Alpha-Lipoic Acid Inhibits Peridural Fibrosis Following Laminectomy through the Inactivation of TGF-β1, PDGF, PAI-1 and IL-6 Expressions

Alfa-Lipoik Asit Laminektomi Sonrasında Oluşan Peridural Fibrozisi TGF-β1, PDGF, PAI-1, ve IL-6 Ekspresyonlarını İnaktive Ederek Önlemektedir

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ABSTRACT

AIM: The objective of this study was to investigate the antifibrotic effect of parenteral administration of alpha-lipoic acid (ALA), which has been reported to reduce fibrosis in the liver, oral mucosa, and peritoneum, in laminectomized rabbits as a potential candidate for the prevention of peridural fibrosis.

MATERIAL and METHODS: Twelve adult New Zealand white male rabbits were divided into control (n=6) and ALA treatment groups (n=6). Laminectomy of the lumbar spine was performed in all animals, and ALA was administered intramuscularly in six rabbits composing the treatment group. Total RNA obtained from the paraffin-embedded tissues was analyzed for transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), plasminogen activator inhibitor-1 (PAI-1) and interleukin-6 (IL-6).

RESULTS: mRNA investigations showed that TGF-β1, PDGF, PAI-1 and IL-6 gene expressions, which constitute strong evidence for the development of fibrosis, were significantly lower in the treatment group compared with the results obtained from the control group. According to the histological peridural grading, the ALA-treated group showed significantly less peridural fibrosis than the control group.

CONCLUSION: Intramuscular administration of ALA is a promising treatment for the prevention of peridural fibrosis in the postoperative period.

KEYWORDS: Failed back surgery syndrome, Alpha-lipoic acid, Peridural fibrosis, Rabbit

ÖZ

AMAÇ: Çalışma, daha önce karaciğer, oral mukoza ve periton fibrozisini önlediği bildirilen alfa lipoik asidin (ALA) peridural fibrozisin önlenmesinde kullanılabileceği düşüncesi ile laminektomi yapılan tavşanlarda parenteral uygulamadan sonraki antifibrotik etkisini araştırmak için yapılmıştır.

YÖNTEM ve GEREÇLER: On iki yetişkin beyaz erkek Yeni Zelanda tavşanı kontrol (n=6) ve ALA-deney (n=6) grupları olarak ikiye ayrıldı. Bütün hayvanlarda laminektomi yapıldı ve deney grubunu oluşturan 6 tavşana intramüsküler ALA uygulandı. Parafine konulmuş olan dokulardan elde edilen RNA'dan transforme edici büyüme faktör-β1 (TGF-β1), platelet-kaynaklı büyüme faktörü (PDGF), plasminojen aktivatör inhibitor-1 (PAI-1) ve interlökin-6 (IL-6) analizleri yapıldı.

BULGULAR: mRNA RT-PCR sonuçları fibrozis oluşumunda güçlü delil olan TGF-β1, PDGF, PAI-1 ve IL-6 gen ekspresyonlarının deney gruplarında kontrol gruplarına göre anlamlı şekilde düşük olduğunu gösterdi. Histolojik peridural fibrozis sınıflandırılmasına göre de deney grubunda kontrol grubuna göre çok daha az fibrozis oluşmuştu.

SONUÇ: İntramüsküler ALA uygulaması, postoperatif dönemde fibrozisin önlenmesinde ümit vadeden bir yöntem olarak dikkati çekmektedir.

ANAHTAR SÖZCÜKLER: Başarısız bel cerrahisi sendromu, Alfa lipoik asit, Peridural fibrozis, Tavşan

INTRODUCTION

Fibrosis is a natural healing process and defined by the overgrowth, hardening, and/or scarring of various tissues, and attributed to excess deposition of cellular matrix components including collagen. Epidural fibrosis is encountered after almost every lumbar spinal operation at a certain rate; its influence on the nerve structures during scar tissue development is very well known and it is a serious cause of the failed back surgery syndrome in up to 25 % of operative cases (50).

Numerous synthetic and natural materials such as, polytetrafiuoroethylene, free fat transplantation, protein-based polymer, high-molecular weight hyaluronan, Oxiplex/SP, DuraGen (52), antineoplastic agents (68), fibrinolytic agents (13), anti-inflammatory agents (21), and low-dose radiation (18) have been evaluated to prevent or reduce postoperative peridural scar formation in both animal and human studies.

