Comparison of the Effects of Contractubex Gel and Benzothiazole After Topical Application in an Experimental Model of Epidural Fibrosis in Rats

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BACKGROUND: **Postoperative epidural adhesion is a frequent cause of failed back surgery syndrome, manifesting with back and leg pain or neurologic deficits. Development of preventive measures for epidural adhesion after laminectomy is critical to improve outcomes of lumbar surgery. We hypothesized that positive effects of topical application of Contractubex (CTX) gel and benzothiazole (BT) individually and in combination could aid in preventing epidural fibrosis in a rat laminectomy model.**

METHODS: **Rats were randomly assigned to 2 control and 5 experimental groups ($n = 8$ for each group). The control(−) group received no surgery, whereas the control(+) group underwent laminectomy without any drug administration. In experimental groups, study agents applied to dura mater after laminectomy were 100mgCTX, 2.5%BT, 5%BT; 100mgCTXplus2.5%BT, and 100mgCTXplus5%BT. Laminectomy was performed at the L3 level for all rats. The extent of epidural fibrosis was assessed 4 weeks later macroscopically and histopathologically. Hepatic and renal toxicity of study drugs was assessed histopathologically.**

RESULTS: **Topical CTX and BT individually and in combination reduced epidural fibrosis after laminectomy in rats. Although a meaningful decrease of epidural fibrosis with individual application of CTX and BT (2.5% or 5%) was obtained ($P < 0.05$), the effect of their combination was more pronounced without meaningful hepatic and renal toxicity ($P < 0.05$).**

CONCLUSIONS: **Combined use of topical CTX and BT could be a potential therapy for epidural fibrosis. Further research with this agents for the prevention of epidural fibrosis is warranted.**

INTRODUCTION

Epidural fibrosis, excessive formation of scar tissue near the nerve roots, is a common occurrence after laminectomy. As laminectomy is a widely accepted treatment for lumbosacral disorders, such as lumbar disc herniation, epidural fibrosis can lead to unsatisfactory results. Failed back surgery syndrome is characterized by long-term unsatisfactory relief or the recurrence of symptoms in patients after laminectomy. The prevalence of epidural fibrosis has been reported to be 24%–100% in patients who undergo back surgery. This variation may depend on the sensitivity of the technique used for diagnosis (e.g., computed tomography, magnetic resonance imaging, or surgical exploration). It also may depend on the distinction made between the space containing epidural adhesions. If the latter is included, our finding of a 95.7% incidence of epidural fibrosis after back surgery is consistent with the very high end of these estimates.[1-4]

Epidural fibrosis causes compression and stretching of the associated nerve roots, leading to persistent back and leg pain. Furthermore, postoperative epidural fibrosis may result in increased complications during revision surgeries, such as inadvertent dural lacerations, nerve root injuries, and epidural bleeding. There is no method of predicting the patients who will develop symptomatic epidural fibrosis, and once the condition occurs, there is no effective treatment. Considerable efforts have been applied to reduce postoperative epidural fibrosis, but none of the proposed solutions are ideal. Epidural fibrosis occurs in

Key words
- Epidural fibrosis
- Laminectomy
- Rat
- Topical BT
- Topical Contractubex gel

Abbreviations and Acronyms
BT: Benzothiazole
CTX: Contractubex

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minimally invasive interventions, with the use of a barrier between the exposed dura and the healing tissue, and despite local drug applications.[4-6] There is a need to reduce the development of epidural fibrosis with new interventions. In the present study, Contractubex (CTX) (Merz Pharma GmbH & Co., Frankfurt am Main, Germany) gel and benzothiazole (BT) alone and in combination were selected as study drugs.

CTX primarily contains allium cepae (onion extract) as well as 50 U sodium heparin and 1% allantoin. In clinical practice, this drug is generally used for the treatment of hypertrophic scars and keloids. Pathophysiologically, hypertrophic scars and keloids are characterized by exaggerated extracellular matrix and collagen deposition. CTX is used to reduce inflammation and fibroblast proliferation, which takes place in the early stages of wound healing.[7-10] In a study by Aysan et al.,[7] the potential toxic effects of CTX on the intact peritoneal cavity after injection of 1 g into the peritoneal cavity of rats without laparotomy were investigated. After sacrifice, the rats exhibited no adhesions, toxic effects, or granuloma formation in the peritoneal cavity related to the CTX injection.

