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Effect of Curcumin on Lipid Peroxidation, Early Ultrastructural Findings and Neurological Recovery after Experimental Spinal Cord Contusion Injury in Rats

Curcuminin Sıçanlarda Deneysel Spinal Kord Kontuzyon Yaralanma Sonrası Lipid Peroksidasyon Erken Ultrastrüktürel Değişiklikler ve Nörolojik İyileşme Üzerine Etkisi

Ahmet Metin SANLI[1], Erhan TURKOGLU[1], Gokhan SERBES[1], Mustafa Fevzi SARGON[2], Omer BESALTI[3], Kamer KILINC[4], Alper IRAK[1], Zeki SEKERCI[1]

[1]M.H. Diskapi Yildirim Beyazit Education and Research Hospital, 1st Neurosurgery Clinic, Ankara, Turkey
[2]Hacettepe University, Faculty of Medicine, Department of Anatomy, Ankara, Turkey
[3]Ankara University, Faculty of Veterinary Medicine, Department of Surgery, Ankara, Turkey
[4]Hacettepe University, Faculty of Medicine, Department of Biochemistry, Ankara, Turkey

Correspondence address: Ahmet Metin SANLI / E-mail: ahmetmetinsanli@hotmail.com

ABSTRACT

AIM: After acute spinal cord injury (SCI), a large number of axons are lost by a cascade of pathophysiological events known as a secondary injury. The main aim of the current study was to investigate the potential neuroprotective effects of curcumin on lipid peroxidation (LPO), neurological function, and ultrastructural findings after SCI.

MATERIAL and METHODS: Forty adult Wistar albino rats were randomized into five groups: control, SCI alone (50 g/cm weight drop), methylprednisolone sodium succinate (MPSS) (30 mg/kg), curcumin + dimethyl sulfoxide (DMSO) (300 mg/kg), and DMSO alone (0.1 mg/kg).

RESULTS: Administration of curcumin significantly decreased LPO in first 24 hours. However, there were no differences in the neurological scores of injured rats between the medication groups and the control group. Curcumin was more effective than DMSO and MPSS in reducing LPO, whereas DMSO was more effective than curcumin and MPSS in minimizing ultrastuctural changes. The results of this study indicate that curcumin exerts a beneficial effect by decreasing LPO and may reduce tissue damage.

CONCLUSION: Since ultrastructural and neurological findings does not support biochemical finding, our findings do not exclude the possibility that curcumin has a protective effect on the spinal cord ultrastructure and neurological recovery after SCI. A combination of curcumin with other vehicle may also have a considerable synergy in protecting spinal cord.

KEYWORDS: Curcumin, Malondialdehyde, Methylprednisolone, Cord Injury, Ultrastructure, Rats

ÖZ

AMAÇ: Spinal kord yaralanma sonrası çok sayıda akson sekonder yarlanma olarak bilinen patofizyolojik olaylar zinciri nedeniyle kaybedilir. Bu çalışmadaki ana amaç, spinal kord yaralanma sonrası, curcuminin lipid peroksidasyonu, nörolojik fonksiyonu ve ultrastrüktüral bulgular üzerindeki potansiyel nöroprotektif etkilerini araştırmaktı.

YÖNTEM ve GEREÇLER: 40 yetişkin albino rat randomize olarak beş gruba ayrıldı: kontrol, yalnızca omurilik yaralaması (50 g/cm ağırlık düşürme), metil prednizolon sodyum suksinat (MPSS) (30 mg/kg), curcumin ve dimetil sülfoksit (DMSO) (300 mg/kg) ve yalnızca dimetil sülfoksit (0,1 mg/kg).

BULGULAR: Curcumin uygulanması ilk 24 saatte lipid peroksidasyonunu önemli oranda azalttı. Ancak hasarlanmış ratların nörolojik değerlendirmelerinde tedavi edilenlerle kontrol grupları arasında fark bulunmadı. Curcumin lipid peroksidasyonu azaltmada DMSO ve MPSS den daha etkili iken, DMSO ultrastrüktürel değişiklikleri azaltmada curcumin ve MPSS'den daha etkilidir. Bu çalışmanın sonuçları curcuminin lipid peroksidasyonu azaltma yoluyla yararlı bir etki gösterdiğini ve doku zararını azaltabileceğine işaret eder.