The accumulation of extracellular matrix protein (ECM) is the key pathological feature of fibrosis. The ECM accumulation level is subject to balance between its synthesis and breakdown. In case of synthesis excess degradation, over accumulation of ECM cause to the development of fibrosis (17, 61).TGF-β plays a critical role in the development of hepatic fibrosis through its stimulating effect on matrix protein generation and its inhibitory effect on matrix protein removal (19, 34). Increment in TGF-β expression has been reported in bile duct-obstructed liver tissue; it has been also found that transcription of genes take part in ECM protein accretion rise (39, 67). Additionally, TGF-β stabilizes ECM proteins through stimulation of protease inhibitors such as PAI -1. To prevent hepatic fibrosis, TGF-β signaling has been employed in diverse therapeutic approaches (40). It is now widely accepted that reactive oxygen species (ROS) play a key role in hepatic fibrosis development by increasing ECM accumulation (6, 23). Several studies have revealed that an increase in ROS secondary to hepatic injury induces TGF-β synthesis that leads ECM-producing gene expression upregulation by Smad activity (27, 35). In addition, TGF-β increases cellular levels of ROS, and thus activates mitogen-activated protein (MAP) kinase pathways that induce redox-sensitive transcription factors AP1 and SP1 (25, 62). Furthermore, PDGF and TGF-β, two major fibrotic growth factors in liver fibrosis, are reported to signal in part through ROS (14,30,58,60).

PAI-1 is the main physiological inhibitor of the tissue and urokinase plasminogen activator and is considered to be the most important inhibitor of fibrinolysis (9, 38, 65). Evidence suggest that PAI-1 is also capable of causing the direct accumulation of ECM and indirectly inhibit matrix metalloproteinases (MMPs) (2, 12, 36). A study has suggested that PAI-1 plays a crucial role in the development of hepatic fibrosis (7). PAI-1 deficiency reduces liver injury and fibrogenesis secondary to experimental bile duct ligation (64, 65).Hu et al. reported that RNAi-mediated down regulation of PAI-1 had a hepatoprotective effecr and resulted in the significant regression of liver fibrogenesis in both bile duct ligation and chemical-induced hepatic fibrosis by increasing matrix degradation (22).

Chronic inflammation triggers an excessive accumulation of ECM components leading to formation of a permanent fibrotic scar. IL-6 acts as a proinflammatory cytokine, and we therefore considered that it may play a role in the development of fibrosis. Since it has been reported that ALA inhibits proinflamatory cytokine-induced vascular inflammation and ROS-induced endothelial injury (32), we decided to investigate the IL-6 levels in fibrotic tissues treated with ALA and realized that IL-6 levels were significantly low compared to the levels in untreated tissues. This is the first study investigating the IL-6 levels and the effects of ALA on these levels in fibrotic tissue.

Alpha-lipoic acid (ALA) inhibits liver fibrosis through its antioxidant activities and its ability to induce matrix metalloproteinase-13 (MMP-13) and to inhibit transforming growth TGF-β, PDGF, and PAI-1 (16). These findings suggest that ALA, which is a naturally occurring thiol antioxidant, may have a clinical application in preventing the development and progression of hepatic fibrosis (37). A protective effect of ALA on the development of oral submucous fibrosis (48) and postoperative peritoneal adhesions and fibrosis (43) has also been shown. Furthermore, a study performed in our institution showed that ALA applied topically to the peridural area after laminectomy reduced peridural fibrosis significantly in rabbits (26).

ALA and its reduced form, dihydrolipoic acid (DHLA), have gained considerable attention because of their roles as biologic thiol antioxidants, which are central to the antioxidant defense in the brain and other tissues. ALA, as a metabolic antioxidant, readily crosses the blood brain barrier and is accepted by human cells as a substrate, and is reduced to DHL A (docosahexaenoic acid) (51). Since hepatic fibrosis is the most widely investigated area and PDGF, TGF-β, PAI-1 are the factors have already been proven to cause hepatic fibrosis, we measured the expression of these molecules in peridural fibrosis in rabbits, and found parallel results. Intramuscular ALA-treatment revealed similar down-regulating effect on these substances as seen in hepatic fibrosis. This is the first detailed study investigating the antifibrotic effect of ALA in peridural fibrosis.

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The results of the studies mentioned above and the findings of our previous experiments suggest that topically-applied ALA prevents postoperative peridural fibrosis in vivo. The aim of this study was to investigate the efficacy and molecular basis of systemic application of ALA via intramuscular administration in preventing epidural scar tissue formation.

MATERIAL and METHODS

Experimental Design

Twelve adult New Zealand white male rabbits weighting 3.5-4 kg were used in this study. The study was conducted at the Kafkas University, Faculty of Medicine, Laboratory for Experimental Animals with the approval of the local ethics commission. All animals received humane care as outlined in the "Guide for the care and use of laboratory animals" (41). The animals were deprived of food for 24 h before surgery, but were allowed free intake of water. The animals were randomly allocated in two groups. In group 1 (control group, n=6) only laminectomy was performed to the animals; in group 2 (ALA applied group, n=6) rabbits received 50 mg/kg/day ALA (Thioctacid 600 T, M EDA Hamburg, Germany) intramuscularly for fifteen days after the laminectomy. Preoperative or postoperative antibiotic prophylaxis was not applied to any group.

