Antifibrotic Effect of Boric Acid in Rats with Epidural Fibrosis

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BACKGROUND: **Epidural fibrosis is a major problem after spine surgery, with some patients having recurrent symptoms secondary to excessive formation of scar tissue resulting in neurologic compression. We used a rat laminectomy model to determine if topical application of boric acid could be helpful in the prevention of epidural fibrosis.**

METHODS: **Rats were randomly assigned to 2 control and 2 experimental groups ($n = 8$ for each group). The negative control group received no surgery, and the positive control group underwent laminectomy only. Experimental groups were classified according to the study agents applied onto the dura mater after laminectomy at the L3 level: 2.5% boric acid solution and 5% boric acid solution. The extent of epidural fibrosis was assessed 4 weeks later macroscopically and histopathologically.**

RESULTS: **Boric acid reduced epidural fibrosis in rats after laminectomy. The effect of 5% boric acid solution was more pronounced ($P < 0.05$) compared with the 2.5% solution.**

CONCLUSIONS: **The antifibrotic effect of boric acid solution for the prevention of epidural fibrosis suggests that boric acid should be further evaluated in future studies for the prevention of epidural fibrosis.**

INTRODUCTION

Laminectomy is a necessary step in the treatment of lumbosacral disorders, such as lumbar disc herniation and lumbar spinal stenosis. Long-term unsatisfactory relief or recurrence of symptoms in patients who had laminectomies is observed in approximately 8%–48% of patients.[1] Epidural fibrosis is a challenging complication after spine surgery, with some patients having recurrent symptoms secondary to excessive formation of scar tissue.[2] Epidural fibrosis leads to compression and tethering of the associated nerve roots, causing persistent back and leg pain.[3] Inadvertently, postoperative epidural fibrosis may result in increased complications in revision surgeries, such as dural lacerations, nerve root injuries, and epidural bleeding.[4] It is not possible to predict who will develop symptomatic epidural fibrosis. Although there are some preventive strategies and experimental therapeutic modalities, once the condition occurs, there is no effective treatment.[1,2] The etiopathogenesis of epidural fibrosis is complex. Reduction of the tissue cellularity and excessive deposition of extracellular matrix components (i.e., collagen, dermatan sulfate, and fibronectin) are contributing factors.[5] Epidural fibrosis causes reparative inflammation, unnaturally extensive cicatrization, and subsequent adhesions that are due to the fibrotic process.[6]

Boron, considered a nutrient element, has been classified as "probably essential" for humans by the World Health Organization.[7] Boron is required for the completion of the life cycle of some higher animals and plays an important role in the replication and development of animal cells.[8] Additionally, a significantly low boron intake impairs bone health, brain function, and immune response.[9] Furthermore, boron decreases the severity and incidence of inflammatory diseases.[10] In nature, boron combines with oxygen and other elements to form boric acid (BA) and inorganic salts called borates. Borax is a boron compound and a salt of BA that affects the activity of approximately 26 different enzymes in animal, chemical, and plant systems.[11] BA decreases nitric oxide production levels in a dose-dependent manner and suppresses important inflammatory mediator genes, inducible nitric oxide synthase, and cyclooxygenase-2.[12]

Apart from its diverse functions, previous studies have shown that BA also has antioxidant activity.[13-15] At the present time, the

Key words
- Boric acid
- Epidural fibrosis
- Laminectomy

Abbreviations and Acronyms
BA: Boric acid

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Table 1. Histopathologic Grading and Scoring of Epidural Fibrosis

Fibrosis	Edema	Chronic Inflammatory Granulation Tissue	Bone Destruction and Healing	Acute Inflammatory Cell Density	Chronic Inflammatory Cell Density
0: No fibrotic tissue	0: No Edematous changes	0: Absent	0: No bone destruction	0: No inflammatory cells	0: No inflammatory cells
1: Superficial or focal fibrosis	1: Edematous changes	1: Present	1: Enchondral ossification and fibrosis	1: Focal and few cells	1: Focal and few cells
2: Superficial spread or deep local fibrotic tissue			2: Destructed bone, spicule formation, fibrosis, and surrounding inflammation response	2: Spreading and many cells	2: Spreading and many cells
3: Deep and spread fibrosis				3: Abscess formation	

Total scores were calculated with a range of 0–12 points according to this scale. Grade 1 = 0–5 points and resembled light inflammation and fibrosis, grade 2 = 6–8 points and resembled moderate inflammation and fibrosis, and grade 3 = 9–12 points and resembled heavy inflammation and fibrosis.

complete antioxidant mechanism of BA is not fully understood.[16] However, BA is a well-known component of cell membrane functions and enzymatic reactions.[17,18] Boron supplementation decreases lipid peroxidation by enhancing antioxidant activity.[13] BA is used as an anti-inflammatory and antioxidant agent to treat cancer and inflammatory diseases, prevent oxidative stress, reduce the toxic effects of heavy metals, and regulate mitochondrial membrane potential.[19-22] In the present study, we hypothesized that the positive effect of topical application of BA could be helpful in the prevention of epidural fibrosis in a rat laminectomy model via its anti-inflammatory and antioxidant activity.