SONUÇ: Ultrastrüktürel ve nörolojik bulguların biokimyasal bulguyu desteklememesi nedeniyle, bulgularımız spinal kord yaralanması sonrası, curcuminin spinal kord ultrasütrüktür ve nörolojik iyileşme üzerindeki koruyucu etki ihtimalinden yoksun bırakmaz. Curcuminin diğer bir taşıyıcı ile kombinasyonu da kordun korunmasında önemli sinerjiye sahip olabilir.

ANAHTAR SÖZCÜKLER: Curcumin, Malondealdehid, Metilprednizolon, Kord yaralanması, Ultrastrüktür, Sıçanlar

INTRODUCTION

Acute spinal cord trauma is a common health problem that often results in social and economic deprivation for the victim (18). Spinal cord injury (SCI) remains a major health problem despite advances in neurotechnology. There are two phases of SCI, primary and secondary injury. Physical impact causes irreversible damage to some axons; however, a large number of axons are lost by a cascade of pathophysiological events known as a secondary injury. The secondary injury is responsible for both motor and sensorial losses after primary damage.

Free radicals play an important role in the pathogenesis of secondary injury (6). In addition to free radicals, inflammation and many other factors lead to apoptosis and are at least partly responsible for neuronal and glial cell damage, as well as destruction of the cell membrane (3,13).

Curcumin is the principal curcuminoid in the Indian curry spice, turmeric, and incorporates several functional groups. Curcumin is known for its antitumor, antihistaminic antioxidant, antiarthritic, antiamyloid and antiinflammatory properties (4,5,19,20).

Experimental cortical ischemic studies in rats demonstrated that curcumin inhibits xanthine oxidase, superoxide dismutase, and glutathione peroxidases, which results in decreased malondialdehyde (MDA) and superoxide anions and thus preserves cerebral capacity while decreasing neuronal damage (1,7,24). In addition, curcumin acts as an antioxidant during the ischemia induced production of free radicals, which causes lipid peroxidation (7,26). Free radicals and other products of peroxidation damage mitochondrial membranes, block cytochrome-C swaying, and activate caspase-3, which results in apoptosis (12,26). Curcumin is a strong antioxidant agent that inhibits oxidative stress, glial activation, mitochondrial dysfunction and apoptosis (26).

The main aim of the current study was to investigate the potential neuroprotective early effects of curcumin on lipid peroxidation, spinal cord ultrastructure and neurological functions after an experimental contusion injury.

MATERIAL and METHODS

Experimental groups

Adult female Wistar albino rats weighting 210-250 g were used for the study. The protocols were approved by the local institutional animal care committee. Animals were given free access to food and water, and kept under constant laboratory conditions of 20°C to 22° C in a humidity and light controlled room. The rats were randomly and blindly divided into five groups, each containing eight rats. Control group: Laminectomy was performed and non-traumatized spinal cord samples were obtained immediately. Trauma group: Laminectomy was performed and spinal cord samples were removed after motor and inclined plane testing at 24 h post-injury. MPSS group: Laminectomy was performed, animals were given a single dose of 30 mg/kg MPSS (Mustafa Nevzat, Istanbul, Turkey) intraperitoneally and immediately after trauma, spinal cord samples were obtained at 24 h post-trauma after motor and inclined plane testing. Curcumin group: Laminectomy was performed; curcumin (C7727) was dissolved in dimethyl sulfoxide (DMSO) solution and the animals were given a single dose of 300 mg/kg curcumin (Sigma-Aldrich, Gmbh Interlab-Istanbul,Turkey) intraperitoneally immediately after trauma. Spinal cord samples were obtained at 24 h post-injury after motor and inclined plane testing. Vehicle group: Laminectomy was performed, animals were given a single dose of 4 ml of DMSO (0.1 mg/kg) intraperitoneally and immediately after trauma, spinal cord samples were obtained at 24 h post-trauma after motor and inclined plane testing.

