

## Effects of cepae extract, allantoin, and heparin mixture on developing and already formed epidural fibrosis in a rat laminectomy model

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**Background/aim:** The study was designed to investigate whether local administration of a mixture composed of cepae extract, allantoin, and heparin (CAH) decreased already formed epidural fibrosis (EF) at the laminectomy site.

**Materials and methods:** Twenty-four adult male Sprague Dawley rats were equally divided into four groups. Laminectomy was performed at the L5 level in all rats. The group 2 and group 4 rats were treated with local drug administration. While the group 1 and 2 rats were sacrificed after 6 weeks, the remaining rats were reoperated and CAH mixture was applied in group 4. The vertebral columns of all rats were removed en bloc. Fibroblast numbers, EF, and arachnoidal involvement (AI) were evaluated.

**Results:** The results of the treatment groups were separately compared with the control groups. The numbers of fibroblasts in the treatment groups were significantly lower than those in the control groups ( $P < 0.001$ ). The grade of EF in group 2 was significantly less than that in group 1 ( $P < 0.05$ ). There was no statistically significant difference regarding EF and AI grade between group 3 and group 4, and local application of the drug on EF and AI yielded better results than in the control groups.

**Conclusion:** The mixture composed of CAH might be a successful candidate for preventing EF in clinical practice.

**Key words:** Laminectomy, rat, fibrosis, cepae, allantoin, heparin

### 1. Introduction

Epidural fibrosis (EF) is a well-known complication of lumbar disc surgery and causes recurrent symptoms including radicular pain. Development of dense scar tissue adjacent to the dura mater after laminectomy is a natural process of healing (1,2). Histological studies have revealed that epidural fat destruction, epidural hematoma, and muscle fiber invasion from spine erector muscles into the laminectomy site are the main factors responsible for dense epidural scar adhesion formation. Inadequate hemostasis, residual cotton debris, and extensive electrocoagulation have been blamed for fibrosis and adhesion (3–6). Postoperative EF unfortunately continues to be a problem despite the use of microsurgical techniques and improved bipolar coagulation technology that reduce tissue trauma (2,7). This fibrotic tissue may extend into the vertebral canal and adhere to the dura mater and nerve roots, leading to failed back surgery syndrome. Furthermore, EF

makes repeat surgery ineffective and hazardous due to the increased risk of nerve root damage, local bleeding, and dural tear following attempts to dissect the fibrotic scar (4,8,9).

The prevention of scar tissue is one of the main concerns in spine surgery since scar excision generally yields poor results. The present experimental study was designed to investigate whether local administration of a cepae extract (100 mg/g), allantoin (10 mg/g), and heparin (50 IU/g) mixture (Contractubex, Merz Co. GmbH, Germany) decreased already formed EF at the laminectomy site.

### 2. Materials and methods

#### 2.1. Animals

We used 24 male Sprague Dawley rats weighing 250–300 g. All experimental procedures were approved by the Animal Research Ethics Committee of Gazi University and the study was conducted at the Animal Breeding

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and Experimental Research Laboratory Center of Gazi University.

## 2.2. Surgical procedure and sample preparation

The surgical procedures were performed under general anesthesia. The rats were sedated with intraperitoneal (IP) xylazine hydrochloride 5 mg/kg (Rompun, Bayer, Turkey) and anesthetized with ketamine hydrochloride 45 mg/kg IP (Ketalar, Eczacıbaşı, Turkey). They were stabilized on the operation table in the prone position after deep anesthesia. Following sterile preparation and isolation, long midline surgical incisions were performed between the posterior lumbar fourth and sixth levels. The lumbar fascia was opened for approximately 2–2.5 cm over the spinous processes. Paravertebral muscles were subperiosteally dissected bilaterally and L4–6 laminae were exposed. Total laminectomy was performed at the L5 vertebra using a Kerrison rongeur. Hemostasis was achieved using gentle compression with a piece of cotton and continued irrigation with saline solution for several minutes. Hemostatic material and bipolar cauterization were not used. The incisions were closed with 3/0 vicryl in an anatomical manner. All surgical procedures were performed under 4× optical magnification (Carl-Zeiss Opmi 9-FC 293191, Germany) by the first author. A sterile cepae extract (100 mg/g), allantoin (10 mg/g), and heparin (50 IU/g) mixture (Contractubex) was used as the therapeutic drug for preventing epidural fibrosis. Sterilization of the cream was performed in an autoclave at 2 atm and 160 °C (10). All the rats were sacrificed with administration of IP thiopental sodium (Pental, Ulagay, İstanbul, Turkey) solution (10 mg/kg). The fourth, fifth, and sixth vertebrae were excised en bloc, including their laminae, dural sacs, nerve roots, and paravertebral soft tissues.

