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An experimental rat model

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BACKGROUND: *Traumatic and ischemic injuries of the spinal cord are effective in the development of neurological dysfunction of tissue damage caused by primary and secondary mechanisms. Free radical changes are effective in the development of early ischemia and progressive tissue ischemia is the main cause of secondary damage. Delaying ischemia is the basis of treatment. In this study, we aimed to demonstrate the presence of neuroprotective effects of alpha-lipoic acid in comparison with methylprednisolone.*
METHODS: *50 Sprague Dawley rats were divided into 5 groups (n = 10) and spinal cord trauma was created by the method, described by Rivlin and Tator. Group 1: Laminectomy group, Group 2: Laminectomy + spinal cord injury (SCI), Group 3: Laminectomy + SCI + alpha-lipoic acid (ALA) (100 mg / kg), Group 4: Laminectomy + SCl + Methyl-prednisolone (30 mg / kg), Group 5: Laminectomy + SCl + ALA + Methyl-prednisolone.*
RESULTS AND DISCUSSION: *Rats with spinal cord injury were found to be paraplegic. There was no significant change in motor function between the groups. When the antioxidant values were compared in the groups, there was a statistically significant difference between Group 2 and Group 3. Oxygen radicals decreased significantly between ALA and Methylprednisolone. The most striking difference was between the monotherapy group and the combined treatment group.*
CONCLUSION: *Our results showed that alpha lipoic acid given after spinal cord trauma in rats decreases anti-oxidant formation.*

KEY WORDS: Alpha-lipoic acid, Methyl-prednisolone, Oxygen radicals, Spinal cord injury

Introduction

Spinal cord injury, whether complete or incomplete, is a major social problem causes loss of major functions of the cord (motor, sensory, autonomic and reflex) [1]. It is hypothesized that there are two mechanisms for the damage caused by acute spinal cord injury. Primary injury resulting from mechanical tissue destruction results in necrotic cell death. Secondary damage, a cascade of events triggered by injury, is the result of activation of endogenous cell death pathways [2-4]. The majority of experimental and clinical studies in neuronal injury are aimed at preventing or reducing secondary injury [5]. High-dose steroids are widely used in the treatment of spinal cord injury targeting many secondary degeneration mediators. But the results are not satisfactory because secondary degeneration mechanisms are not well understood [2,6,7]. Excitotoxicity, oxidative damage, ischemia, secondary injury are the contents of the cascade [5,8,9].
The prominent factors in the occurrence of secondary injury is energy deficiency due to ischemia [9,10]. Theories of ischemia have been suggested as a decrease in tissue pH due to lactic acidosis, venous stasis and congestion due to fibrin and platelet accumulation, capillary endothelial damage, edema, petechial hemorrhages, and presence of vasoactive agents. Ischemia causes insufficient

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glucose and oxygen intake to tissues and indirectly leads to a lack of energy and a decrease in ATP stores [1,11]. Ischemia initiates the cascade of secondary pathogenetic mechanisms defined as excitotoxicity due to its dependence on endogenous excitatory amino acid neurotransmitters [9,12,13]. In traumatic injury tissue repair, the inflammatory response begins, in which the activity of leukocytes is critical. leukocytes remove cellular debris by phagocytosis, release enzymes that relax the extracellular matrix and secrete cytokines that direct proliferation of endothelial epithelial and connective tissue cells in the injured area [14,15]. Cytokines accelerate the central nervous system (CNS) inflammatory response by inducing the expression of reactive oxygen and nitrogen derivatives of additional cytokines, chemokines, nitric oxide, inflammatory response [16]. When the first neural cell dies, it releases toxins that attack other living neurons. Some of these toxins are fugitive oxygen molecules called free radicals. Prevention of intensive free radical formation is vital for cell life [17].