Surgical procedure

The surgical procedure was performed under general anesthesia induced by 10 mg/kg intramuscular xylasine (Bayer, Istanbul, Turkey) and 60 mg/kg ketamine hydrochloride (Parke Davis, Istanbul, Turkey). The rats were numbered with ear tags. Their middorsal area was shaved and disinfected with 10% of polyvinylpyrrolidone/iodine. The surgery was performed with the rats in the prone position. Following a T6-T12 midline skin incision, paravertebral muscles were dissected bilaterally. The T7-10 total laminectomy was performed. The dura was left intact. For creating moderate SCI, spinal cord contusion injury was produced by the 50 g/cm weight-drop method. The force was applied via a stainless steel rod with rounded surface (3 mm in diameter, weighing 10 g) through a 5 cm guiding tube positioned perpendicular to the center of the spinal cord. The rod made contact with the spinal cord after being dropped vertically though this tube (2). After the trauma, the exposed cord was closed. After 24 hours, approximately 15 mm of spinal cord segments between Th7 and Th9 were obtained from each rat for biochemical analyses. At the end of the experiment, all rats were sacrificed. All samples were kept in randomly numbered containers, and ultrastructural analyses were performed by researchers blinded to the treatment group.

Neurological examination

All rats were evaluated before and 24 h after surgery using inclined plane testing. The animals were allowed to move freely on the table while an observer recorded the motor score based on their movement. The neurological function of the hind limbs was assessed by the modified Tarlov's motor scale: 0 for no spontaneous movement; 1 for movement that was not reflexive and movement in the hip or knee but no ankle; 2 for movement of the limb in all 3 major joints; 3 for active support and uncoordinated gait or occasional short bouts of coordinated gait; 4 for coordination of forelimbs and hind limbs in gait (trotting), including some walking on knuckles or the medial surface of the foot or a few toe drags; and, 5 for normal walking behavior (21). In the inclined plane method, the rat was placed on a mat with the body axis perpendicular to the axis of an inclined plane. The angle of the plane was maximized so that a rat could maintain itself for at least 5 seconds (17).

Determination of MDA

MDA is one of the most frequently used indicators of lipid peroxidation. Tissue samples were taken from each group of rats were cleaned of blood with a scalpel and had the meninges carefully removed. The cord was immediately frozen and stored at -20 ° C to assay for MDA, which was measured using thiobarbituric acid reactive (TBAR) material following the method of Uchiyama and Mihara (25). The samples were homogenized in 10 volumes (w/v) of cold phosphate buffer (pH 7.4); about 0.5 ml of homogenate was mixed with 3 ml of 1% H_3PO_4. After the addition of 1 ml of 0.67% thiobarbituric (TBA), the mixture was heated in boiling water for 45 min. Color was extracted into N-Butanol and the absorption at 532 nm was measured. Using tetramethoxypropane as a standard, tissue lipid peroxide levels were calculated as nmol/g wet tissue.

Ultrastructural examination

Tissue samples were cleared of blood using a scalpel and the meninges were carefully removed. The cords were immediately fixed in 2.5% glutaraldehyde for 24 hours, washed in phosphate buffer (pH 7.4), postfixed in 1% osmium tetroxide in phosphate buffer (pH 7.4), and dehydrated using a graded alcohol series. The tissues were then washed with propylene oxide and embedded in epoxy resin. Semithin sections about 1 to 2 µm thick and ultrathin sections about 60 to 90 nm thick were cut using an ultramicrotome (LKB-Nova, Broma, Sweeden) with a glass knife. The semithin sections were stained with toluidine blue and examined using a light microscope. The ultrathin sections were collected on a copper mesh grid, stained with uranyl acetate and lead citrate, and examined using a transmission electron microscope (TEM; JEM 1200 EX; Jeal, Tokyo, Japan).For each sample, 100 each of the large-diameter myelinated axons, medium-diameter myelinated axon, small-diameter myelinated axon, and mitochondria were counted, evaluated and scored from 0 to 3 (Table I) as described by Kaptanoğlu et al. (11).