## 2.3. Experimental groups

The rats were randomly allocated into 4 groups (groups 1–4) with 6 rats per group. Groups 1 and 3 were the control groups.

Group 1 (n: 6): This was the first control group. The surgical field was irrigated with saline solution after laminectomy was performed. No antifibrosis agent was used. The rats were sacrificed after 6 weeks.

Group 2 (n: 6): This was the first treatment group. The laminectomy site was filled with 1 cc of the CAH mixture in the form of sterilized cream (Contractubex) (10). The rats were sacrificed after 6 weeks.

Group 3 (n: 6): This was the second control group. The surgical field was irrigated with saline solution after laminectomy was performed. Six weeks after the index operation, the laminectomy site was opened, and the fibrous tissue at the laminectomy site exposed and again irrigated with saline. No antifibrosis agent was used. The rats were sacrificed 6 weeks after the second operation.

Group 4 (n: 6): This was the second treatment group. The surgical field was irrigated with saline solution after laminectomy was performed. Six weeks after the index operation, the laminectomy site was opened, fibrous tissue at the laminectomy site was exposed, and 1 cc of the CAH mixture was applied in the form of a sterilized cream (Contractubex) (10). The rats were sacrificed 6 weeks after the second operation.

## 2.4. Histological analysis

Vertebral columns were resected en bloc including the whole laminectomy area. Materials were fixed in 10% formaldehyde and then decalcified for 10 days in De Castro solution (11). Section 5 µm thick that were obtained from previously prepared paraffin blocks were stained with hematoxylin and eosin (H&E) and Masson trichrome. These preparations were examined under a light microscope. The histological examination was conducted in a blinded manner by an experience examiner.

The laminectomy field was divided into three distinct regions to determine the number of fibroblasts. Three separate areas 100,000 µm<sup>2</sup> were determined in each region. Six different areas were counted for each animal. Stereological analyses of fibroblasts were conducted according to the principles described previously (12–15). A stereological workstation composed of a digital camera (mbf/Bioscience, Qimaging), an automatically controlled specimen stage, a light microscope (Leica, DM400B), and software (mbf Bioscience, Stereo investigator, version 9) was used to count the fibroblasts.

We chose an area fraction approach with an unbiased counting frame area of 900 µm<sup>2</sup>. Meander sampling of each sectioned fibroblast was performed using a 70 µm by 70 µm step size in a systematic and random manner.

The number of fibroblasts counted in the selected areas was adapted to a 1 mm<sup>2</sup> area for each animal. Grading of epidural fibrosis and arachnoidal involvement was performed according to the definition given by He et al. (16) (Table 1).

## 2.5. Statistical analysis

Data analysis was performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Whether the distributions of continuous variables were normally or not was determined by using Kolmogorov–Smirnov test. Data were shown as mean ± SD, where applicable.

The mean differences among groups were analyzed by one-way ANOVA. When the P values from one-way ANOVA were statistically significant post hoc LSD were used to know which group differed from which others. The chi-squared test was used for analysis of nominal (categorical) data.

A P value less than 0.05 was considered statistically significant.

**Table 1.** Assessment of the epidural fibrosis and arachnoidal involvement.

Grade	Arachnoidal involvement	Epidural fibrosis
Grade 0	Undetectable	The dura is free of scar tissue
Grade 1	Minimal	Only thin fibrous bands are observed between the scar tissue and the dura
Grade 2	Moderate	Continuous adherence is observed in less than two-thirds of the laminectomy defect
Grade 3	Severe	Scar tissue adherence is large, affecting more than two-thirds of the laminectomy defect