Alpha-lipoic acid is a substance synthesized naturally in our body and can be taken from food [18,19]. There are two important functions in our body. The former acts as a coenzyme in the metabolic pathway, and the latter is an important antioxidant. In the experiments on rat model, alpha-lipoic acid enhances endoneurial blood flow, increases the physiological antioxidant level of glutathione and reduces free oxygen radicals in the diabetic nerve. These effects seen in the experimental state show that the function of peripheral nerves can be corrected with alpha-lipoic acid [20-26].

Material and Methods

All experimental steps taken of this animal study is designed to eliminate pain and suffering with internationally accepted guidelines. Our experimental protocols were approved by University Animal Care and Use Committee.

50 Sprague Dawley rats with normal motor activity ranging between 200 and 250 g were included in the study. Rats were kept under standard laboratory conditions (12 hours day - 12 hours night lighting, 20-22 °C room temperature, 50-60% humidity). They were given enough water and food. They were randomly divided into 5 groups. Group 1: Laminectomy without any injury to spinal cord was performed. Group 2: Performed injury to the spinal cord but untreated. Group 3: Intramuscular Alpha-lipoic acid (ALA) was administered (100mg / kg) after laminectomy and nerve injury. Group 4: Intramuscular Methyl-prednisolone (30 mg / kg) was administered after laminectomy and nerve injury. Group 5: Combined treatment with ALA + Methyl-prednisolone after laminectomy and injury.

Injury: spinal cord injury was performed by the method, described by Rivlin and Tator27. The rats were fasted the day before and then anesthetized with Ketamine (60 mg/kg) + Xylazine (9 mg/kg) intramuscularly. The interscapular distance of the rats was referenced and a 3x2 cm area was shaved in the dorsal region and local antisepsis was applied with povidone iodure. Midline incision was performed at the T5-12 level in the prone position. The skin, subcutaneous tissues and paravertebral muscle fascia were passed through, and blunt dissection were implemented to the muscles for exploration of T7-10 laminae. Total laminectomy was performed at T7 level and extra care was taken not to damage the dura of the rats. At this level, the spinal cord was clamped with a Yasargil aneurysm clip (Aesculap FE 721K), which applied 63 g of force for standard trauma, for one minute to create spinal cord injury. The clip was then removed, and the anatomical layers were closed with 3/0 silk. The rats were placed in their cages. Bladders were emptied by manual compression twice daily and allowing free feeding. Treatments were administered according to group plans after the surgery.

Collecting the samples: 24 hours later intracardiac blood collected under Ketamine (60 mg / kg) + Xylazine (9 mg / kg) anesthesia After sacrifice the spinal cord was sectioned at the region of injury. Plasma samples obtained by rapid centrifugation from blood samples were transferred to plastic eppendorf cap tubes for biochemical analysis. Total antioxidant status (TAS), Total oxidant status (TOS), nitric oxide (NO), paraoxonase (PONX) activities were evaluated in samples by the same biochemist who was blind to groups.

Evaluation of functional recovery: Physical examinations were performed regularly to evaluate the functional recovery of rats. Motor functions of rats were evaluated immediately by Drummond and Moore criteria 24 hours after surgery (137). 0: paraplegic, no motor function in the lower extremities, 1: Motor function in the lower extremity is weak, only weak motion against gravity, 2: Moderate lower extremity motor function, good against gravity but cannot pull legs under the body, 3: Motor function Very good, he can pull his legs under the body and jump, but not completely normal, 4: Normal motor function.

Statistical analyze: Differences between groups were analyzed by Mann-Whitney U test.

Results

No mortality was seen in the groups after surgical intervention. There was no wound infection. Motor function of all rats was evaluated according to Drummond-Moore criteria (Table I). There was no significant difference between the groups ($p > 0.005$). TAS, TOS and NO values were compared between Group 2 and Group 3 and noticed that Sildenafil significantly increased TAS and NO values and decreased TOS value (TAS $p = 0.002$, TOS $p = 0.002$, NO $p = 0.003$). But there was no significant

TABLE I - *Motor functions of the rats scored after surgery (Drummon – Moore score: 1. Motor function in the lower extremity is weak, only weak motion against gravity, 2. Moderate lower extremity motor function, good against gravity but cannot pull legs under the body, 3:.Motor function Very good, he can pull his legs under the body and jump, but not completely normal, 4. Normal motor function)*