Table I: Grading System for Quantitative Evaluation of Ultrastructural Findings in Rats with Spinal Cord İnjury

Category	Score
Mitochondria	
Normal	0
Mitochondria with prominent cristae	1
Swollen mitochondria	2
Accumulation of amorphous substance	3
Small-diameter myelinated axons	
Normal	0
Separation in myelin configuration	1
Interruption in myelin configuration	2
Honeycomb appearance	3
Medium-diameter myelinated axons	
Normal	0
Separation in myelin configuration	1
Interruption in myelin configuration	2
Honeycomb appearance	3
Large-diameter myelinated axons	
Normal	0
Separation in myelin configuration	1
Interruption in myelin configuration	2
Honeycomb appearance	3

Statistical Analysis

All data were obtained and originally analyzed using SPSS 10.0.1 for Windows (SPSS Inc., Chicago, IL, USA) by researchers who were blinded to the treatment the rats received. To compare differences between three or more groups, one-way analysis of variance (ANOVA) was used. When a significant difference existed in ANOVA, the post-hoc multiple comparison test was applied to demonstrate the differences. Data are presented in the texts as the mean ± SD. For TEM scores, descriptive statistic is described as mean. After using Kolmogorow-Smirnov normality test, studying variants no normal distribution were found. The Kruskal-Wallis test was used to compare differentiation among the groups. A $p<0.05$ was accepted as statistically significant.

RESULTS

Tissue MDA Levels

The MDA levels of the trauma and control groups were statistically significant ($p<0.005$), and MDA levels were very high in the injured spinal cords. The MDA levels were highest in the trauma group, and lowest in the curcumin treatment group (Figure 1). When trauma groups were compared with MPSS, curcumin and DMSO treatment groups, the results showed significant statistical differences ($p<0.005$, respectively). In addition, MPSS inhibited lipid peroxidation less than the curcumin and DMSO groups ($p>0.005$). Comparisons between the curcumin and DMSO groups revealed significant statistical differences ($p<0.005$). The combination of curcumin and DMSO in the SCI model inhibited lipid peroxidation and decreased MDA levels more effectively than DMSO alone. In other words; curcumin treatment was more effective than MPSS and also decreased MDA levels to the levels observed before trauma.

Inclined plane values

All data were obtained and analyzed originally using the inclined plane developed by Rivlin and Tator (17). When the control group was compared with the trauma groups, MPSS, curcumin and DMSO groups, the results were statistically significant ($p<0.005$); but there were no significant differences between any of the trauma, MPSS, curcumin and DMSO groups ($p>0.005$) (Figure 2).

Neurological examination

All rats were evaluated neurologically before and 24 h after surgery with a modified Tarlov's scale (21). When the control group was compared with the trauma, MPSS, curcumin

and DMSO groups, the results were statistically significant (p<0.005); but there were no significant differences between any of the trauma, MPSS and curcumin and DMSO groups (p>0.005) (Figure 3).

Ultrastructural examination

Large- diameter myelinated axons: There was no statistically significant difference between any of the trauma, MPSS, or curcumin (Figure 4-upper left and Figure 5-left). There was a statistically significant difference between control and DMSO groups (p< 0.05), with DMSO protecting large-diameter myelinated axons (Figure 5-right).