**3. Results**

**3.1. Wound healing and evaluation of safety**

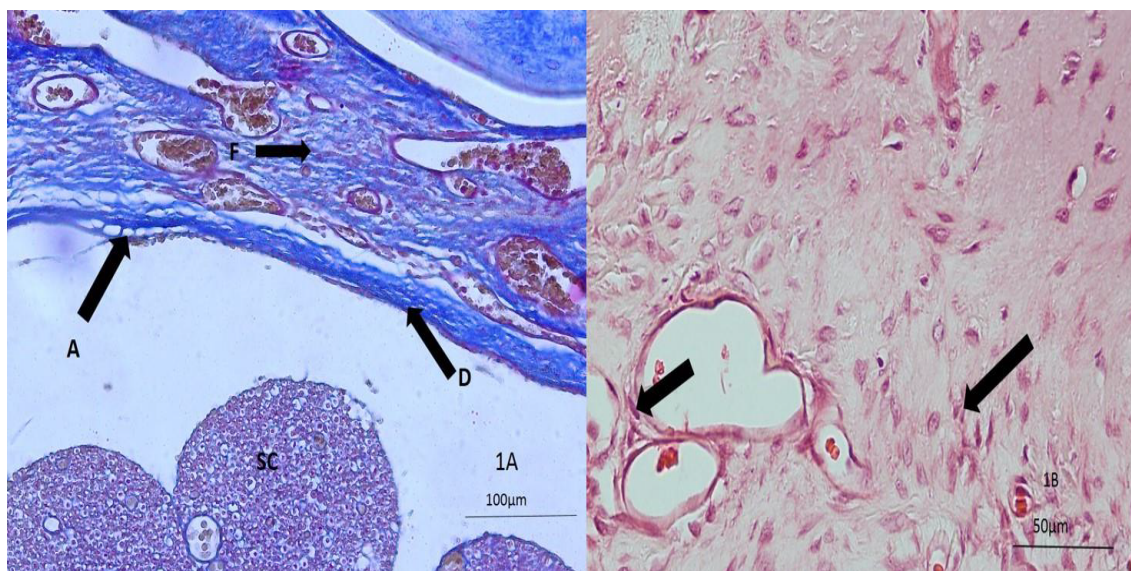
There was no mortality or morbidity related to the procedure. The CAH mixture did not affect the surrounding tissue or wound healing in any rats. No wound infection, abnormal foreign-body reaction, or abscess formation was observed. Motor functions were normal and there was no cerebrospinal fluid leakage during surgery. No hematoma occurred in the early postoperative period.

**3.2. Assessment of the fibroblast count**

The fibroblast count was  $984.16 \pm 245.99$  in group 1,  $460.83 \pm 63.75$  in group 2,  $925.0 \pm 113.75$  in group 3, and  $425.83 \pm 86.22$  in group 4. The differences in fibroblast count between group 1 and group 2, between group 1 and group 4, between group 2 and group 3, and between group 3 and group 4 were statistically significant ( $P < 0.001$ ) (Table 2; Figures 1–4). These results indicate that the CAH mixture decreased the fibroblast count in developing as well as formed epidural fibrosis at the laminectomy site.

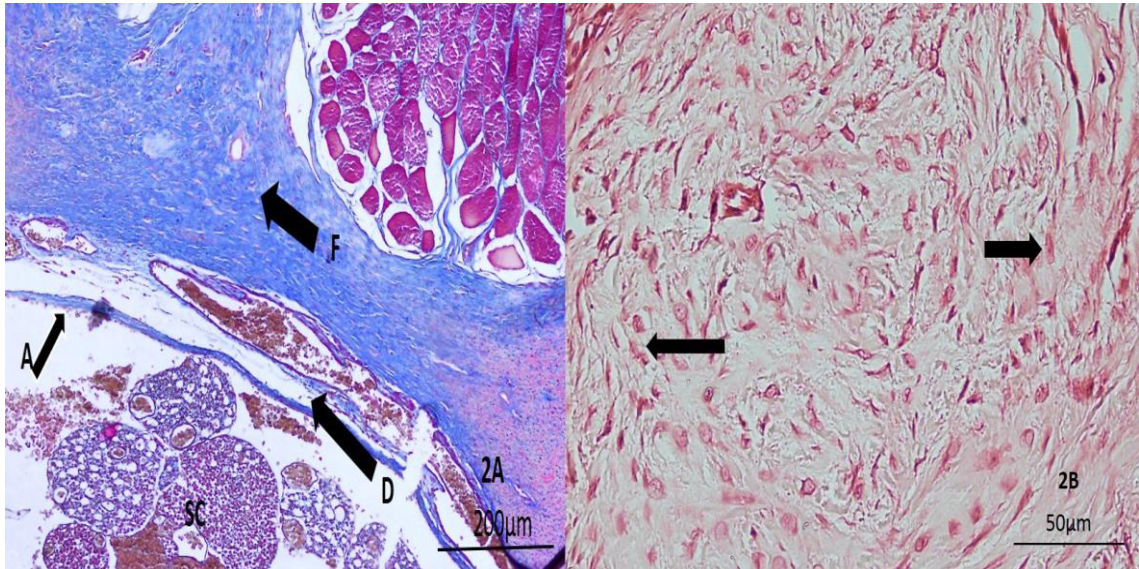
**Table 2.** Results of histological analysis; the fibroblast count, epidural fibrosis score, and arachnoidal involvement score. SD: Standard deviation.  $P < 0.05$  was deemed statistically significant, a: group 1 and group 2, b: group 1 and group 3, c: group 1 and group 4, d: group 2 and group 3, e: group 2 and group 4, f: group 3 and group 4.