MATERIALS AND METHODS

Animals

All the experimental procedures used in this investigation were reviewed and approved by the local Animal Research Ethics Committee of Sivas Cumhuriyet University. Animal care and all the experiments adhered to the European Union Council Directive of November 24, 1986 (86/609/EEC) related to the protection of animals for experimental use. Thirty-two male Wistar albino rats weighing 250–300 g were used. All the rats were kept in environmentally controlled conditions at 22°C–25°C, with appropriate humidity and a 12-hour light cycle. The rats were granted free access to food and water and were randomly assigned to the following 4 groups: negative control group ($n = 8$), no surgical procedure; positive control group ($n = 8$), laminectomy performed (described next); 2.5% BA group ($n = 8$), 2.5% BA solution (Sigma-Aldrich, Istanbul, Turkey) applied to the dura mater after laminectomy; and 5% BA group ($n = 8$), 5% BA solution applied to the dura mater after laminectomy.

Surgical Procedure

Cephazolin sodium was injected 1 hour before surgical intervention via the intramuscular route (20 mg/kg). The animals were anesthetized with an intraperitoneal injection of 10 mg/kg xylazine (Rompun; Bayer, Istanbul, Turkey) and 50 mg/kg ketamine (Ketalar, Pfizer, Turkey) and allowed to breathe spontaneously. A rectal probe was inserted, and the animals were positioned on a heating pad to maintain their body temperature at 37°C.

The rats were stabilized on the operating table in the prone position. After their lower backs were shaved, the surgical sites were sterilized using povidone. Following sterile isolation, a longitudinal midline skin incision was performed over the L2-L4 levels. On the left side, the lumbosacral fascia was incised, the paravertebral muscles were dissected in a subperiosteal fashion, and the L3 laminae were exposed. A hemilaminectomy was performed at the L3 level until the dura mater and epidural spaces were exposed; then the ligamentum flavum and epidural fat tissue were cleared from the surgical site. The dura mater was fully exposed and left intact. After application of the topical agents, the wounds were closed in anatomic layers using 4-0 polypropylene (Prolene) sutures. There were no complications, wound infections, or adverse effects observed related to the application of the study drugs. All the procedures were performed by the same surgeon (H.B.) using a surgical microscope to avoid injury to the neural tissues.

The rats were granted access to free food and water consumption for 4 weeks after the surgery. After 4 weeks, the rats were sacrificed via intraperitoneally administered thiopental sodium solution (10 mg/kg). The second to fourth vertebrae were excised with their laminae, dural sacs, nerve roots, and paravertebral tissues including the muscles and skin.

Macroscopic Assessment of Epidural Scar Adhesion

For macroscopic assessment, the surgical sites were reopened carefully, and epidural scar adhesion was evaluated by a neurosurgeon (B.G.) blinded to the treatment groups according to the Rydell classification.[23] This classification scheme includes the following grades: grade 0, epidural scar tissue was not adherent to the dura mater; grade 1, epidural scar tissue was adherent to the dura mater but was easily dissected; grade 2, epidural scar tissue was adherent to the dura mater and was dissected with difficulty without disrupting the dura mater; and grade

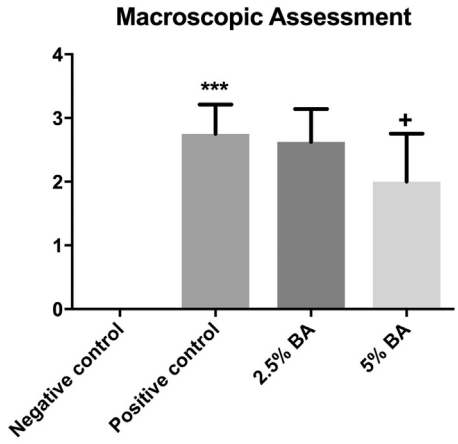

Figure 1. Macroscopic assessment of epidural scar adhesion score of negative control, positive control, 2.5% boric acid, and 5% boric acid groups. Data are presented as mean ± SD. After laminectomy, severe epidural adhesions were observed in the positive control group compared with the negative control group (***$P < 0.001$). Epidural scar adhesion score was decreased statistically significantly in the 5% BA group compared with the positive control group ($^{+}P < 0.05$). BA, boric acid.