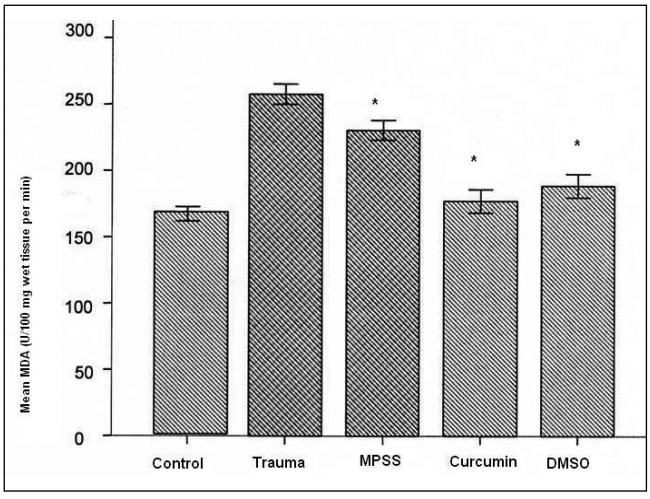

Figure 1: Spinal cord tissue MDA levels in control, trauma and treatment groups. The MDA content of the spinal cord is expressed as U/100 mg wet tissue per minute (mean±SD). DMSO, 0.1 mg/kg dimethyl sulfoxide; MPSS, 30 mg/kg methylprednisolone; MDA, Malondialdehyde. *Statistically significant difference from trauma group.(ANOVA/post-hoc multiple comparison, p<0.005).

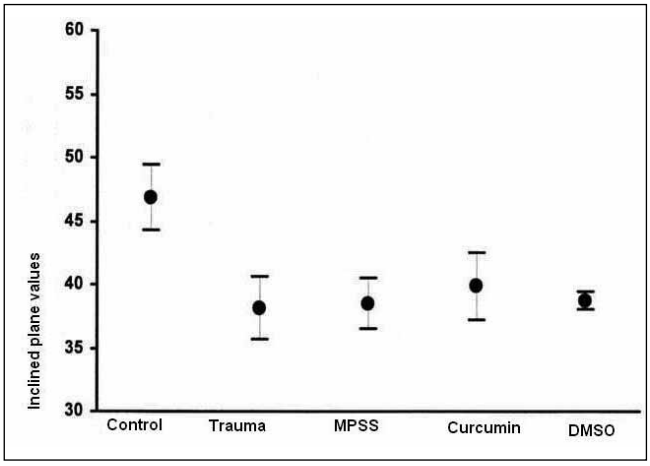

Figure 2: Inclined plane values in each group at 24 h. There was no statistical difference between trauma and therapy groups. DMSO, 0.1 mg/kg dimethyl sulfoxide; MPSS, 30 mg/kg methylprednisolone. (ANOVA/post-hoc multiple comparison, p>0.005).

Medium myelinated-diameter axons: There was a statistically significant difference between the trauma and control groups, with trauma found to injure medium-diameter myelinated axons (p<0.001). However, there was no statistically significant difference between any of trauma, MPSS, or curcumin. Similarly, there was no statistically significant difference between control and DMSO groups. There was a statistcally significant difference between DMSO and the trauma, between DMSO and MPSS, and between DMSO and curcumin, with DMSO a providing protective effect (p<0.001)(Figure 4-upper right).

Small-diameter myelinated axons: There was no statistically significant difference between any of control, MPSS, or DMSO groups. There was a statistically significant difference between trauma and curcumin groups (p< 0.05), indicating that pathologic changes with curcumin treatment in the small myelinated axons is more than the trauma group (Figure 4-lower left).

Mitochondria: There was a statistically significant difference between the trauma and control groups, with trauma found to injure mitochondria. Similarly, there was a statistically significant difference between the trauma and MPSS, between the trauma and curcumin, and between the trauma and DMSO (p<0.001), with MPSS, curcumin and DMSO providing protective effect. However, there was no statistically difference between MPSS and curcumin. There was a statistically significant difference between DMSO and curcumin (p<0.001), indicating that DMSO has more protective effect on mitochondria than curcumin (Figure 4-lower right).

DISCUSSION

Traumatic injuries to the spinal cord cause tissue damage through primary and secondary mechanisms. Free radical-induced lipid peroxidation is believed to play an important role in the pathogenesis of secondary injury (8,14,15,23). In addition, free radicals cause the most destructive effect on