Histological analysis	Group 1 Mean $\pm$ SD	Group 2 Mean $\pm$ SD	Group 3 Mean $\pm$ SD	Group 4 Mean $\pm$ SD	P-value
Fibroblast count	$984.16 \pm 245.9$ a,c,f	$460.83 \pm 3.7$ a,d,f	$925.0 \pm 113.7$ d,f	$425.83 \pm 86.2$ c,f	<0.001
Epidural fibrosis score	$2.33 \pm 0.51$ a	$1.00 \pm 0.63$ a	$2.16 \pm 0.75$	$1.16 \pm 0.75$	<0.050
Arachnoidal involvement score	$2.33 \pm 0.51$	$1.00 \pm 0.89$	$1.833 \pm 0.75$	$1.16 \pm 0.75$	<0.050

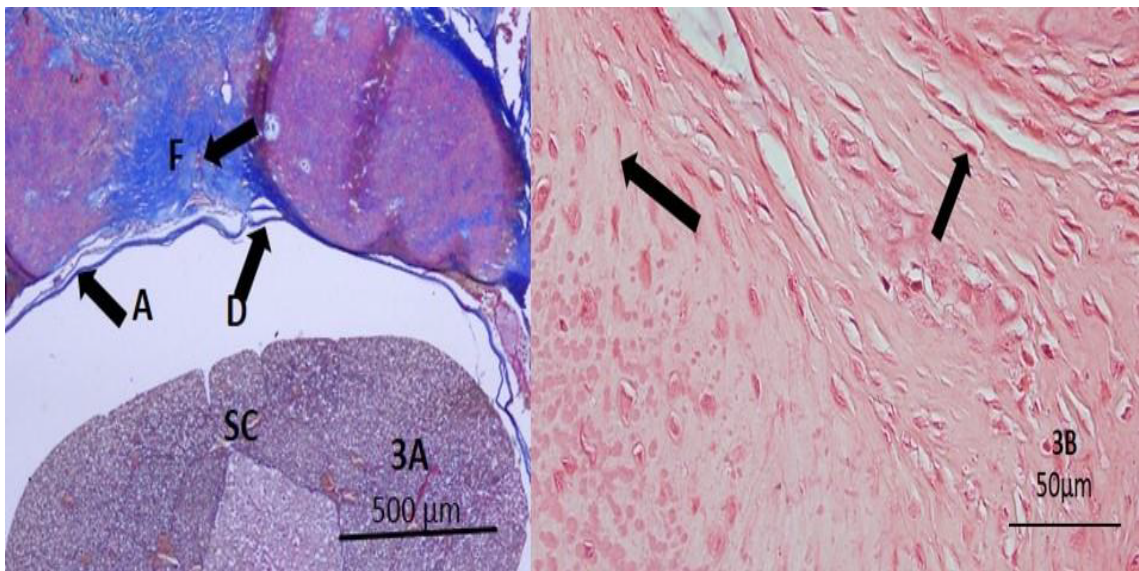


**Figure 1.** 1A; Photomicrographs demonstrating fibrosis in group 1 (first control group). Direct contact between the underlying spinal cord (SC) and the epidural fibrosis tissue (F) is evident; D: Dura mater, A: Arachnoid mater, Masson trichrome, Bar: 100 µm. 1B: Arrow; fibroblast density, note the increased number of fibroblast cells, H&E, Bar: 50 µm.





**Figure 2.** 2A; Photomicrographs demonstrating fibrosis in group 2 (first treatment group). No direct contact between the underlying spinal cord (SC) and the epidural fibrosis tissue (F) is evident, D: Dura mater, A: Arachnoid mater, Masson trichrome, Bar: 200 µm. 2B: Arrow; fibroblast density, note the lower number of fibroblast cells, H&E, Bar: 50 µm.