BTs, a group of xenobiotic compounds containing a benzene ring fused with a thiazole ring, are used worldwide for a variety of therapeutic applications (e.g., anticancer, antioxidant, antimicrobial, and anti-inflammatory). The design of new compounds to manage inflammation has become one of the most important areas of pharmaceutical research today because there is no clinically accepted drug to mediate inflammation and help control wound healing at surgical sites, including the lumbar spine. Considering their wide spectrum of activities, BTs are excellent prospective compounds for the development of properly designed and synthesized agents for a variety of clinical and surgical applications.[11,12]

The underlying mechanisms responsible for epidural fibrosis are complex. Epidural fibrosis results in a reduction of the tissue cellularity and excessive deposition of extracellular matrix components, such as collagen, fibronectin, and dermatan sulfate.[13] Because of the complex nature of epidural fibrosis, there is no effective technique currently available to mitigate its formation after lumbar disc surgery. In the literature, the preventive effects of CTX and BT individually or in combination have not been compared in the same settings in a postlaminectomy epidural fibrosis model. In the present study, we used a rat laminectomy model to examine the effects of topical application of both CTX and BT individually and in combination on the prevention of epidural fibrosis.

MATERIALS AND METHODS

Animals

All the experimental procedures used in this investigation were reviewed and approved by the Animal Research Ethics Committee of our university. Animal care and all experiments adhered to the European Communities Council Directive of November 24, 1986 (86/609/EEC) related to the protection of animals for experimental use. We used 50 male Wistar albino rats weighing 250–300 g. All 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 7 study groups with 8 animals in each group:

1. Control(−): no surgical procedure
2. Control(+): laminectomy performed, as described in next section
3. 100mgCTX: 100 mg CTX applied to the dura mater after laminectomy
4. 2.5%BT: 2.5% BT (Sigma-Aldrich, St. Louis, Missouri, USA) applied to the dura mater after laminectomy
5. 5%BT: 5% BT applied to the dura mater after laminectomy
6. 100mgCTXplus2.5%BT: 100 mg CTX plus 2.5% BT applied to the dura mater after laminectomy
7. 100mgCTXplus5%BT: 100 mg CTX plus 5% BT applied to the dura mater after laminectomy.

Surgical Procedure

Cephazolin sodium was injected via the intramuscular route (20 mg/kg) 1 hour before surgical intervention. The animals were anesthetized with an intraperitoneal injection of 10 mg/kg xylazine (Rompun; Bayer, Turkey) and 50 mg/kg ketamine (Ketalar; Parke Davis, Turkey, Istanbul) 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. All procedures were performed carefully using a surgical microscope to avoid injury to the neural tissues. All surgical procedures were performed by the same surgeon (H.B.).

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 L2-4 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. Minor bleeding was controlled with meticulous bipolar coagulation. After the application of the topical agents (I.K.), the wounds were closed in anatomic layers using 4-0 polypropylene sutures. There were no complications, wound infections, or adverse effects observed relevant to the application of the study drugs.

The rats were granted access to free food and water consumption for 4 weeks after the surgery. After 4 weeks, the rats were euthanized with intraperitoneally administered thiopental sodium solution (10 mg/kg) (H.O.). The second to fourth vertebrae were excised with laminae, dural sacs, nerve roots, and paravertebral tissues intact, 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 professional neurosurgeon blinded to the treatment groups according to the Rydell classification (Figure 1).[3,14] This classification scheme

