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ORIGINAL ARTICLE

The effectiveness of organic vegetable oils with high biocompatibility in preventing epidural fibrosis: An experimental study

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Background and purpose – Epidural fibrosis after all spinal surgeries is an important surgical issue. Various biological and non-biological materials have been tried to inhibit epidural fibrosis, which is deemed to be the most important cause of pain after spinal surgery. Olive oil, nigella sativa oil and soybean oil employed in oral nutrition in clinics involving liquid fatty acids, palmatic acid, linoleic acid, stearic acid and palmitoleic acid. The effectiveness of olive oil, nigella sativa oil and soybean oil on epidural fibrosis was researched on for the first time in laminectomy model.

Methods – Fifty adult male Wistar albino rats weighing between 300 and 400 grams were used in the research. A total of 5 groups were formed: sham (Group I) (n = 10), no application was created; Group II (n = 10) 1 cc saline; Group III (n = 10) 1 cc olive oil; Group IV (n = 10) 1 cc nigella sativa oil; Group V (n = 10); 1 cc soybean oil was applied topically to the epidural region after laminectomy. The total spine of the rats was dissected, histopathological and immunochemical measurements were conducted. Neuro-histopathological results were scored semi-quantitatively in terms of vascular modification, neuron degeneration, gliosis and bleeding criteria.

Results – The lowest level of fibrosis and connective tissue proliferation was observed in the group where nigella sativa oil was used after the operation, followed by the group treated with olive oil and lastly with the group given soybean oil.

A magas biokompatibilitású szerves növényi olajok hatékonysága az epiduralis fibrosis megelőzésében: Kísérleti tanulmány

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Háttér és cél – Az epiduralis fibrosis minden gerincműtét után fontos sebészeti probléma. Különböző biológiai és nem biológiai anyagokkal próbálták gátolni az epiduralis fibrosist, amit a gerincműtétek utáni fájdalom legfontosabb okának tartanak. Az olívaolaj, a *Nigella sativa* (fekete kömény) olaj és a szójaolaj a klinikákon a táplálásban szájon át alkalmazott, palmatinsav-, linolsav-, sztearinsav- és palmitoleinsav-tartalmú folyékony zsírsavak. Az olívaolaj, a *Nigella sativa*-olaj és a szójaolaj hatékonyságát az epiduralis fibrosisra kutatócsoportunk vizsgálta először laminectomiás modellben.

Módszerek – Ötven felnőtt, 300–400 gramm közötti súlyú hím Wistar albínó patkányt használtunk a kutatásban. Összesen öt csoportot alakítottunk ki: sham (I. csoport) (n = 10), nem volt kezelve; II. csoport (n = 10) 1 koncentrált sóoldat; III. csoport (n = 10) 1 koncentrált olívaolaj; IV. csoport (n = 10) 1 koncentrált *Nigella sativa*-olaj; V. csoport (n = 10); 1 koncentrált szójaolajat helyileg alkalmaztunk az epiduralis régióra a laminectomia után. A patkányok teljes gerincét felboncoltuk, szövettani és immunkémiai méréseket végeztünk. A neurohisztopatológiai eredményeket félkvantitatív módon pontoztuk az érrendszeri elváltozás, a neuronok degenerációja, a gliosis és a vérzési kritériumok alapján.

Eredmények – A fibrosis és a kötőszöveti proliferáció legalacsonyabb szintje abban a csoportban volt megfigyelhető, ahol a műtét után *Nigella sativa*-olajat használtak, ezt követte az olívaolajjal kezelt csoport, végül pedig a szójaolajjal kezelt csoport.

Conclusion – Nigella sativa oil and olive oil are very efficient for lowering the degree of epidural fibrosis and adhesions following laminectomy and can be employed as a simple, inexpensive and highly biocompatible material in clinical practice.

Keywords: epidural fibrosis, laminectomy, nigella sativa, olive oil , soybean oil

Következtetés – A *Nigella sativa*-olaj és az olívaolaj nagyon hatékonyan csökkenti a laminectomiát követő epiduralis fibrosist és az összenövések mértékét, és egyszerű, olcsó és nagymértékben biokompatibilis anyagként alkalmazhatók a klinikai gyakorlatban.

Kulcsszavak: epiduralis fibrosis, laminectomia, *Nigella sativa,* olívaolaj, szójaolaj

Intervertebral disc degeneration is a physiological process. A higher number of people pass through surgery of the lumbosacral area, and laminectomy is a kind of surgery where part of the vertebral lamina is deducted for decompression of the spinal cord or roots. The formation of epidural fibrosis can be seen normally following surgery[1, 2]. However, it causes some compression symptoms and reduces the progress of spinal surgery with compression and/or stretching the nerve root or the dura mater. Furthermore, neuronal atrophy and axonal degeneration have been reported under the scar tissue[3].