**Figure 3.** 3A; Photomicrographs demonstrating fibrosis in group 3 (second control group). Direct contact between the underlying spinal cord (SC) and the epidural fibrosis tissue (F) is evident; D: Dura mater, A: Arachnoid mater, Masson trichrome, Bar: 500 µm. 3B: Arrow; fibroblast density, note the increased number of fibroblast cells, H&E, Bar: 50 µm.

### 3.3. Assessment of epidural fibrosis

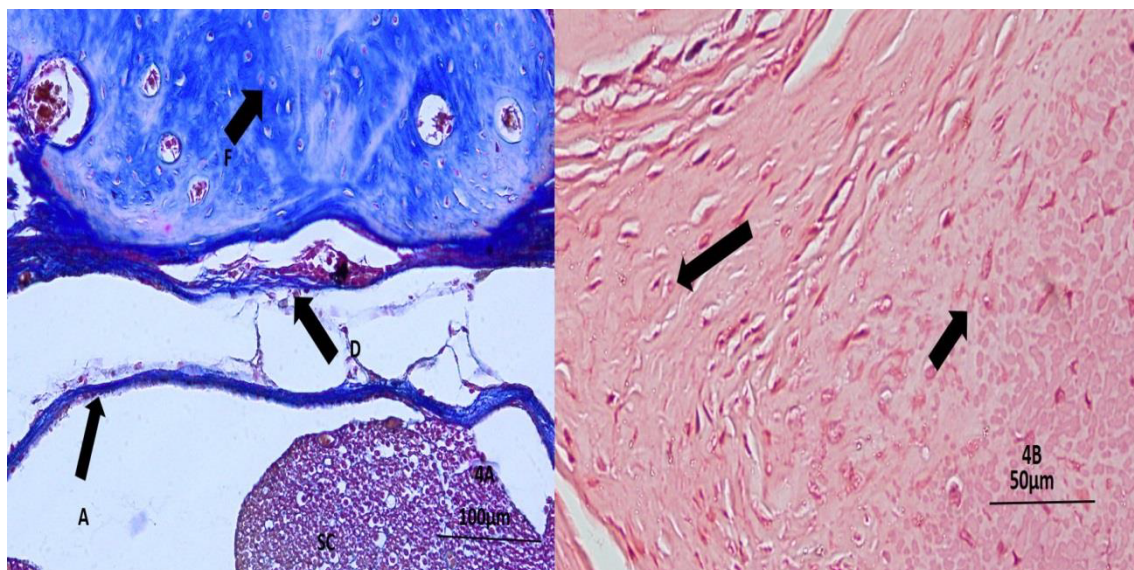
The EF score was  $2.33 \pm 0.51$  in group 1,  $1.00 \pm 0.63$  in group 2,  $2.16 \pm 0.75$  in group 3, and  $1.16 \pm 0.75$  in group 4. The differences in EF values between group 1 and group 2 ( $P: 0.032$ ) were statistically significant (Table 2; Figures 1 and 2). The group 4 EF score was much lower than the group 3 score, but there was no statistically significant difference between them ( $P: 0.241$ ) (Table 2; Figures 3 and 4). These results indicate that the CAH mixture has a

significant effect compared to saline on preventing EF in the first stage of EF but there was no significant effect on already formed EF.

### 3.4. Assessment of arachnoidal involvement

The arachnoidal involvement score was  $2.33 \pm 0.51$  in group 1,  $1.00 \pm 0.89$  in group 2,  $1.833 \pm 0.75$  in group 3, and  $1.16 \pm 0.75$  in group 4. In group 2 and group 4, AI values were much lower than those in group 1 and group 3 but there was no statistically significant difference between





**Figure 4.** 4A; Photomicrographs demonstrating fibrosis in group 4 (second treatment group). No direct contact between the underlying spinal cord (SC) and the epidural fibrosis tissue (F) is evident; D: Dura mater, A: Arachnoid mater, Masson trichrome, Bar: 100 µm. 4B: Arrow; fibroblast density, note the lower number of fibroblast cells, H&E, Bar: 50 µm.

the treatment groups and control groups (for group 1 and group 2,  $P: 0.08$ ; for group 3 and group 4,  $P: 0.494$ ) (Table 2; Figures 1–4). According to our results it might be suggested that although there was no significant effect on AI, the CAH mixture was more effective than saline in preventing AI, which is formed by the adhesive effect of EF.