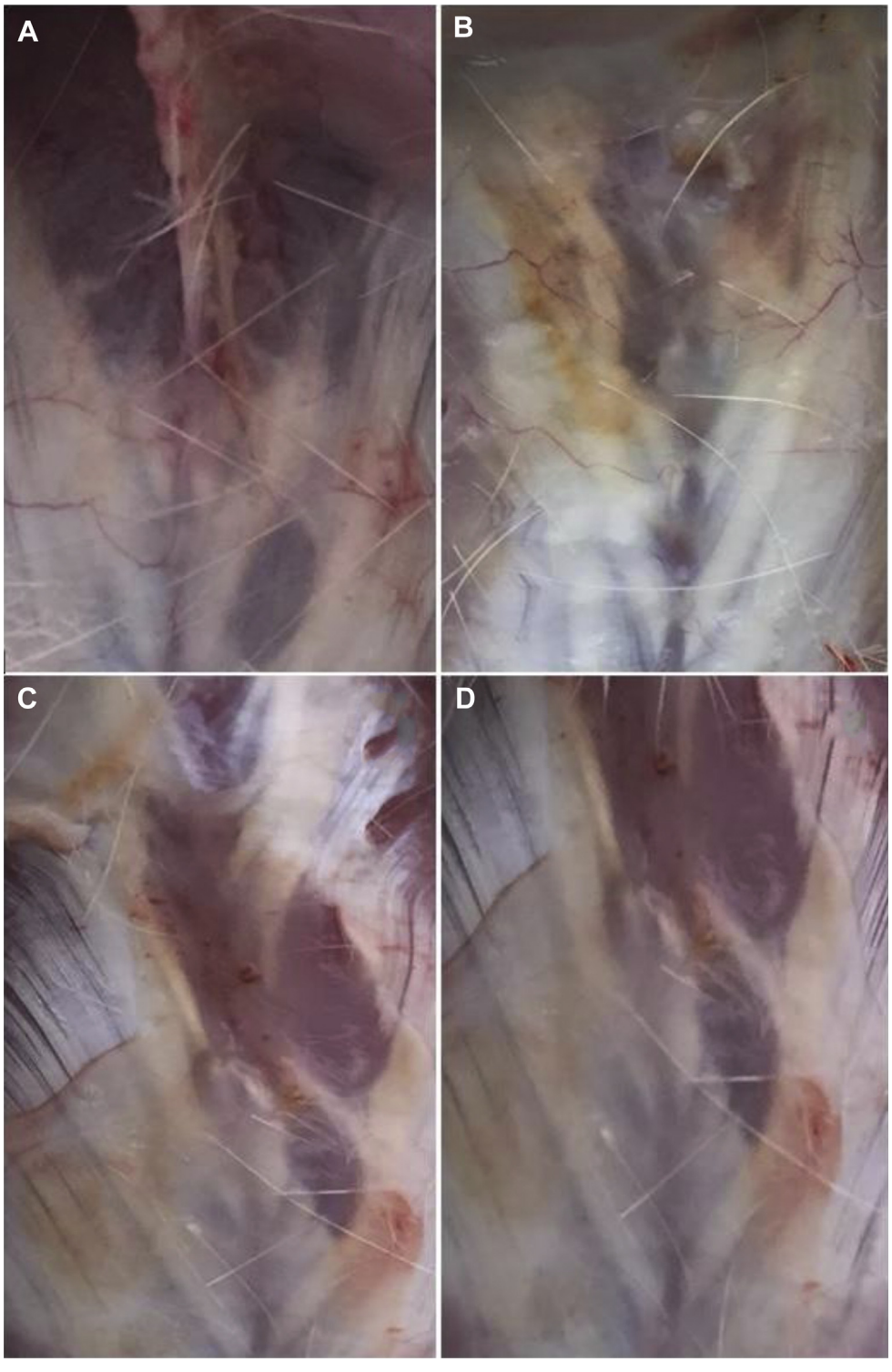

Figure 1. (**A**–**D**) Representative macroscopic images of epidural fibrosis. (**A**) Control(+) group. (**B**) Contractubex +2.5% benzothiazole group. (**C**) Contractubex +5% benzothiazole group. (**D**) Control(−) group.