Epidural fibrosis is a challenging topic in neurosurgery. In clinical practice, epidural fibrosis is a component of "post-laminectomy syndrome" or "failed-back surgery" which is a main source of strain and anxiety in daily activities, as well as of a decreased quality of life following spinal surgery. About 8% to 48% of patients who had surgery for lumbar disc herniation experienced post-laminectomy syndrome or failed-back surgery[4]. Re-operation to excise fibrotic tissues has a danger of dural tears, nerve injuries and excessive bleeding[5].

Considering the high complication rates and the gradually reduced progress rates of repetitive operations, it was concluded that the most significant approach is to hinder the advancement of epidural fibrosis. Presently, there is no efficient treatment of epidural fibrosis, and prophylaxis is a suggested alternative. In the recent years, a number of studies have been carried out and biological and non-biological constituents to hinder epidural fibrosis have been investigated in various experiments[6, 7].

In the literature, to our knowledge, there is no study about clinical or experimental research on the effectiveness of organic vegetable oils on epidural fibrosis following spinal operations. The major reason for selecting organic vegetable oils is that they can be employed as a simple, inexpensive and greatly biocompatible material in clinical practice. As a result, our research might be a guide for a prospective clinical trial.

Materials and methods

All the experimental processes employed in this research were unveiled and offered by the local Animal Research Ethics Committee of Kirikkale University. Animal care and all the tests followed the European Union Council Directive of November 24, 1986 (86/609/EEC) associated to the care of animals for experimental use. This research was carried out at Kirikkale University School of Medicine, Experimental Animals Research Laboratory.

Fifty male Sprague–Dawley rats weighing approximately 250–300 g were employed. Animals were housed with a single animal per cage at the Animal Experimental Research Centre and fed a standard rodent chow diet and water ad libitum and kept at a consistent temperature (22°C) on a 12:12 h light/ dark cycle. Maximum effort was expended to minimise the discomfort of the animals during surgery and sacrifice. The rats were randomly assigned to five groups with 10 rats per group.

The groups were as following: Group 1: Sham (n = 10); Group 2: Control (n = 10), laminectomy was conducted, as explained below, afterwards, 1 cc of saline was used topically to the epidural region; Group 3: Olive oil (n = 10), laminectomy was conducted, and afterwards, 1 cc of olive-oil was used topically to the epidural region; Group 4: Nigella sativa oil (n = 10), laminectomy was carried out, and afterwards, 1 cc of nigella sativa-oil was used topically to the epidural region; Group 5: Soybean oil (n = 10), laminectomy was conducted, and afterwards, 1 cc of soybean-oil was used topically to the epidural region.

Every rat had the same surgical process. One dose of 50 mg/kg ceftriaxone (Rocephine, Roche, Turkey) was given through the intraperitoneal route for prophylaxis 30 min before the operation. Rats were placed on an operating board in a prone position after receiving intraperitoneal injections of ketamine hydrochloride (90 mg/kg, Ketalar; Pfizer, Istanbul, Turkey) and xylazine

hydrochloride (10 mg/kg, Rompun 2%; Bayer, Istanbul, Turkey). The dorsal hair was shaved off from the skin and the surgical field was disinfected with povidone-iodine and draped with sterile towels. A longitudinal midline skin incision was created between the LII and LIII spinous processes. The lumbosacral fascia was uncovered longitudinally, and the paraspinous muscles were dissected bilaterally in a subperiosteal fashion to open the laminae of the LIII–LV vertebrae. LIII–LV laminectomy and flavectomy were performed, and epidural fat was removed, leaving the dura mater clean and dry. Haemostasis was achieved using cotton pads. No cautery or bipolar coagulation was used. The wounds were closed in an anatomical fashion via a propylene suture (Prolene polypropylene sutures; Ethicon; Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA). There were no comorbidities or adverse effects due to the materials used. For postoperative analgesia, all of the rats were provided ketorolac (50 mg/kg, intraperitoneal) for 5 days. Rats were sacrificed 6 weeks later with an overdose of intraperitoneal sodium thiopental (100 mg/kg). When obtaining the samples, the animals were inspected for dura tear, nerve damage and illnesses. There was no spotted dura tear or illnesses in the rats. The lumbar spine, including the surgical site, was removed en bloc and then fixed in 10% formic acid.