	Motor functions of the rats scored after surgery									
	Rat 1	**Rat 2**	**Rat 3**	**Rat 4**	**Rat 5**	**Rat 6**	**Rat 7**	**Rat 8**	**Rat 9**	**Rat 10**
Grup 1	4	4	4	4	3	4	4	3	4	4
Grup 2	1	1	1	1	2	1	1	2	1	1
Grup 3	2	2	1	0	0	1	1	2	0	0
Grup 4	2	2	1	0	0	0	0	0	1	1
Grup 5	2	2	1	0	2	2	1	1	0	0

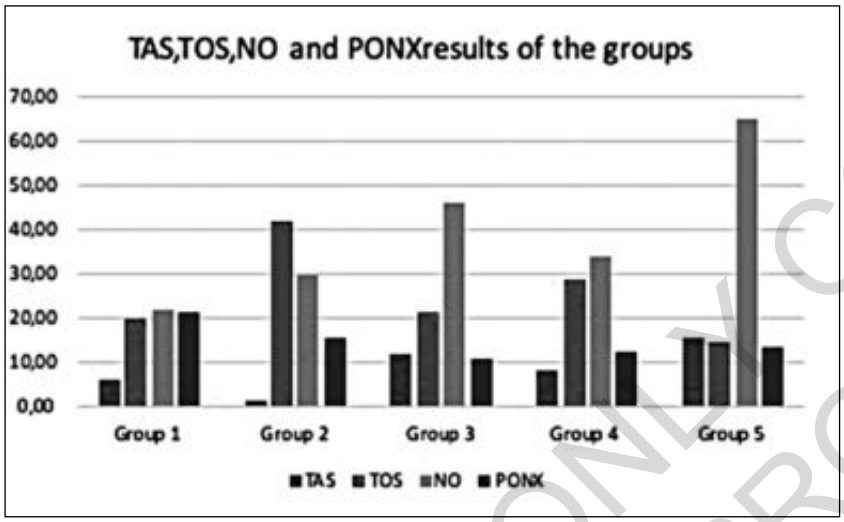

Fig. 1: TAS, TOS, NO and PONX value of groups. (TAS: Total antioxidant status, TOS: Total oxidant status, NO: nitric oxide, PONX: paraoxonase)

difference in PONX values (p = 0.221). The similar results were repeated between the group2 and 4, treated with methyl-prednisolone. There was no significant difference in PONX and NO values (PONX p = 0.157, NO p = 0.941), TAS and TOS values were similar to Sildenafil treated group (TAS p = 0.002, TOS p = 0.034). While the difference between group 2 and Sildenafil + Methyl-prednisolone combined treatment group (group 5) was similar in terms of TAS and TOS (TAS p = 0.002, TOS p = 0.002), NO values were significantly increased with sildenafil effect (p = 0.003). When group 3 and group 4 were compared, it was observed that sildenafil significantly increased TAS (p = 0.01), decreased TOS (p = 0.001), but did not make a significant change in NO and PONX (NO p = 0.103, PONX p = 0.701). The significant effect was seen in the combined treatment group. In the comparison of Group 3 and Group 5, TAS, TOS and NO values were significantly different (TAS p = 0.031, TOS p = 0.002, NO p = 0.002), PONX was not significant in this group (p = 0.597) (Fig. 1).

Discussion

After Rivlin and Tator described the myelotomy model with experimental spinal cord contusion, various treatment approaches for spinal cord injury were presented [27]. Many studies have been performed on the pathophysiology of spinal cord injury. Traumatic injuries of the spinal cord can cause primary and secondary tissue damage, which is also named direct and indirect damage. Experimental studies over the past twenty years have shown that these secondary mechanisms play a major role in the development of neurological dysfunction in spinal cord injury.