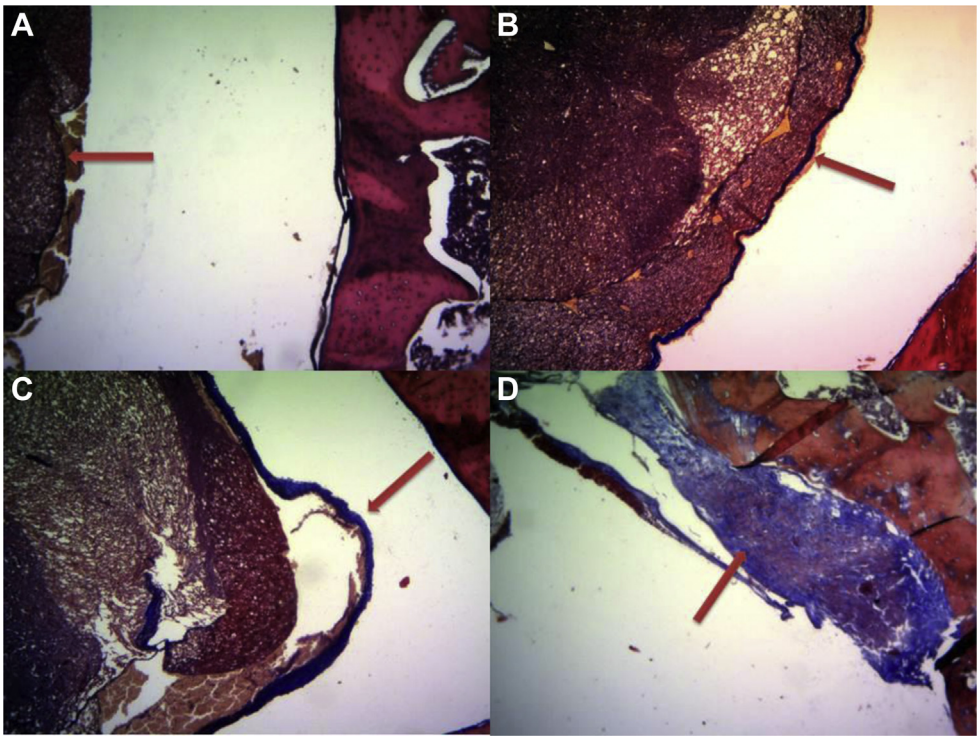

Figure 2. (**A**–**D**) Representative images of histopathologic grading of epidural fibrosis (grades 0–3) (*arrows*). (panels **A** and **D**, Masson trichrome, 10×.)

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

Histopathologic Evaluation of Epidural Fibrosis

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. Formalin-fixed paraffin-embedded tissues were cut into 5-μm-thick serial sections that were stained with hematoxylin and eosin and with Masson trichrome.

The formalin-fixed paraffinized tissue sections contained whole tissue layers including skin, subcutaneous tissue, paravertebral muscles, bone, and dura mater with 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 professional 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, and the criteria described subsequently were used to classify the extent of inflammation and fibrosis (Figure 2). All microscopic examinations were performed by the same investigator who was blinded during the evaluation (R.E.). Inflammation/fibrosis scores and inflammation/fibrosis grades were assigned according to the scoring system in Table 1.

Histopathologic Evaluation of Hepatic and Renal Toxicity

The kidneys and liver of the study rats were removed and 2- to 3-mm specimens from each organ were refixed in the same fixative for 12 hours and 24 hours, dehydrated using ascending grades of alcohol (70%–100%) for 1–2 hours, and cleared in xylene. The specimens were embedded in paraffin at 58°C and then were cut into 5- to 7-μm-thick sections and stained with hematoxylin and eosin for further examination for the presence of toxicity related to the study drugs.

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: Destroyed 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 between 0 and 12 points according to this scale: 0–5 points were characterized as degree 1 and resembled light inflammation and fibrosis; 6–8 points were characterized as degree 2 and resembled moderate inflammation and fibrosis; 9–12 points were characterized as degree 3 and resembled heavy inflammation and fibrosis.

Statistical Analysis

Data analysis was performed using IBM SPSS Version 23 (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 analysis of variance. When the P values from the analysis of variance 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 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 killed.

Macroscopic Assessment of Epidural Scar Adhesion

After laminectomy, severe epidural adhesions (78.5% grade 3 and 37.4% grade 2) were observed in the control(+) group. Overall, moderate epidural adhesions (23.1% grade 3, 67.4% grade 2, and 9.5% grade 1) were found in the 5%BT, 100mgCTX, and 2.5%BT groups. Moderate epidural adhesions (68.2% grade 2 and 31.2% grade 1) were also found in the 100mgCTXplus5%BT and 100mgCTXplus2.5%BT groups.