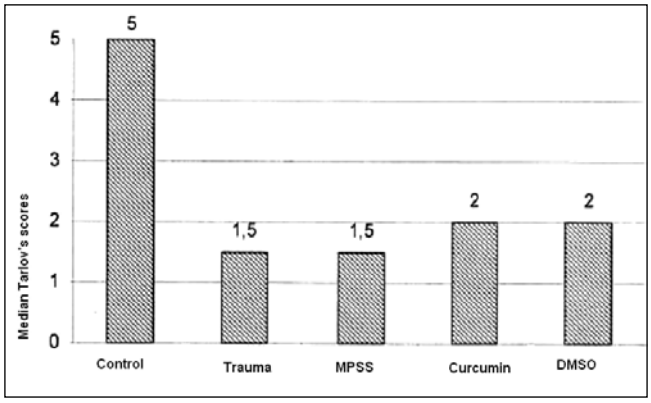

Figure 3: All rats are evaluated neurologically before and 24 h after surgery with a modified Tarlov's scale. There were no statistically significant differences between trauma and treatment groups. DMSO, 0.1 mg/kg dimethyl sulfoxide; MPSS, 30 mg/kg methylprednisolone. (ANOVA/post-hoc multiple comparison, p>0.005).

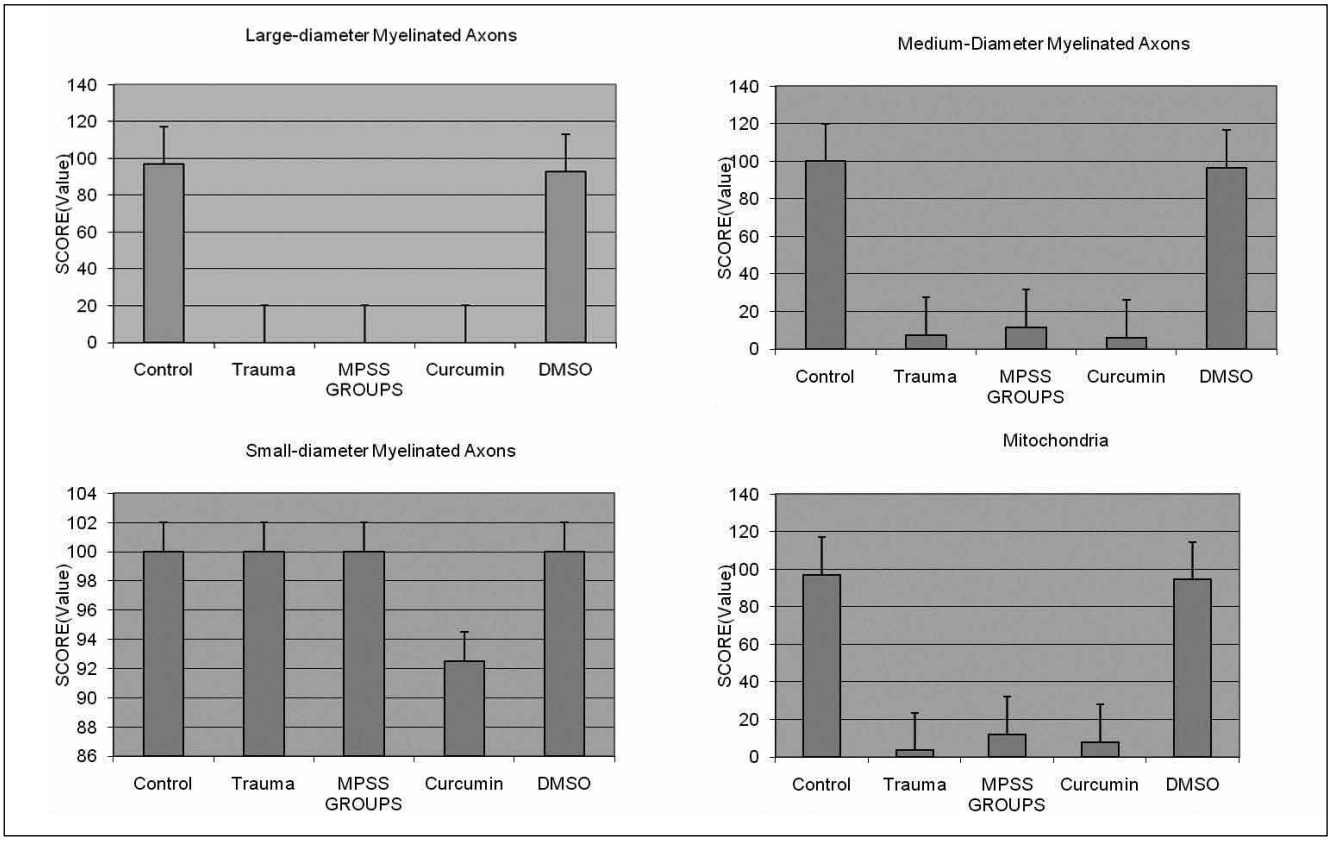

Figure 4: Graphics shows the effect of trauma and treatments on spinal cord ultrastructures. Note that ultrastructural score in the trauma group lower than control. Treatments with MPSS and curcumin shows lower scores, indicating less preservation of spinal cord. Especially, treatments with DMSO show higher scores than MPSS and curcumin and scores with DMSO are similar with control group [**upper-left,** large (LMA)-diameter myelinated axons, (Kolmogorow-Smirnov normality test, $p<0.05$); **upper-right,** medium (MMA)-diameter myelinated axons, (Kolmogorow-Smirnov normality test, $p<0.001$); **lower-left,** small(SMA)-diameter myelinated axons (Kolmogorow-Smirnov normality test, $p<0.05$); **lower-right,** mitochondria(MITO), (Kolimogrow-Smirnow normality testt, $p<0.001$)] .