Acute treatments after spinal cord trauma are performed with neuroprotective drugs such as antioxidants, neurotransmitter receptor blockers, phosphokinase stimulators, phosphatase inhibitors. In the literature, many treatment methods for spinal cord injuries after experimental trauma have been investigated. In particular, Glutamate, Na channel blockers, erythropoietin, minocycline, erythropoietin, opiate antagonists, Ca channel blockers, gangliosides, amino acids, NOS, interleukin, lipopolysaccharides have been studied in many studies, but it is concluded that these treatments are healing enhancing treatments instead of direct treatment of the damage [3,28]. Lipoic acid is an important coenzyme and antioxidant in the mechanism of pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase. Lipoic acid has superiority over other antioxidants due to its water and oil dissolvability properties and it has been used as a treatment

in many diseases and new studies are still continuing. It has been used in the treatment of neurodegenerative diseases such as diabetic neuropathy, atherosclerosis and MS, joint disorders and infections like AIDS [1,10,29,30]. In clinical studies, treatment of polyneuropathy and mononeuropathy due to diabetes, alpha lipoic acid has been shown to reduce neuropathic complaints of patients [1,29,31].

Clinical studies show that the spinal cord lesion is enlarged by secondary injury. The underlying molecular and cellular mechanisms are not fully understood. Current evidence suggests that free oxygen radical formation and peroxidation of membrane lipids play a role. The efficacy of some therapeutic approaches has been evaluated experimentally by determining the level of lipid peroxidation [18,19,32-36]. Peroxidation has been evaluated by measuring the amount of malondialdehyde (MAD), one of the lipid peroxidation products, in the tissue [16,18,32,33]. Although naturally occurring antioxidant compounds control harmful effects in normal cells, excessive free radical production in pathological conditions such as spinal cord injury exceeds antioxidant capacity. Free radicals lead to lipid peroxidation and, consequently, cell membrane dissolution. Antioxidants in the central nervous system are ascorbate, glutathione and alpha tocopherol. These antioxidants neutralize free radicals. Trauma reduces these substances [33,37].

Prevention of intensive free radical formation is an important first vital step for cell life. Methylprednisolone is one of the most important treatment protocols used to prevent the formation of free radicals. Other agents used are Glutamate, Na channel blockers, hypothermia, erythropoietin, minocycline, erythropoietin, opiate antagonists, Ca channel blockers, gangliosides, amino acids, NOS, interleukin, lipopolysaccharides. None of these substances used alone has been shown to be therapeutic, but it was found to be effective in combined use [18,19,34-36,38-40]. The experiment was designed to compare antioxidative effect of alpha lipoic acid with Methylprednisolone which was commonly used in treatment of oxidative stress.

German researchers have found that lipoic acid has positive effects on long-term memory in older mice. Similar benefits have not yet been demonstrated in younger mice. Researchers have shown that lipoic acid compensates for long-term memory impairment rather than correcting general memory. Researchers at the University of Rochester medical center have reported a possible role in the treatment of chronic and acute neurological disorders such as Parkinson's and Huntington's disease [13].

In conclusion, oxidative stress is the prime element in secondary injury of the spinal cord trauma. Avoid of intensive free radicals is crucial and antioxidant treatment should be used.

Alpha lipoic acid given after spinal cord trauma in rats increased the anti-oxidant formation and could be a treatment option on the patient who suffer from spinal cord trauma or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript followed.

Riassunto

Le lesioni traumatiche e ischemiche del midollo spinale sono causa di disfunzione neurologica da danno tissutale per meccanismi primari e secondari. I cambiamenti dei radicali liberi sono dannosi per lo sviluppo dell'ischemia precoce e l'ischemia progressiva dei tessuti è la principale causa di danno secondario. Ritardare l'ischemia è la base del trattamento. In questo studio, abbiamo mirato a dimostrare la presenza di effetti neuroprotettivi dell'acido alfa-lipoico rispetto al metilprednisolone.