Histopathologic Assessment of Epidural Fibrosis

Figure 3 shows the mean fibrosis grade for the control(−), 100mgCTXplus5%BT, 100mgCTXplus2.5%BT, 5%BT, 100mgCTX, 2.5%BT, and control(+) groups. The fibrosis grade was significantly decreased in the following order with the application of the study drugs: control(+) > 2.5%BT, 100mgCTX, 5%BT > 100mgCTXplus5%BT and 100mgCTXplus2.5%BT > control(−) ($P < 0.05$). There was no significant difference among the fibrosis grades of the 2.5%BT, 100mgCTX, and 5%BT groups or between the fibrosis grades of the 100mgCTXplus5%BT and 100mgCTXplus2.5%BT groups ($P > 0.05$).

Figure 4 presents the mean total score of the control(−), 100mgCTXplus5%BT, 100mgCTXplus2.5%BT, 5%BT, 100mgCTX, 2.5%BT, and control(+) groups. The total score was significantly decreased with the application of the study drugs in the following order: control(+) > 2.5%BT, 100mgCTX, 5%BT > 100mgCTXplus5%BT and 100mgCTXplus2.5%BT > control(−) ($P < 0.05$). There was no significant difference among the total score of the 2.5%BT, 100mgCTX, and 5%BT groups or between the total score of the 100mgCTXplus5%BT and 100mgCTXplus2.5%BT groups ($P > 0.05$). The effects of the study drugs were in accordance with the fibrosis grades and total scores. The combined effect of the study drugs was significantly higher than their individual effects ($P < 0.05$).

Histopathologic Evaluation of Hepatic and Renal Toxicity

Overall, we observed no significant hepatic or renal toxicity related to the application of the study drugs individually or in

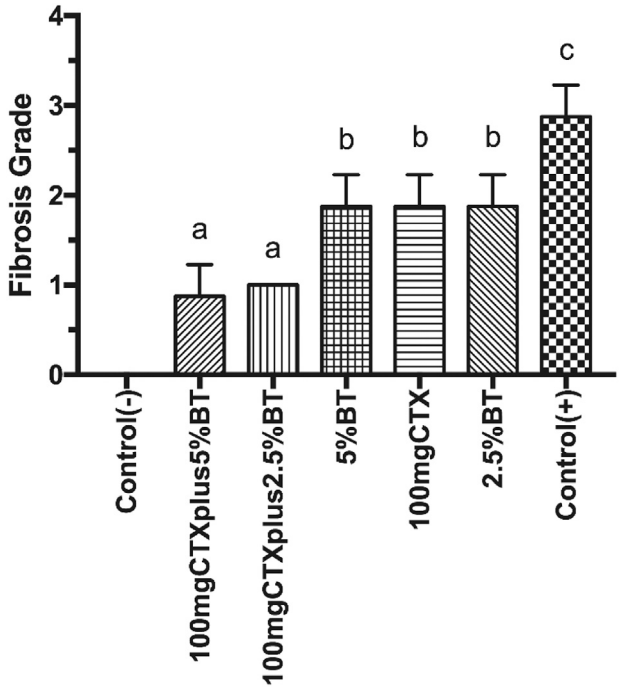

Figure 3. Fibrosis grades for control(−), 100mgCTXplus5%BT, 100mgCTXplus2.5%BT, 5%BT, 100mgCTX, 2.5%BT, and control(+) groups. Data are presented as mean ± SD. The fibrosis grade was decreased in the following order with the application of the study drugs: [a]control(+) < [b]2.5%BT, 100mgCTX, and 5%BT < [c]100mgCTXplus5%BT and 100mgCTXplus2.5%BT < control(−) ($P < 0.05$). CTX, Contractubex; BT, benzothiazole.