#### 4. Discussion

In the present study, the effect of treatment with a CAH mixture was evaluated in a rat laminectomy model for EF. The main findings of this study was the significant preventive effect of treatment with the CAH mixture against developing EF, as this preventive effect was by means of significantly decreased EF size and fibroblast cell counting in the fibrous tissue. Another important outcome of our study was the reducing effect of the CAH mixture on formed EF and to the best of our knowledge this is the first report that provides evidence of this effect.

Contractubex 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 antiinflammatory effects. Heparin intensifies the antiinflammatory effects of cepae extract by increasing the microcirculation and therefore decreasing scar formation (17–19). Allantoin is an auxiliary agent for primary and secondary wound healing (20). The mechanism of action involves blocking excessive connective tissue synthesis and therefore preventing progression of hypertrophic scars and keloids (21,22). The combined effects of the CAH 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 the wound healing process (21,23). It has therefore been used for many years to achieve a hypertrophic scar-free wound healing process (21,24). In addition, it has been reported that the CAH mixture is able to prevent EF (21) and our results also support this notion. Our experimental study demonstrated that the CAH mixture decreased the number of fibroblasts and EF score at the laminectomy site when compared to the first control group ( $P < 0.05$  for group 1 and group 2) (Table 2). The results of our study provide the second experimental evidence of the preventive effects of the CAH mixture in EF. However, our study was designed to investigate whether locally administered CAH mixture decreases already formed epidural fibrosis at the laminectomy site.

There is no effective treatment for a scar that has already developed at the laminectomy site. It is possible to remove extensive epidural scar adhesions and release the tethered nerve roots with revision surgery but the adhesions unfortunately recur afterwards (25,26). A treatment that can reduce epidural fibrosis and scar adhesions reliably and without side effects is therefore needed. Studies have shown that the CAH mixture is more effective than local steroids in the treatment of hypertrophic scars (27). Our data revealed that the local application of the CAH mixture was effective in reducing the number of fibroblasts in epidural fibrosis formation. Although there was no statistically significant difference regarding EF grade

between group 3 and group 4 ( $P: 0.051$ ), local application of the CAH mixture on EF (group 4) yielded better results than in the second control group (group 3). The present study demonstrated that the CAH mixture effectively diminished developing as well as already formed EF (Table 2). The use of a sterilized mixture during revision surgery for failed back surgery syndrome might decrease the mass and adhesion-creating effect of EF and prevent the recurrence of EF after surgery.

The more difficult spinal canal dissection in the presence of EF makes the results less predictable than with primary surgery and increases the intraoperative complication risk (3,4). However, diagnostic and therapeutic approaches such as injections and adhesiolysis are possible even in the presence of EF with the relatively new and minimally invasive endoscopic technique of epiduroscopy (25,28). As might have been expected from our results, the sterilized form of the CAH mixture might be applied safely via epiduroscopy and could be the first treatment step to decrease any epidural fibrosis before considering surgical options.

Fibrous tissue characteristics such as the number of fibroblasts are usually used for determining EF density. Previous studies have suggested counting the fibrous tissue fibroblast cells in three different areas and then calculating a mean value for grading fibroblast density (6,29,30). We counted fibroblasts from six different areas in three separate sections in each animal. Stereological analyses of fibroblasts were conducted according to previously described principles. Stereological methods

are commonly used in studies on the experimental peripheral nerve injury model to provide correct and trustworthy estimates of histomorphological data (12–15). We performed stereological morphometric analysis of the fibroblast densities obtained from all rat groups. To the best of our knowledge, this is the first report with this level of histopathological evaluation of this topic. The present study indicates that the CAH mixture significantly decreased the fibroblast count in developing as well as formed epidural fibrosis at the surgical site. Consequently, the CAH mixture promotes regression of EF through the downregulation of fibrotic activity, possibly by means of its antiproliferative capacity on fibroblast cells.

The CAH mixture did not lead to any side effects such as adverse effect on wound healing, abnormal foreign-body reaction, or abscess formation.

In conclusion, it is conceivable that the CAH mixture, which has been previously used safely in humans for wound healing, might be safely used for preventing development of EF and decreasing already formed EF according to the results of our study. The limitations of the study include the relatively low number of rats in each group and the lack of dose-dependent effect evaluation. We also did not use electrophysiological parameters and did not make functional assessments. Further investigation should be organized with different protocols such as histomorphometric examination with a quantitative biochemical test like determination of tissue type I collagen amount.

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