Sono stati impiegati sperimentalmente 50 ratti Sprague Dawley, divisi in 5 gruppi (ciascuno di 10 unità) e il trauma del midollo spinale è stato creato con il metodo, descritto da Rivlin e Tator. Gruppo 1: gruppo Laminectomia, Gruppo 2: Laminectomia + lesione del midollo spinale (SCI), Gruppo 3: Laminectomia + SCI + acido alfa-lipoico (ALA) (100 mg / kg), Gruppo 4: Laminectomia + SCl + Metil-prednisolone (30 mg / kg), Gruppo 5: Laminectomia + SCl + ALA + Metil-prednisolone.

Risultati e Discussione: I ratti con lesione del midollo spinale sono risultati paraplegici. Non vi è stato alcun cambiamento significativo nella funzione motoria tra i gruppi. Quando i valori di antiossidanti sono stati confrontati nei gruppi, c'era una differenza statisticamente significativa tra il gruppo 2 e il gruppo 3. I radicali dell'ossigeno sono diminuiti significativamente tra ALA e metilprednisolone. La differenza più evidente era tra il gruppo di monoterapia e il gruppo di trattamento combinato.

In conclusione questi risultati hanno indicato che l'acido alfa lipoico somministrato dopo un trauma del midollo spinale nei ratti diminuisce la formazione di antiossidanti.

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Alpha-lipoic acid is sometimes taken as a supplement under the presumption it can improve certain metabolic functions, including fat burning, collagen production, and blood glucose control. There is growing evidence of at least some of these claims.Â While this approach would be impractical in clinical practice, it does hint at the potential benefit of alpha-lipoic acid in preventing the onset of type 2 diabetes. By contrast, there is no evidence that the supplement can prevent or treat type 1 diabetes, the form of the disease typically associated with an immune system malfunction. AIm: Spinal Cord Injury (SCI) is a devastating health problem both for the patient and the clinician. Numerous treatment modalities have been studied to reverse the effects of spinal cord injury. Herein is reported the effects and the comparison of Alpha Lipoic Acid and N-Acetyl Cysteine on rats with SCI.Â Though neural tissue has limited antioxidative capacity (7), it could be postulated that administration of antioxidants such as Î±-LA and NAC have the potential to protect the neural tissue from deleterious ROS effects. The goal of the present study was to compare of the neuro-protective effects of Î±-LA and NAC, as antioxidant agents, following administration in the secondary injury phase after traumatic spinal cord injury in rats. Alpha-lipoic acid, Methyl-prednisolone, Oxygen radicals, Spinal cord injury.Â Background: Traumatic and ischemic injuries of the spinal cord are effective in the development of neurological dysfunction of tissue damage caused by primary and secondary mechanisms. Free radical changes are effective in the development of early ischemia and progressive tissue ischemia is the main cause of secondary damage. Delaying ischemia is the basis of treatment. In this study, we aimed to demonstrate the presence of neuroprotective effects of alpha-lipoic acid in comparison with methylprednisolone. Methods: 50 Sprague Dawley rats were divided into 5 groups (n = 10) and spinal cord trau Alpha lipoic acid, also known as ALA, is a compound naturally produced by the body. It acts as a cofactor in the production of energy. When taken orally, the amount of alpha lipoic acid delivered to the body varies.Â Alpha-lipoic acid is an antioxidant. Although there is some evidence it may help treat conditions related to diabetes, confirming studies are needed. Alpha lipoic acid (ALA) is a compound naturally produced by the body that acts as a cofactor in the production of energy. It is often referred to and marketed as a universal antioxidant. Lab studies show that ALA and its metabolite, dihydrolipoic acid (DHLA), have chelating, scavenging, and protective properties. Alpha lipoic acid (ALA) is one of the most potent antioxidants. It improves the development of ovarian follicles and also boosts insulin sensitivity. Zinc is a key factor in making many parts of the reproductive system function properly.Â The anthocyanins increase the production and integrity of collagen and have strong antioxidative effect. Vitamin C contributes to collagen formation which is required for the normal functioning of the skin. ADVANTAGES.