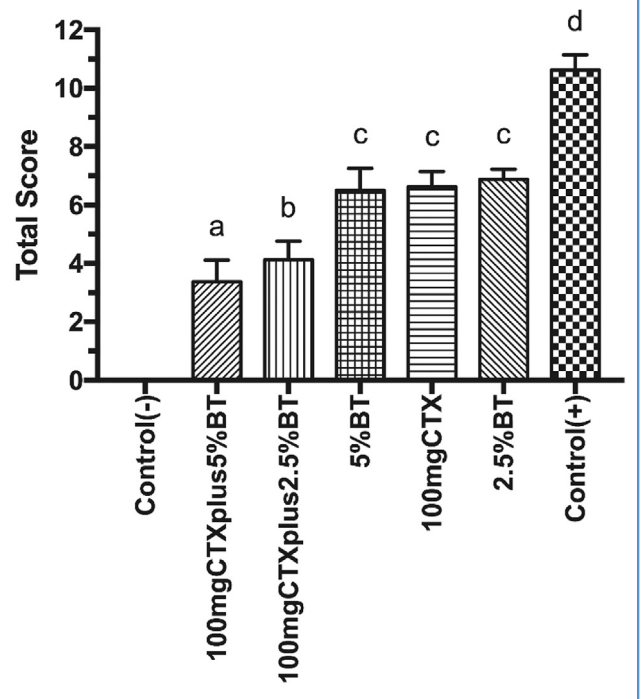

Figure 4. Total scores for control(−), 100mgCTXplus5%BT, 100mgCTXplus2.5%BT, 5%BT, 100mgCTX, 2.5%BT, and control(+) groups. Data are presented as mean ± SD. The total score was decreased in the following order with the application of the study drugs: [a]control(+) < [b]2.5%BT, 100mgCTX, and 5%BT < [c]100mgCTXplus5%BT and 100mgCTXplus2.5%BT < control(−) ($P < 0.05$). CTX, Contractubex; BT, benzothiazole.

combination. Acute tubular necrosis, tubular degeneration, tubular edema, and congestion in kidney; centrotubular necrosis in liver; and atrophy, vacuolar degeneration, hepatosteatosis, sinusoidal dilation, and peliosis foci in centrotubular hepatocytes were screened in histologic sections. This shows that the combination of CTX and BT is not toxic.

DISCUSSION

In the present study, the effects of CTX and BT alone and in combination on the decrease of epidural fibrosis in rats after laminectomy were evaluated. Although a meaningful decrease of epidural fibrosis was observed with the individual application of CTX and BT (2.5% or 5%), the effect of the drugs was more pronounced in combination. These results may be mainly related to their anti-inflammatory and antiproliferative effects. The presence of no significant side effects of study drugs on hepatic and renal systems supports the potential use of our protocol in further studies.

The development of postoperative epidural fibrosis is a natural process of healing after surgical laminectomy, with the development of dense scar tissue adjacent to the dura mater.[15] The scar formation is nonphysiologic and typically occurs at the site of neurosurgical access into the spinal canal, near the origin of the radicular sheath of nerves. This extradural fibrotic tissue may extend into the vertebral canal and adhere to the dura mater and to nerve roots, causing recurrent symptoms, including radicular pain.[15,16]

From the onset, epidural fibrosis behaves as a reparative inflammation and may result in failed back surgery syndrome.[17] The condition manifests with a cluster of symptoms after spine surgery, including persistent, chronic, disabling pain that is nonresponsive to various modalities of conservative and interventional treatments.[18] Although the debate continues regarding the role of epidural fibrosis as a major cause of pain after lumbar spine surgery,[19] it is generally accepted that morbidity mainly occurs along with the renewal of pain and even neurologic deficits. Because of the exponential increase of surgical interventions, it appears that the cost of persistent pain after lumbar spine surgery will also continue to increase.[18,20]

Considering the clinical course of patients with epidural fibrosis, the prevention of scar tissue is accepted as one of the main problems in spine surgery, as scar excision generally yields

poor results. To reduce the incidence of epidural fibrosis in human studies, several measures have been attempted with varying results, such as topical administration of epidural steroids,[21] an oxidized hyaluronic acid/adipic acid dihydrazide hydrogel,[10] high-molecular-weight hyaluronan gel,[22] omental graft,[23] and fat grafts. Because there is no agent considered to be clinically successful for the prevention of epidural fibrosis, along with clinical studies, there is a continuing increase in trials of preventive agents to minimize epidural fibrosis, such as ranibizumab.[24] Numerous methods, such as Silastic-Dacron gelatin sponge, animal collagen membranes, Adcon-L (Gliatech, Cleveland, Ohio, USA), autologous lipid graft, local cortisone application, tenoxicam application, and combined bevacizumab and 5-fluorouracil, have been attempted. However, many of these methods are not employed in routine practice.[24,25] In another study, bevacizumab was applied to the dura mater for 5 minutes, and histologic samples were collected 3 weeks later. Histopathologic examination revealed positive effects from the study drug.[23] Light epidural fibrosis with no adhesion to the dura mater was noted in specimens treated with TachoComb (Nycomed, Ismaning, Germany) and Spongostan (Ferrosan A/S, Søborg, Denmark). All other slices showed marked epidural fibrosis with dura adherence regardless of the implanted material. Epidural fibrosis after the application of TachoComb was decreased compared with all other materials. However, complete prevention of scar tissue formation was not achieved.[26] The treatment group was treated with cotton pads (5 × 5 mm) soaked in 0.005 mg/mL colchicine and applied to the laminectomy sites for 10 minutes. In the sham group, only saline irrigation was performed. In the control group, no medication or irrigation was applied. The wound was closed in layers using the same material in each group.[27]