3, epidural scar tissue was firmly adherent to the dura mater and could not be dissected.

Histopathologic Evaluation

For histopathologic assessment, the spine was cut axially through the upper L2 to lower L4 levels to isolate the laminectomy en bloc. All specimens were placed in 10% formalin solution for preparation for histopathologic evaluation. Specimens were cut into 2-mm-thick axial slices and left for 48 hours for formalin fixation. Each tissue sample was decalcified with 10% nitric acid solution for 48 hours. All specimens were then washed with tap water for 12 hours. Histologic processes consisted of decalcification, dehydration, and preparation of paraffin-embedded blocks. From formalin-fixed paraffin-embedded tissues, 5-µm-thick serial sections were cut and stained with hematoxylin and eosin and Masson trichrome.

The formalin-fixed paraffinized tissue sections contained whole tissue layers, including skin, subcutaneous tissue, paravertebral muscles, bone, and dura mater nervous tissue. Inflammatory changes and scar tissue development were observed mostly in the epidural areas but reached the subcutaneous tissues in some areas. All the laminectomy sections were evaluated in a blinded manner by a histopathologist (R.E.). Inflammation, scar tissue development, and other histopathologic changes were determined for the entire thickness of the tissue layers under 10-fold optical magnification. The tissue sections were examined microscopically; the criteria used to classify the extent of inflammation and fibrosis are summarized in Table 1.[24]

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows Version 24.0. (IBM Corp., Armonk, New York, USA). The Shapiro-Wilk test was used to determine whether the distributions of continuous variables were normal. Data were presented as median values (minimum—maximum). The differences in the median values among the groups were compared using one-way analysis of variance. When the P values from the one-way analysis of variance test were statistically significant, we used the Tukey test for pairwise comparisons. A P value < 0.05 was considered statistically significant.

RESULTS

Wound Healing and Complications Related to the Procedure

No mortality or morbidity occurred related to the procedure. Application of the study drugs had no adverse effects on the surrounding tissue or on wound healing in any rat. We observed no wound infections, erythema, hematomas, or cerebrospinal fluid leaks. All the animals were ambulatory at the time they were sacrificed.

Macroscopic Assessment of Epidural Scar Adhesion

After laminectomy, severe epidural adhesions (75% grade 3 and 25% grade 2) were observed in the positive control group compared with negative control group ($P < 0.001$). Severe to moderate epidural adhesions (62.5% grade 3 and 37.5% grade 2) were found in the 2.5% BA group. Moderate to mild epidural adhesions (25% grade 3, 50% grade 2, and 25% grade 1) were

Table 2. Mean Fibrosis and Total Score of Experimental Groups

	Fibrosis		Total	
Groups	H&E	MT	H&E	MT
Negative control	0	0	0	0
Positive control	2.87 ± 0.35	3	7.75 ± 1.28	7.87 ± 1.12
2.5% BA	1.62 ± 0.74	1.37 ± 0.51	2.62 ± 0.91	2.25 ± 1.03
5% BA	0.87 ± 0.83	0.87 ± 0.83	1.25 ± 1.03	1.25 ± 1.03

H&E, hematoxylin and eosin; MT, Masson trichrome; BA, boric acid.

