2+} -dependent enzymes that degrade many key cytoskeletal and membrane proteins.[29] Within minutes of SCI, extracellular levels of excitatory amino acids, particularly glutamate, have been found to rise to neurotoxic levels. This results in excessive activation of glutamate receptors in the central nervous system. This leads to neuronal cell death.[26] GSN has been suggested to be a regulator of many ion channels responsible for intracellular calcium and glutamate excitotoxicity through regulation of the cellular actin cytoskeleton.[30,31]

The mammalian apoptotic cell death is regulated by posttranslational activation of a class of cysteine proteases known as caspases, which have the unique property of cleaving proteins on the carboxyl side of aspartic acid. In particular, caspase-3 is important to neuronal development and injury by inducing fragmentation of nuclear DNA.[32,33] Gelsolin has been reported to be complex with phosphatidyl-inositol 4, 5-bisphosphate and limit the activities of caspase-3 and caspase-9.[16] Nevertheless, we did not determine any significant differences in caspase-3 levels between the sham, MP, or gelsolin group. This may be due to two reasons: One is that the gelsolin dosages were very low in this study, and the other one is that we had to take the blood samples and spinal cord biopsy of the rabbits in the first 24 h after the SCI with the ethical reasons. The effects of gelsolin especially in caspase-3 levels may be determined in later hours, because there was an upward trend in caspase-3 levels in the MP group in the 24th hour; however, this trend was downward in the gelsolin group, although the differences were not statistically significant.

Histopathologically, apoptosis, Wallerian degeneration, and glial scar formation are among the observed effects of the secondary phase of tSCI. Novel treatments for SCI have focused primarily on the regulation of the cellular and molecular changes that characterize this phase, as the secondary response to SCI occurs over a prolonged period after injury and is therefore theoretically amenable to clinical management. Astrocytes change their appearance and properties to overcome the pathological condition in response to injury. These changes are known as gliosis.[34] In this respect, to demonstrate the neuroprotective effects of gelsolin in SCI, our positive histopathological findings are important, especially in terms of general structure, meninx assembly, and glial structure.

The small number of animals and the low dose of gelsolin used in this study are the main limitations of this study, and the latter one is due to economic constraints. Conversely, due to ethical reasons, only the early results, in the first 24 h, of the blood, CSF, and spinal cord biopsies could be obtained. Another important limitation is that we administered gelsolin or MP immediately after experimental tSCI.

Giving a neuroprotective substance at the time of injury does not mimic clinical reality. Unfortunately, the neuroprotective substances in clinical use are always administered during a window of a few hours after the initial insult. Despite all these limitations, we have obtained promising results on the neuroprotective effects of gelsolin in spinal cord injury.

Ethics Committee Approval: The Necmettin Erbakan University Experimental Animals Ethics Committee granted approval for this study (date: 30.01.2013, number: 2013-004).

Authorship Contributions: Concept: DA, AA; Design: DA, AA, HK; Supervision: DA, AB; Fundings: DA, Rİ; Materials: DA, AA, HK; Data Collection or Processing: DA, FA, Rİ; Analysis or Interpretation: DA, FA, MK; Literature Search: DA, AB, AA; Writing: DA, AA; Critical Review: DD, AA.

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