Many aspects related to the formation of epidural fibrosis have been studied using several animal models. Many surgical modifications, materials, and drugs have been suggested for preventing or limiting the development of fibrosing tissue after lumbar discectomy. In the study by Temiz et al.,[28] the positive effects of aloe cepea extract—allantoin and heparin mixture on epidural scar formation were demonstrated with decreased acute and chronic inflammation compared with physiologic saline. The authors suggested that this effect of the above-mentioned mixture resulted from both the inhibition of inflammatory cell migration and the decrease of chronic inflammatory granulation tissue formation. They demonstrated that the mixture also facilitated bone reparation. Ozay et al.[29] investigated local administration of a mixture composed of cepae extract, allantoin, and heparin on developing and already formed epidural fibrosis in a rat laminectomy model. They demonstrated that the cepae extract, allantoin, and heparin mixture decreased already formed epidural fibrosis, in addition to its preventive effect against epidural fibrosis development through a meaningful decrease of the fibrosis size and fibroblast cell count in fibrous tissue.

CTX is a mixture in gel form that consists mainly of allium cepae (an onion derivative), heparin, and allantoin. Allium cepae is a purine oxidation metabolite that has bactericidal and anti-inflammatory effects. Heparin strengthens the anti-inflammatory effects of onion extract and can enhance collagen restoration and increase microcirculation, consequently decreasing scar formation.[30,31] The anti-inflammatory effects of onion extract are hypothesized to be due to cepaenes and its antimicrobial effects against thiosulfinates.[32] Allantoin is an auxiliary agent used for primary and secondary wound healing. The mechanism of action involves blocking excessive connective tissue synthesis and therefore preventing the progression of hypertrophic scars and keloids. The combination effects of the cepae extract, allantoin, and heparin mixture show time-related differences. The drug reduces inflammation and fibroblast proliferation in the first stage and decreases the accumulation of connective tissue elements, such as proteoglycans and collagen, in the terminal stages of wound healing. Therefore, it has been used for many years to achieve hypertrophic scar-free wound healing.[28]

BTs are a class of heterocyclic compounds containing sulfur and nitrogen. The analogues of BT and their derivatives have attracted a great deal of interest because of their wide range of biologic activities (e.g., anticancer, antimicrobial, and anti-inflammatory). The therapeutic properties of heterocyclic compounds have encouraged medicinal chemists to synthesize many novel chemotherapeutic agents. However, in the recent scientific literature focusing on the different biologic activities of BT compounds, there is no study evaluating their activities in the control of fibrosis after laminectomy.[33]

This investigation has some limitations. We did not perform immunohistochemistry trials to confirm the anti-inflammatory and antiproliferative effects of the study drugs. Moreover, we did not perform apoptosis trials to confirm their antiproliferative effects or ultrastructural trials to demonstrate their effects in a more detailed manner. However, with macroscopic and standard light microscopy findings, we clearly observed that the study drugs were more successful with combined use. This is the first study to support the combined use of CTX and BT for the prevention of epidural fibrosis.

CONCLUSIONS

Topical application of CTX and BT (2.5% or 5%) individually reduces epidural fibrosis in a rat model of epidural fibrosis after laminectomy; however, their combined effect is more pronounced. Because it is necessary to develop novel therapeutic methods that reliably reduce the formation of epidural scar adhesion after laminectomy, the effects of combined use of these medications at the molecular level need to be investigated to support our results. In the present study, the prominent effect of combination therapy with CTX and BT in the prevention of epidural fibrosis as well as the lack of hepatic and renal toxicity suggests that these agents need to considered in further studies to develop new formulations for topical use during spinal surgery to reduce morbidity related to epidural fibrosis.

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