Surgical Procedure

Rabbits in the control and treatment groups were anesthetized via the intramuscular route by 60 mg/kg ketamine (Ketalar. Pfizer, Istanbul) and 9 mg/kg xylazine (Rompun. Bayer, Istanbul). An additional dose was administered for extending the anesthesia duration if required and this was at 20% of the original dose of medications mentioned above. Following anesthesia, the animals were stabilized on the operation table in the prone position. The lumbar region was shaved and cleaned with the antiseptic povidone iodine (Drogsan, Istanbul). The rectal temperature was recorded continuously and we elaborately strived to be keep it around 37°C during the whole surgical procedure. Following a 4-cm midline skin incision starting from the L5 level and going upwards, the lumbar fascia was opened bilaterally from the midline and bilateral subperiosteal dissection of paravertebral muscles was carried out. The L5 level was determined by palpation of the iliac wings. Following the removal of the spinous processes, L3 and L4 total laminectomy was performed with a one-mm Kerrison Rongeur under the operating microscope (Möller-Wedel, Wedel, Germany) at x10 magnification. The ligamentum flavum and epidural fat tissue were removed and the dura mater exposed, Following hemostasis, the operation field was irrigated and cleaned with physiological saline solution; the muscles, paravertebral fascia and skin were closed with 3/0 vicryl.

Six rabbits in the experiment group were treated with 50 mg/kg/day ALA (Thioctacid 600 T, MEDA Hamburg, Germany) intramuscularly for fifteen days.

The rabbits were sacrificed at the 45th postoperative day (6th week) as described previously by others (13) with an overdose of ketamine (100 mg/kg). The paravertebral region was exposed and each vertebral column was resected in an en bloc fashion.

RT- PCR

Total RNA was isolated from FFPE (Formalin-fixed paraffin embedded) tissues by using TRIzol reagent (1). TGFβ1, IL-6, PDGF, PAI-1and β-actin were used for RT-PCR. Total RNA was treated with RQ1 DNAse I (Promega). Reverse transcription (RT) was performed according to the manufacturer's (Fermentas) directions using 1 unit of MMLV reverse transcriptase with 5 μg of total RNA and oligo dT22 primer. PCR was performed with 1 μL of diluted cDNA (1:10) in a total volume of 25 μL using Taq DNA Polymerase enzyme for 27 cycles in the exponential range with primers (Table I) were used to confirm that equal amounts of total RNA were used for each time point in the reverse transcription.

Pathological Examination and Grading

Vertebral column segments were fixed in 10 % buffered formalin overnight and decalcified with 5% hydrochloric acid solution for 48 h. Vertebral columns were sectioned in 4-mm-thick slices horizontally. One section from uninvolved thoracic vertebrae acted as an internal control, and four consequent sections from the laminectomized vertebra (Figure 1) were taken and embedded in paraffin blocks separately. Routine hematoxylin-eosin (H&E) and Masson-Trichrome staining was performed on the 5-μm-thick sections of vertebrae.

Microscopical sections were evaluated blindly by the pathologist (H.U) in experimental groups using an Olympus BX5I microscope. Dural fibrosis was graded according to He et al. (21), as summarized in Table II. Sections were stained with myogenin (Biosb, CA, USA) for myofibroblast presentation.

Statistics

For the statistical analysis, a non-parametric test (Mann-Whitney U test) was used in order to compare two groups. Analyses were performed with SPSS for Windows (version 15.0.0; SPSS, Chicago, IL) using a personal computer.

Table I: The Primers Used in the Study

TGFβ1	F; 5'ATGCCGCCCTCCGGGCTGCGG 3' R; 5'TCAGCTGCACTTGCAGGAGCG 3'
PAI-1	F; 5' ATGGAATTCCCGTGGAACAAGAAT GAGATCAG 3' R; 5'TGAGCCATCATGGGCACAGAG 3'
PDGF	F; 5'CCTCATAGACCGCACCAA 3' R; 5'CGCACAATCTCGATCTTTCT 3'
IL-6	F; 5'TCCTGGAGACCATCAAGGAG 3' R; 5'GGGTGGCTTCTTCATTCAAA 3'
β-actin	F; 5'TGATGACATCAAGAAGGTGGTGAAG 3' R;5'TCCTTGGAGGCCATGTGGGCCAT3'