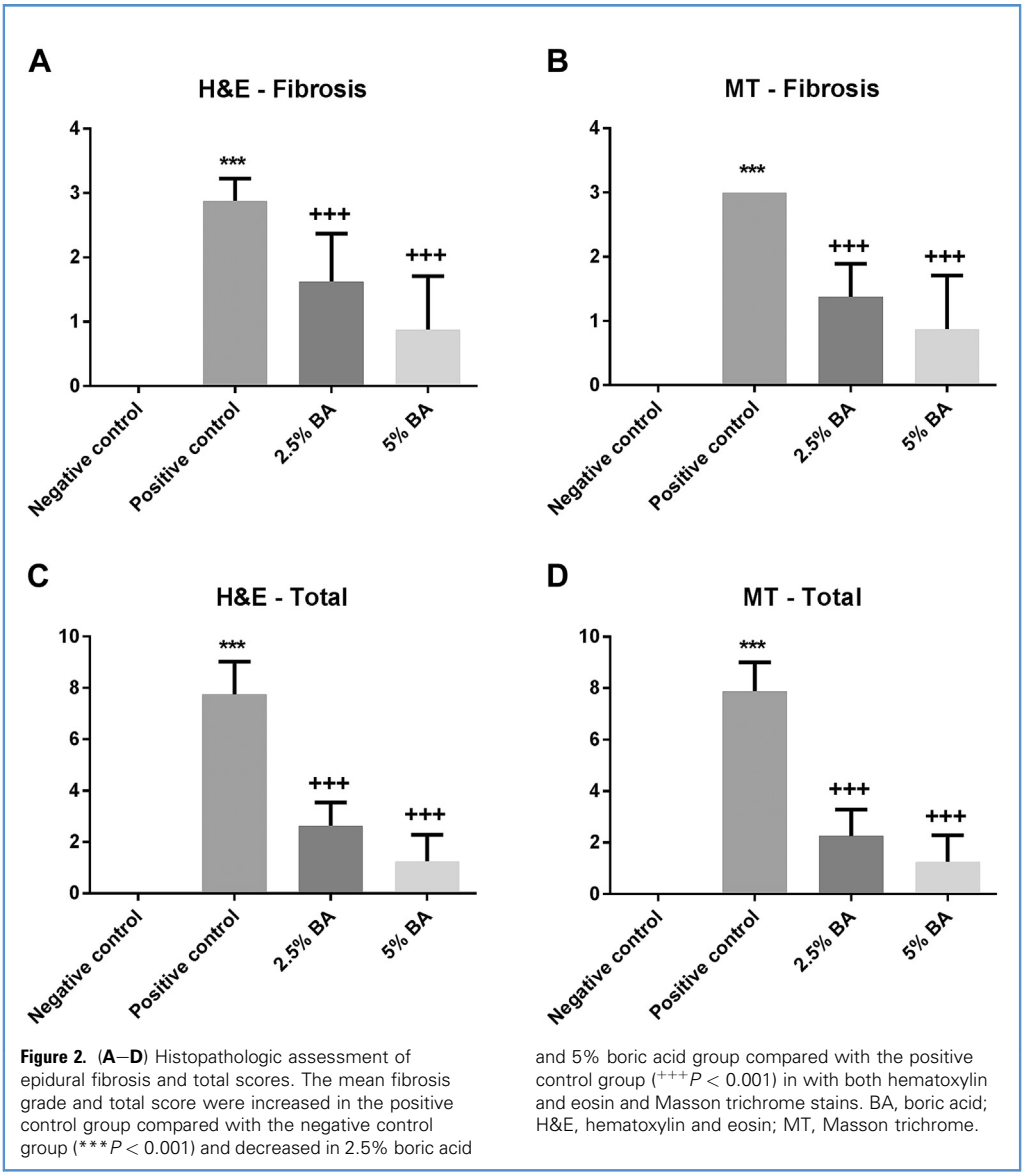

Figure 2. (**A**–**D**) Histopathologic assessment of epidural fibrosis and total scores. The mean fibrosis grade and total score were increased in the positive control group compared with the negative control group (***$P < 0.001$) and decreased in 2.5% boric acid and 5% boric acid group compared with the positive control group ($^{+++}P < 0.001$) in with both hematoxylin and eosin and Masson trichrome stains. BA, boric acid; H&E, hematoxylin and eosin; MT, Masson trichrome.

found in the 5% BA group, and the epidural scar adhesion severity score was decreased statistically significantly in this group compared with positive control group ($P < 0.05$) (Figure 1).

Histopathologic Assessment

The mean fibrosis grade and total score were increased in the positive control group compared with the negative control group ($P < 0.001$). Topical BA application decreased postlaminectomy fibrosis histopathologic grade significantly in both the 2.5% and the 5% concentration groups compared with the positive control group ($P < 0.001$) with both hematoxylin and eosin and Masson trichrome stains (Table 2; Figures 2 and 3). There was no statistically significant difference between the 2.5% BA and 5% BA groups.