After postfixation in 10% formaldehyde solution, the vertebral samples were placed in fixation and decalcification solution (Biocal C, code RRDC3/G, composition: EDTA <1%, potassium sodium tartrate <1%, sodium tartrate <1%, hydrochloric acid <1%, Biostain [UK]) for 36 hours. The tissues were trimmed, washed, dehydrated and embedded in paraffin wax for histopathologic examination. Using standard histological protocols, axial sections of 4 μm thickness were obtained and stained with hematoxylin–eosin. Furthermore, sections were stained with Masson's trichrome (Bio Optica, Italy) to assess fibrosis. All sections were examined by a pathologist who was blinded to the rats' treatment. Light microscopy (Leica DFC450C, Germany) was used to examine the slides, and digital photomicrographs were taken. Histomorphometric examinations were conducted using Leica QWin image analysis software. The fibrosis density was determined using Leica QWin image analysis software and 20 × objective lens (Leica Microsystems Imaging Solutions, N Plan). The incorporated optical density of all progressive staining was measured, and the mean fibrosis-positive area/total area was calculated using Leica QWin Plus v4. After calculating the proportion (% pixels) of the stained area to the whole field, the mean (in % pixels) staining area for each slide was determined[8].

Statistical analysis

IBM SPSS Statistics for Windows Version 24.0. was used to analyse the data (IBM Corp., Armonk, New York, USA). The Shapiro–Wilk test was employed to evaluate whether the representation of continuous variables was normal. The nonparametric Kruskal–Wallis test was used to compare differences in groups, while the difference between subgroups was analysed using the Mann–Whitney U Test. A likelihood ratio test was used to determine the presence of arachnoidal involvement. A p-value less than 0.05 was considered statistically significant.

Results

No mortality or morbidity happened after the procedure. The application of the study oils had no adverse effects on the surrounding tissue or on wound healing in any rat. We observed no wound infections, haematomas or cerebrospinal fluid leaks. The evaluation of tissue fibrosis response and the results of the histomorphometric analysis of the degree of fibrosis between the groups are demonstrated in **Table 1** and **Table 2**.

Histopathological evaluations of connective tissue formation and fibrosis in dura mater-related tissues after surgery revealed that the highest degree of connective tissue and fibrosis was formed in the Control group (Group 1) ($p = 0.001$). However, dura mater, spinal cord and vertebral bone tissue were detected in normal histological appearance in the sham group (Group 2). The lowest level of fibrosis and connective tissue proliferation was seen in the nigella sativa oil group (Group 4) , followed by the olive oil applied group (Group 3) and finally, the soybean oil applied group (Group 5) ($p < 0.05$). Although there was no statistically significant difference in fibrosis between the nigella sativa oil and olive oil group ($p > 0.05$), both groups had significantly less fibrosis than the soybean oil group ($p < 0.05$). The histopathological evaluation results of the fibrotic changes formed in the operation area, as well as the degree of fibrosis between the dura mater and the dorsal fascia and the bone roof are given.

In Group 2, fibrosis was diffusely concentrated in the dorsal vertebral region, and dense collagen tissue content

Table 1. *Evaluation of tissue fibrosis response*

Items	Tissue fibrosis response scores			
	0	1	2	3
Fibrosis	No	Few fibroblasts	Fibroblastic proliferation and increased collagen	Fibrosis, collagen bundles

was detected with a cellular appearance due to fibroblastic activity, particularly in regions where adhesions were formed. In areas of severe fibrosis, newly formed capillaries and enlarged venous vessels filled with erythrocytes were observed. Despite all of these findings, almost no inflammatory cells were found.

The most severe histopathological changes were observed in the soybean oil group. Connective tissue repair activities at the dorsal vertebral level were characterised by advanced fibroblastic activity and collagen matrix. The collagen matrix was unusually stained in dark blue. In addition, multiple neovascularisation activities were also present in this group. In the connective tissue and healing areas, polymorphous nuclear leukocytes and macrophage activity were outlined, although their numbers were variable. In particular, the intense macrophage activity can be assessed as the inflammation-increasing effect of soybean oil.