RESULTS

In ALA-treated animals, over expression of the genes TGFβ1, PDGF, PAI-1 and IL-6 was additionally confirmed by RT-PCR (Figure 5). The mRNA expression levels of TGFβ1, PDGF, PAI-1 and IL-6 were investigated by using the RT-PCR method. In the mRNA levels of TGFβ1, PDGF, PAI-1 and IL-6 are shown in figure 5. The β-actin gene was used as control, and the level of β-actin transcript was equal at all time intervals (Figure 5). mRNA investigations showed that TGF-β1, PDGF, (PAI-1) and IL-6 gene expressions were significantly lower in the treatment group compared with the results obtained from the control group. Internal controls of both control and ALA groups were free of fibrosis (Figure 2A, B, C-grade 0). Animals treated with ALA produced significantly less peridural fibrosis (Figure 3 A, B-grade 1-2) than the control group (Figure 4 A, B-grade 3). Dense fibrosis, observed in the control group, was inhibited with the use of ALA (Table III). Myogenin immunohistochemical staining demonstrated increased myofibroblast staining in the control group. Staining was significantly less in the treatment groups.

DISCUSSION

When tissues and endothelial cells are damaged, they release inflammatory mediators that initiate the anti-fibrinolytic coagulation cascade (28) that triggers blood clot and provisional extracellular matrix (ECM) formation. Since platelets are exposed to ECM components, they trigger aggregation, clot formation and hemostasis. Degranulation of platelets also induces vasodilation and blood vessel permeability, while myofibroblasts (activated collagen secreting, α- smooth muscle actin+ (α-SMA+) fibroblasts] and epithelial and/or endothelial cells produce matrix metalloproteinases (MMPs), which disrupt the basement membrane, allowing inflammatory cells to be easily recruited to the site of injury. Growth factors, chemokines and cytokines, which stimulate the proliferation and recruitment of leukocytes across the provisional ECM are also produced.

Table II: Pathological Grading System

Grade 0	The dura is free of scar tissue
Grade 1	Presence of only thin fibrous bands between dura and scar tissue
Grade 2	Continuous adherence between dura and scar tissue involving <2/3 of laminectomy defect
Grade 3	Scar tissue adherence ≥2/3 of laminectomy defect and/or extended to nerve roots

Macrophages, and neutrophils, which eliminate tissue debris, dead cells and any invading organisms,respond early. Moreover, they produce cytokines and chemokines, which are mytogenic and chemotactic for endothelial cells, which begin to surround the injured site. They also help formation of new blood vessels since epithelial/endothelial cells migrate towards the centre of the wound. In the meantime, lymphocytes and other cells are activated and start to secrete including TGF β, IL-13 and PDGF (33, 45, 66). They then activate macrophages and fibroblasts. After activation of fibroblasts, they change into SMA-expressing myofibroblasts. Thus, they can migrate along the fibrin lattice into the wound. Subsequent to activation, myofibroblasts lead to wound contraction, the edges of the wound migrate towards the centre, and the wound-healing process is completed (45).

On the other hand, chronic inflammation and repair can trigger over deposition of ECM components. This accumulation results in the formation of a permanent fibrotic cicatrix. Collagen conversion and remodeling of ECM are regulated by diverse MMPs and their inhibitors including tissue inhibitors of metalloproteinases. Shifts occur in synthesis against the ECM catabolism regulate the net collagen increment or decrement in wound (44). If collagen production is more than its degradation in myofibroblats, fibrosis takes place. Thus, the total collagen amount increases in time.

Wound healing by fibrosis is a major medical problem in humans and animals, often resulting in loss of function, restriction of tissue movement and adverse psychological effects. Peridural fibrosis inevitably occurs after lumbar spinal operations but sometimes manifests as the sole reason for failed back surgery syndrome (15, 69). Although excessive scarring may cause tethering of neural elements and radicular symptoms, it also increases incidental durotomy rates during revision surgeries and can cause poorer outcomes (63). Fibrosis is defined as the overgrowth, hardening, and/or scarring of various tissues and attributed to excess deposition of extracellular matrix components, including collagen. The key cellular mediator of fibrosis is the myofibroblasts, which when activated serve as the primary collagen-producing cell (66), In the process of scar tissue development, a number of different inflammatory substances present initially.

Important regulators of fibrosis are cytokines (IL-13, IL-21, TGF-βI), chemokines (MCP- I, MIP-1β), angiogenic factors (VEGF), growth factors (PDGF), peroxisome-proliferator-activated receptors (PPPARs), acute phase proteins (SAP), caspases, and components of the renin-angiotensin-aldosterone system (ANG II). These regulators, therefore, are considered as potential targets for antifibrotic therapy (5 ,31, 66). Overproduction

Table III: Comparison of Control and ALA Groups

Group	Mean Grade	± SD	Median Grade
Control n=6	2.70	0.43	3
ALA n=6	1.45	0.55	1

p=0.005.

of TGF-β1 and suppression of PGE2 and TGF-β3 are found in excessive wound scarring compared with normal wound healing (29, 56) stated that the migration of fibroblasts (derived from the erector spinae muscles) into the hematoma in the epidural space causes intensive scar formation and epidural fibrosis. The basic content of epidural fibrosis is collagen and produced by fibroblasts. Barbera et al. (4) reported that collagen was the main substance that was derived from spinal muscles and filled the laminectomy defect, and its quantity was also reported to be proportional with scar tissue.