DISCUSSION

Epidural fibrosis is one of the most common postoperative problems associated with spinal surgery and was first discussed in 1948.[25] Since that time, despite experimental research, no effective clinical treatment has been developed. The formation of epidural scar tissue is an expected postlaminectomy consequence, causing tractions on the dura mater and nerve roots that may result in lower back and leg pain.[3] Inflammatory reactions and oxidative stress at the laminectomy area contribute to excessive scar tissue formation.[26] Epidural fibrosis results from the proliferation of fibroblasts, transformation of fibroblasts to myoblasts, and accumulation of the disorganized extracellular matrix proteins.[4] The prevention of epidural fibrosis can be achieved by meticulous hemostasis, minimal tissue trauma, and sterile surgical techniques.[1] In the literature, the preventive effect of BA

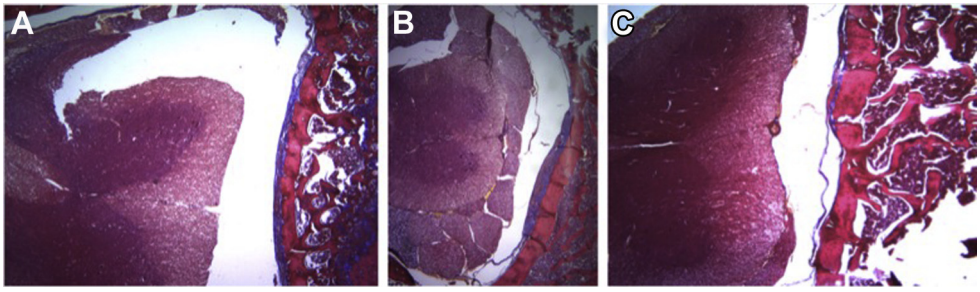

Figure 3. (**A**) Representative photomicrograph of epidural fibrosis analysis of the study groups. In the positive control group (**B**), severe epidural fibrosis is observed. In both 2.5% boric acid (**C**) and 5% boric acid groups, epidural fibrosis was significantly ($P < 0.001$) augmented (Masson trichrome, ×40 objective).

solution has not been investigated in a postlaminectomy epidural fibrosis model. In the present study, we used a rat laminectomy model to examine the effects of topical application of BA on the prevention of epidural fibrosis.

Boron does not exist as an elemental form in the environment; it is generally found as borates, borax, BA, colemanite, or ulexite.[27] It is found in considerable quantity in fruits and vegetables, such as apples, grapes, celery, tomatoes, soy meal, dried fruits, legumes, nuts, almonds, avocados, and bananas.[28,29] Boron can be completely absorbed by the gastrointestinal tract from drinking water and plant-derived foods and circulates in the blood as BA.[30] Previously published studies consistently pointed out that boron is an essential element for plants and beneficial in certain concentrations for humans.[17,31] Boron supplementation has a beneficial effect on bone mineral density, brain function, cognitive performance, regulation of the normal inflammatory response, and lipid levels in serum, and boron can be protective against lipid peroxidation, oxidative stress, and DNA damage.[27] Although the biochemical mechanism of BA is not fully understood, most studies have focused on 2 mechanisms: cell-membrane functions and regulation of enzyme activities especially in oxidative metabolism.[13,32,33] BA has an inhibitory effect on enzymes such as aldehyde dehydrogenase, cytochrome-*b* reductase, nitric oxide synthase, peptidases, proteases, and xanthine oxidase.[21]

Reactive oxygen species contribute to the inflammation process in epidural fibrosis.[26] BA is thought to play a role as both an anti-inflammatory and an antioxidant agent.[34] BA, which acts as an inhibitor for serine proteases, regulates the process of inflammation through reducing the degradation of connective tissue structures and membrane components.[32,35] Boron prevents the activation of proinflammatory cytokines through nuclear factor κB transcription factor, and therefore it blocks the inflammation process.[36] Low doses of various boron compounds in animal systems can increase antioxidant capacity by increasing the activity of enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, glutathione reductases, and glucose-6-phosphate dehydrogenase.[14,15] It also decreases lipid peroxidation and increases antioxidant defense levels.[13,21] BA may have a possible indirectly preventive effect on apoptosis.[37] In the present study, macroscopic and histopathologic assessment revealed that topical BA application decreased fibrosis significantly via its possible anti-inflammatory and antioxidant activities.

BA may have some potential side effects owing to fast absorption and slow elimination profile. Further studies are needed to evaluate the potential side effects and toxicity of BA after topical application for epidural fibrosis.

CONCLUSIONS

Macroscopic and histopathologic results revealed that topical application of BA showed significant preventive effects in regard to epidural fibrosis via multiple mechanisms. The results of our study provide the first experimental evidence of preventive effects of BA in regard to epidural fibrosis. Therefore, in light of these results, we propose that BA may be a potential preventive agent against postlaminectomy epidural fibrosis.

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