Table 2. *Histomorphometric analysis results of the degree of fibrosis between groups*

	Control	Sham	Soybean-oil	Olive-oil	Nigella-sativa-oil
Case 1	1.14	0.05	0.93	0.17	0.47
Case 2	2.09	0.26	1.00	0.24	0.07
Case 3	2.22	0.12	0.63	0.25	0.21
Case 4	2.03	0.16	1.09	0.52	0.27
Case 5	1.41	0.22	1.18	0.14	0.25
Case 6	1.42	0.03	1.04	0.10	0.21
Case 7	2.14	0.04	0.77	0.31	0.03
Case 8	2.06	0.06	1.15	0.13	0.07
Case 9	2.15	0.10	1.05	0.24	0.20
Case 10	1.78	0.14	0.78	0.18	0.09
Mean	1.78	0.13	0.95	0.25	0.22

It was outlined that in the nigella sativa and olive oil groups, minimal fibrosis was formed similarly to each other. In particular, it was characterised by focal or mild fibroblastic activity in the dorsal area. All rats survived during the clinical follow-up. The histopathological changes are shown in **Figure 1**.

Discussion

The degenerative spine, seen with today's industrial working conditions and increasing life expectancy, has made low back pain one of the most common medical problems in clinical practice[9]. Additionally, more spine procedures are being performed for a variety of reasons, including spinal stenosis, lumbar disc herniation, spondylolisthesis, fracture and infectious diseases. One of the most often used operations is laminectomy[10]. Epidural fibrosis is a well-known complication and is widely seen after conducting laminectomy[11]. It is known that fibrosis develops as a result of fibroblast activation secondary to the increase in inflammatory cytokines in the operation area. These fibroblasts produce mounts of collagen fibres in the laminectomy defect sites[12]. It has been found that fibroblasts turn into fibrocytes with the formation of collagen fibres before the scar tissue is formed from fibrous connective tissue[12]. Although it has been reported that the post-laminectomy membrane is formed due to the invasion of fibroblasts originating from spinal muscles, the exact mechanism behind the formation of postoperative peridural fibrosis has not yet been fully elucidated[13].

Developing fibrosis is among the causes of postoperative low back pain and failed-back syndrome[14]. It is believed that by limiting the growth of fibrosis, this difficult problem for surgeons can be greatly avoided. It is believed that traction in the dura and nerve roots as a result of fibrosis are the causes of pain[15]. Prolongation of hospitalisation, increase in hospital costs and development of neurological deficits occur due to this epidural scar malformation[16]. It is stated that after the development of fibrosis, the surgical operation will be complicated due to the risk of dural tear and haematoma, and the correct approach is the attempt to prevent the development of fibrosis[16].

Potential fibrosis development varies depending on the patient's metabolic activity and surgical circumstances. Well-known fibrosis-increasing surgical agents defined so far are the anatomical region, the surgical style, the development of postoperative infection and the amount of peri/postoperative haemorrhage. Transforming growth factor-1b (TGF-1B) is thought to play a leading role in fibrosis formation[17, 18]. Consequently, the inhibition of the migration of fibroblasts from the paraspinal muscles or haematoma related to surgery could prevent or reduce epidural fibrosis formation.

Many studies have been performed, and many substances have been used to prevent epidural fibrosis developing after spinal surgery. They examined the effectiveness of other compounds for the prevention of epidural fibrosis[19], such as steroids, non-steroidal anti-inflammatory drugs, pedicle fat grafts, synthetic membranes, haemostatic sponges, and anti-adhesion barrier gels[20, 21]. The use and results of anti-inflammatory agents that prevent the induction of TGF-1B and haemostatic agents that provide efficient control of bleeding have also been reported in the literature[22]. It has

been stated that quite satisfactory results were collected. Olive oil and nigella sativa oil, which are employed in our study, two well-known Mediterranean foods whose consumption has been associated with beneficial effects on human health. There are current studies in the literature that these healthy foods can modulate inflammation through antioxidant and epigenetic mechanisms[23]. Furthermore, the major difference between soybean and olive/nigella sativa oil lies between their fat type, i.e. soybean oil contains polyunsaturated fat, while olive oil contains monounsaturated fats. The outcomes of these natural ingredients, which are popular and have various structures, were compared in our study.

Ozkan et al. examined the effects of 5-fluorouracil (5-FU) and bevacizumab (BV), alone and combined, on epidural fibrosis in rat laminectomy model[24]. *Savran* et al. analysed the prevention of epidural fibrosis in rats by local or systemic administration of citicoline[25]. *Bahrami* et al. investigated the effect of N-acetyl-cistein[26]. According to some studies, alpha-tricalcium phosphate (α-TCP) may prevent the development of fibrosis not only through its direct actions on fibroblasts but also by lowering TGF-β levels because of the crucial role that TGF-β plays in collagen synthesis[22].