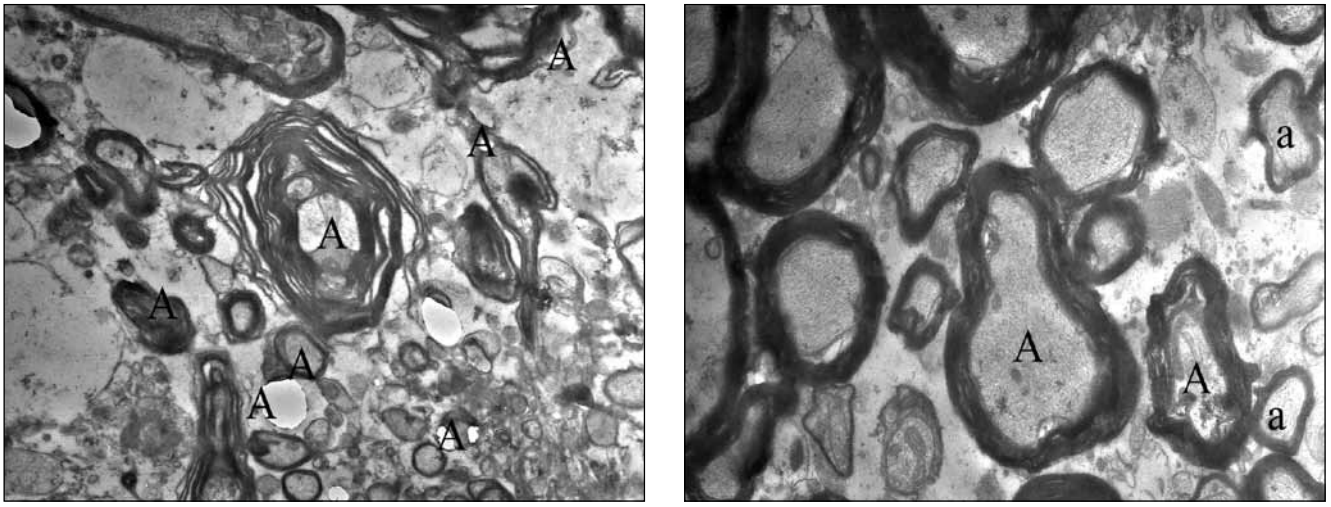

Figure 5: Transmission electron micrograph of spinal cord sections from spinal cord injured rats with Curcumin and DMSO Treatment. Original magnification x7500. **Left:** Curcumin; pathological changes in the myelinated axons is more than the trauma group. Separation and interruption in myelin configuration were observed in large-sized, medium sized and small-sized myelinated axons. **Right:** DMSO; ultrastructural findings were similar with the control group. Separation in myelin configuration was observed in a small number of large and medium-sized myelinated axons. The small-sized myelinated axons, unmyelinated axons, the nuclei and cytoplasms of neurons were normal ultrastructurally. Pathological myelinated axons (A) and normal myelinated axons, (a).

the central nervous system with lipid peroxidation. One of the most important causes of secondary injury is the inability of the ischemic cell to supply energy from normal biochemical pathways. Such secondary damage leads to a large number of cellular, molecular, and biochemical events that result in tissue necrosis and functional deficits because of the disruption of cell membranes (9).