Another factor causing inflammation in the laminectomy site, which in turn leads peridural fibrosis, is the phospholipase A$_2$ cascade. After laminectomy or discectomy, daily activities of the patient cause traction of the dura and nerve roots. Therefore, phospholipase A2 is released and leads to chronic inflammation at the discectomy site (53). A study of human intervertebral disc material obtained from patients who underwent laminectomy and discectomy has shown that the nucleus pulposus contains extremely high levels of potentially inflammatory phospholipase A2 (53).

Further studies have revealed that phospholipase A2 triggers off the arachidonic cascade and produces inflammatory intermediates, such as prostaglandins, prostanoids, leukotrienes, platelet activated factor, and lysophospholipids in addition to exerting a direct inflammatory effect on cell membranes.

Prostaglandins E1 and E2 and leukotriene B generation aggravate the inflammatory process (21, 24).

Taking into consideration of phospholipase A2 cascade, it might be postulated that the inflammatory process taking place in wounds after laminectomy or discectomy can be expected to be two-three folds of those in natural wound healing and consequently, more fibrotic tissue accumulation would be expected to occur. Robertson placed ultrafiltrate catheters in the epidural spaces of dogs that were subjected to both simple laminectomy and discectomy (50). The catheters collected cell-free serous fluid, which was then analyzed for levels of prostaglandin E2. The values were significantly higher at the discectomy and laminectomy sites
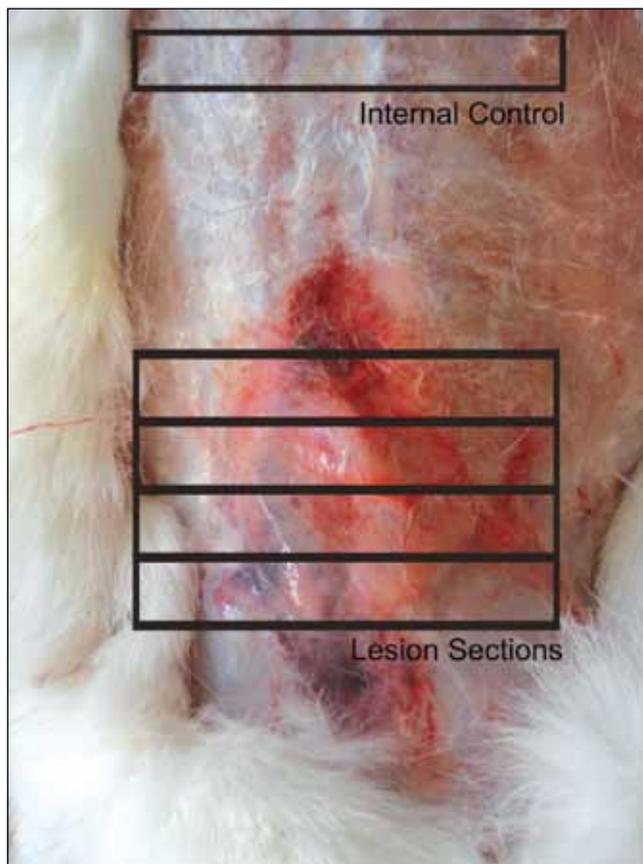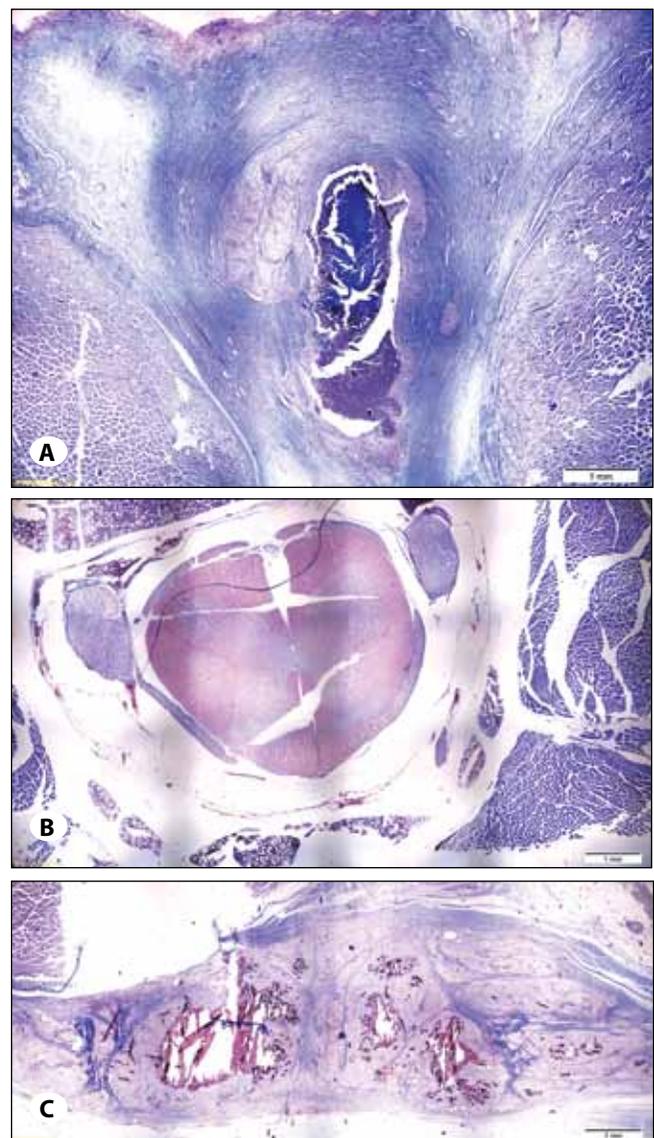