The fact that more and more information has been gained about the fundamental uses of vegetable oils and their positive contributions to human health, thanks to the bioactive components they contain, has led to an increasing interest of consumers in vegetable oils produced by cold pressing and consumed without refining. It is well recognised that the main cause of these effects is the oxidative stability of vegetable oils[23].

In our study, we analysed the effects of relatively inexpensive organic vegetable oils, which are easy to obtain and are frequently used in daily life. Since they are organic, biocompatible and inexpensive, their use as raw materials in the production of active substances and their involvement in clinical practice will be relatively easy. Nigella sativa oil is also among the oils with high oxidation stability. A significant decrease in fibrosis rates was found in all of the active ingredients we used, and the best result was obtained with nigella sativa oil. More detailed cohort studies are needed to apply our satisfactory results in clinical practise.

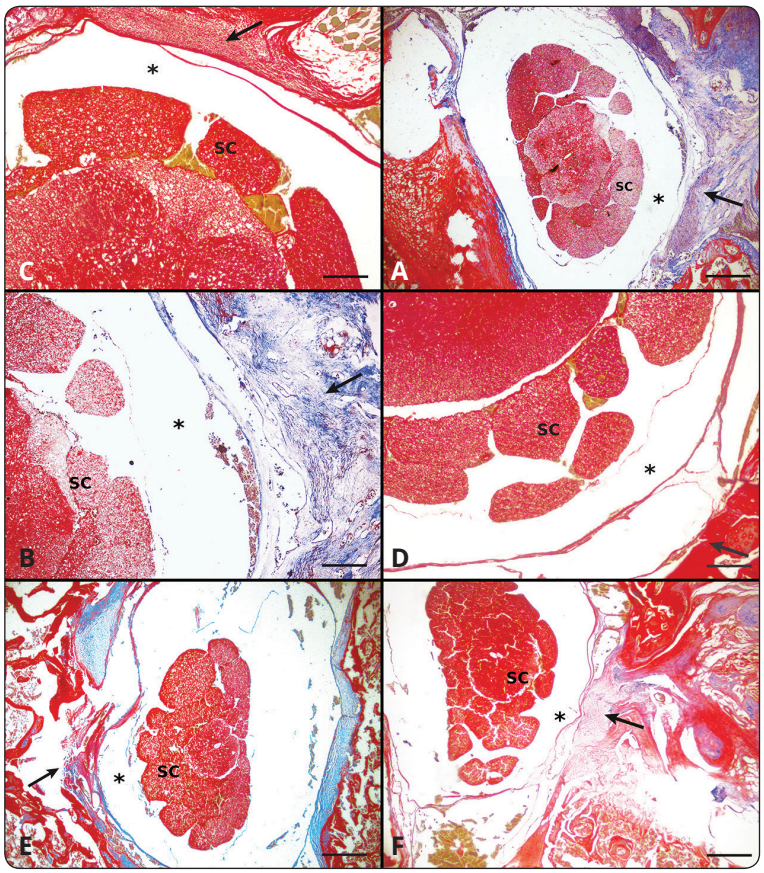

Figure 1. *Histopathological sections of the spinal cord. All sections were stained with Masson's trichrome. In the group without laminectomy (Group 1), normal structure of spinal cord (SC) and subdural space (asterisk) are seen, bar=320 μm* **(A)**.
In the group that did not receive any treatment after laminectomy (L3-4) (Group 2), intense fibroblastic activity (arrow) and local osteoid differentiation are observed in the dorsal root laminectomy area, bar=210 μm **(B and C)**.
In the group in which olive oil was applied after laminectomy (L3-4) (Group 3), a low level of fibroblastic activity (arrow) is seen, with the exception of minimal fibrous adhesions, bar=210 μm **(D)**.
In the group using Nigella sativa oil after laminectomy (L3-4) (Group4), mild to moderate fibrosis and fibroblastic activity (arrow) with collagen are seen in the regeneration area, bar=320 μm **(E)**.
In the group given soybean oil after laminectomy (L3-4) (Group 5), an area of fibrosis (arrow) in the dorsal laminectomy region that progresses further into the spinal space, bar=320 μm **(F)** *is seen*

Limitations

First, there are likely to be species differences in the inflammatory reaction to surgery. Second, sacrificing time is another limitation of the study. Epidural fibrosis level may be higher after a long-time period. Finally, to improve the statistical power of the data, more rats should be included in each group.

Conclusion

Based on our study, organic oils reduce epidural fibrosis after laminectomy in rats. It is proposed that these natural products can safely be used in other species, including human.

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