Curcumin is known for its antitumor, antioxidant, antiarthritic, antiamyloid, antiischemic and antiinflammatory properties. It acts as a free radical scavenger and antioxidant, inhibiting lipid peroxidation and oxidative DNA damage. Curcuminoids induce glutathione S-transferase and are potent inhibitors of cytochrome P450. Consequently, as a cumulative effect, curcumin attenuates Ca and Na influx in neurons and inhibits neutrophil chemotaxis (12,26).

MDA levels are important criteria for determining the degree of the peroxidation reaction. Mu et al. reported that MDA levels had increased 1 h after injury and remained at high levels for 24 h (13). In the present study, tissue MDA levels were similar to other studies in the literature. Generally, the worsening of neurological function in patients with SCI was seen 24 hours after the trauma (16). If MDA levels after the trauma were low, functional neurological recovery and the rate of healing would be better in the acute period (13). We tried to determine if this is correct for spinal cord injury. The membrane attack by free radicals and phospholipases causes lipid peroxidation, leading to the production of MDA and 4-hydroxy-2(E)-noneal (4-HNE). 4-HNE has been shown to be a strong chemotactic agent for rat neutrophils (8). Curcumin inhibits apoptosis and decreases the subsequent period of neurological recovery. We demonstrated that a single dose of 300 mg/kg of curcumin decreases the spinal cord MDA level.

Although there has been recent controversy regarding the effectiveness and complications of MPSS, some authors suggested that all pharmacological agents used in SCI studies should be compared with MPSS. This agent is the only one used by many centers (8,16). We compared the results of curcumin treatment with MPSS, and the results of the present study demonstrated that spinal cord MDA levels at the 24th hour in the MPSS group were lower than in the trauma group but higher than in the curcumin group, and the differences were statistically significant ($p<0.005$). DMSO alone did not decrease spinal cord MDA levels as much as curcumin. Neurological recovery was also much more satisfactory with curcumin upon examination at 24th hour, but difference was not statistically significant ($p>0.005$).

Since dimethyl sulfoxide (DMSO) readily crosses most tissue membranes and penetration of other molecules, it was used as a vehicle. In addition, DMSO is a widely used solvent for hydrophobic pharmaceutical agent and recognized as being a relatively effective hydroxyl radical scavenger (22). Researchers indicate that DMSO shows faster sensory-motor recovery, reduced neural damage to the cord, lower swelling of tissue after trauma, increased muscle tone return, and earlier return of somatosensory evoked potentials than comparable treatments. These protective effects have been showed in animal models of CNS injury and in humans with traumatic brain injury and ischemic stroke (10). In the present study, although strongest protective effects on spinal cord ultrastructure was observed after DMSO treatment alone, ultrastructural findings indicated that large and medium myelinated axons and mitochondria were lightly protected from injury when rats were treated with curcumin treatment. In addition, these findings indicated that combining curcumin with DMSO did not result in considerable synergy in protecting residual rat's spinal cord after an experimental contusion injury.

In conclusion, the results of our study show that intraperitoneally administrated curcumin (300 mg/kg) has a benificial effect on SCI by decreasing MDA concentration. Curcumin may protect the spinal cord from lipid peroxidation but such biochemical finding was not supported by ultrastructural and neurological findings. In other words, curcumin has more of a biochemical effect than ultrastructural change in neuroprotection effect and that it will need to be combined with DMSO for effective action. These findings clearly indicate for the first time that a single effector molecule as in DMSO may be more effective on spinal cord ultrastructure than a combination of curcumin and DMSO. The ultrastructural change should be studied with administration of curcumin alone to prevent bias. Studies with combining curcumin with other solvent may also result in considerable synergistic activity in protecting spinal cord ultrastructure. Effect of Curcumin on delayed spinal cord injury needs to be studied in addition.

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