Figure 2: A) Control group-Internal control- grade 0- Original magnification x400-Panoramic-Masson-Trichrome. **B)** Control group, grade 0- Original magnification x400-Panoramic-Masson-Trichrome. **C)** Control group-grade 0- Original magnification x400-Panoramic-Masson-Trichrome.

Figure 1: Sections taken from each vertebral column of animals.

compared to the subcutaneous site, which resembles normal wound healing.

Hereditary biological response or vascular tissues to hazardous agents including pathogens, damaged cells, or irritants leads to inflammation. Organism make an attempt to remove stimulation of injury, protect the surrounding tissue and
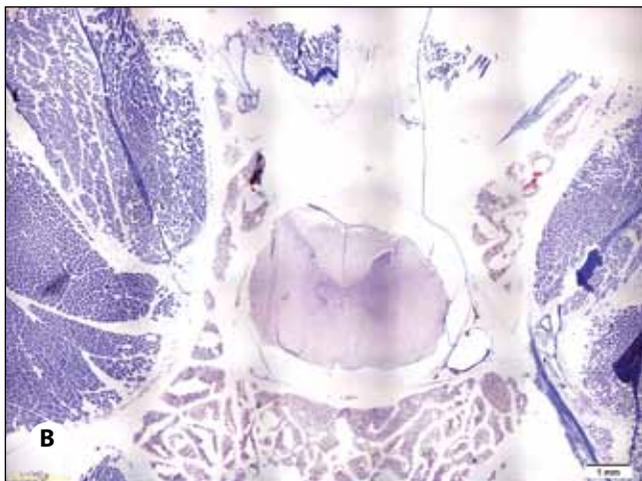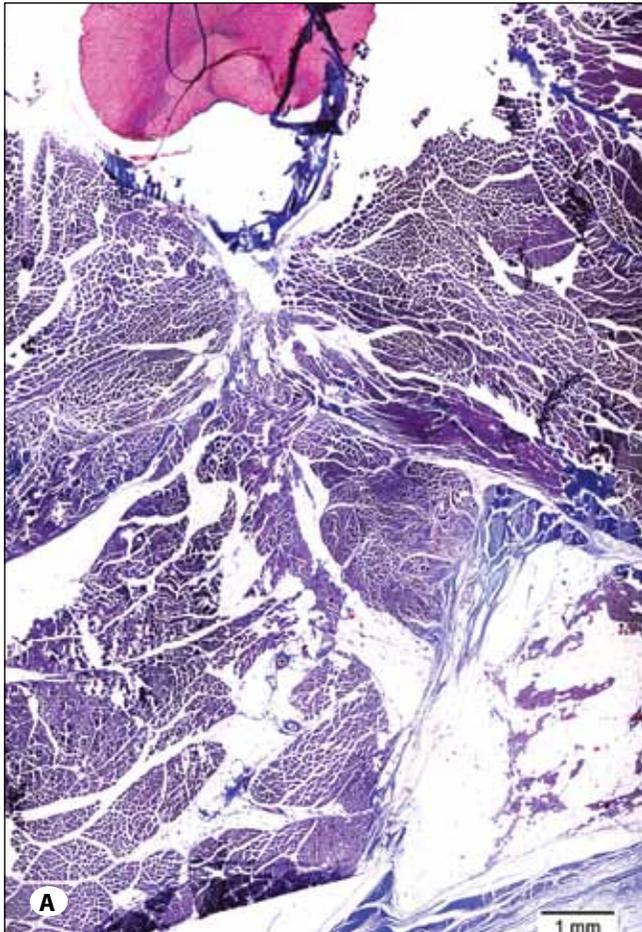

Figure 3: A) Grade-1-scar tissue, Original magnification x400-Panoramic-Masson-Trichrome. **B)** Grade-2-spinal canal, Original magnification x200- Masson-Trichrome.
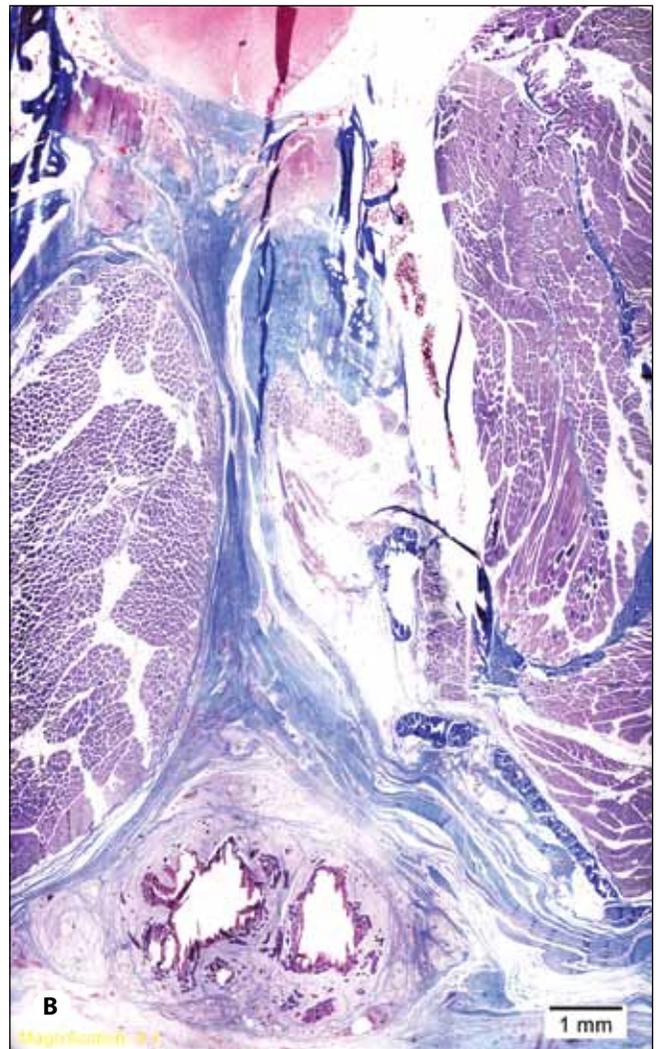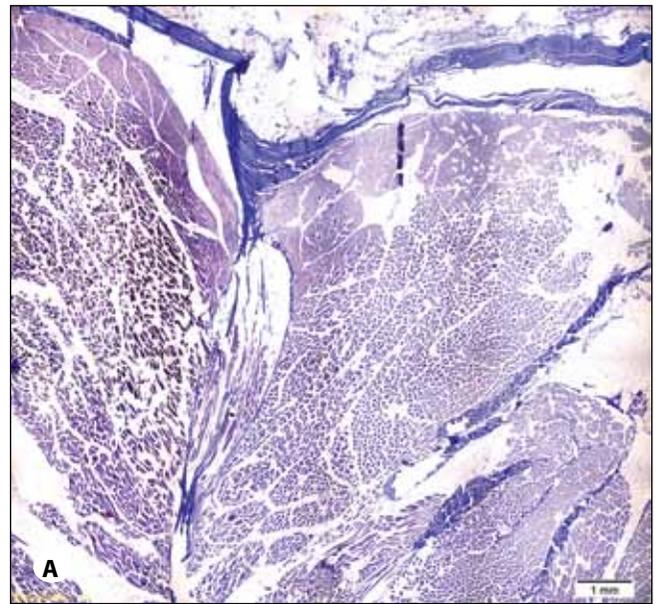

Figure 4: A) Grade-3-scar tissue, Original magnification x400-Panoramic-Masson-Trichrome. **B)** Grade-3-spinal canal, Original magnification x200- Masson-Trichrome.
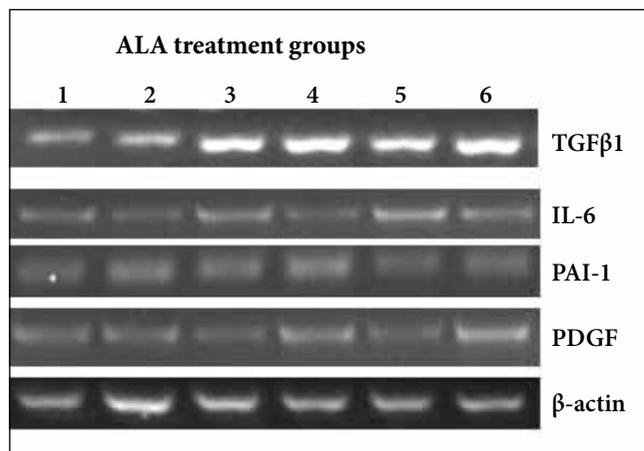
Figure 5: Agarose gel electrophoresis of the RT-PCR amplified fragment of TGFβ1, IL-6, PAI-1 and PDGF (A) and the amplified internal control (actin; B). After RT-PCR, cDNA products were analyzed with 1% agarose gel including ethidium bromide.

lead the healing process. In addition, chronic inflammation contributes to host disease such as atherosclerosis, asthma, and rheumatoid arthritis, including fibrosis. High oxidative stress levels play a key role in chronic inflammation (55). Although some studies have suggested that ongoing inflammation is needed to reverse established and progressive fibrosis (24), current treatment for fibrotic diseases such as idiopathic pulmonary fibrosis, liver cirrhosis, systemic sclerosis, progressive kidney disease and cardiovascular fibrosis typically target the inflammatory response. Oxidative stress-associated inflammation is thought to provoke early vascular events in atherogenesis, including the upregulation of vascular adhesion molecules and matrix metalloproteinase activity.

Inflammation is naturally oxidative, and medical approaches, studied on several inflammation models, therefore aim to moderate oxidative damage and the production of oxidants. In this context, the antioxidant properties of ALA have been studied in cytokine-induced inflammation (55).

ALA or 1, 2- dithiolane-3-pentanoic acid is a naturally occurring compound synthesized enzymatically in the mitochondrion from octanoic acid. Oxidized (ALA) and reduced forms (DHLA) generate a potent redox couple with a reduction potential of 0,32 V making DHLA a powerful naturally occurring antioxidant (3, 54). It is widely recognized to prevent diabetic polyneuropathies (70), scavenge free radicals (59), chelate metals (57), and restore intracellular glutathione levels (11). Current approaches aimed at treating fibrosis are primarily directed at inhibiting cytokines (TGF β1, IL-13), chemokines, specific MMPs, adhesion molecules, integrins and inducers of angiogenesis, such as VGF (49). There are also reports in recent years that ALA inhibits liver fibrosis through the attenuation of reactive oxygen species (ROS)-triggered signaling in hepatic stellate cells activated by PDGF and TGF-β (16, 29).

Considering the data accumulated until now, and results of studies on the attenuating effect of ALA in the development of fibrosis, we topically applied ALA on the exposed dura of rabbits after laminectomy was performed. We found that animals treated with ALA produced significantly less fibrosis compared to the control group (44). The results obtained from this study prompted us to investigate systemic application of ALA to discover whether it exerts similar results in preventing the development of fibrosis. Results obtained from intramuscular application of ALA were exactly identical as of the topical application. Deposition of fibrosis in ALA treated animals was significantly lesser comparing the control group animals. In the present study we demonstrated that ALA inhibited fibrosis and (PAI-1) expression in peridural fibrosis induced by laminectomy in rabbits. Ala decreased TGF-β-induced PAI-1 gene expression through the inhibition of TGF-β. Our present results also show that ALA suppresses the level of PDGF, a widely known fibrogenetic factor, in peridural fibrotic tissues.

To date, the anti-inflammatory properties of ALA have rarely been investigated in humans. One of the trials showed a 15% decrease in serum interleukin-6 levels following 4 weeks of ALA (300 mg/day) addition (42, 55). In our study, IL-6 measurements revealed that ALA suppresses this cytokine in peridural fibrosis. This is the first experiment revealing the suppressive effect of ALA on the IL-6 level in fibrosis. This finding may prove important to human health because IL-6 is a recognized marker of inflammation and also regulates the expression of other inflammatory cytokines such as interleukin-1 and TNF-α.

Reduced myogenin staining in ALA-treated tissues was another proof of ALA reducing peridural fibrosis as myofibroblasts are the key mediators of fibrosis.

CONCLUSIONS

Many experimental and clinical studies have proved a beneficial effect of lipoic acid in diabetes, atherosclerosis, AIDS, ageing, neurodegenerative disorders, reperfusion injury and degenerative joint disorders (8). ALA could be used to prevent or reduce the peridural fibrosis especially in the early preoperative and postoperative periods. Furthermore, this scar-improving drug could have widespread benefits and prevent complications in neural tissues by facilitating neural reconnections in the central and peripheral nervous system through the elimination of glial scarring. However, the current body of evidence is too limited to be conclusive. Further work on safety in higher animal models and eventual clinical trials are required prior to making any conclusions regarding the potential utility of the drug in humans.

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