

Examining the effectiveness of nintedanib in preventing post-laminectomy epidural fibrosis in rats

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ABSTRACT

BACKGROUND: In this rat model study, we examined the effects of topical and systemic nintedanib treatment on the development of post-laminectomy epidural fibrosis.

METHODS: Thirty-two rats were divided into four equal groups (n=8 per group). An L1–L2 laminectomy was performed using standard microsurgical procedures. The control group underwent laminectomy only; the sterile saline group underwent laminectomy followed by sterile saline irrigation; the topical nintedanib group underwent laminectomy followed by topical nintedanib application; and the systemic nintedanib group underwent laminectomy followed by oral nintedanib administration. The degree of fibrosis was evaluated by histological examination. Plasma levels of matrix metalloproteinase-9 (MMP-9), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), transforming growth factor beta-1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), hydroxyproline (HYP), and myeloperoxidase (MPO) were compared among the groups.

RESULTS: In the control group, two rats developed grade 2 epidural fibrosis, while six animals developed grade 3 fibrosis. The sterile saline group demonstrated a similar degree of fibrosis to the control group. In the topical nintedanib group, three, four, and one rat developed grade 1, grade 2, and grade 3 epidural fibrosis, respectively. In the systemic nintedanib group, five rats had grade 1 epidural fibrosis, whereas three rats had grade 2 fibrosis. Groups 3 and 4 showed significantly decreased plasma levels of MMP-9, IL-6, VEGF, TGF-β1, TNF-α, and HYP compared to Groups 1 and 2 (p<0.05). Plasma levels of these markers were lower in Group 4 than in Group 3; however, the difference was not statistically significant (p>0.05). Plasma MPO activity in the study groups was not altered following nintedanib treatment (p>0.05).

CONCLUSION: The histological and biochemical findings of the present study indicate that nintedanib is a promising pharmacological agent for the prevention of post-laminectomy epidural fibrosis. Further studies with larger sample sizes and interval assessments are needed to clarify the effects of different dosages.

Keywords: Epidural fibrosis; nintedanib; inflammation; hydroxyproline; myeloperoxidase.

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INTRODUCTION

Laminectomy may lead to failed back syndrome (FBS), a condition characterized by pain in the back and lower extremities, caused by epidural fibrosis (EF), a common postoperative complication.^[1,2] As EF progresses after surgery, it causes the dura mater and nerve roots to adhere to the disc and vertebrae anteriorly, and to the spinal erector muscles posteriorly. FBS results from the compression and immobilization of nerve roots caused by the formation of this scar tissue.^[3] Postoperative pain, which is frequently observed in many surgeries involving the epidural region, may occur as a result of this complication. By decreasing the availability of cerebrospinal fluid and obstructing regional vascular support, this fibrosis can cause hypoxia, which in turn intensifies pain.^[4] Reoperation in regions with substantial fibrosis presents considerable technical challenges and carries inherent risks that must be carefully considered.

In recent years, several studies have investigated two main strategies to reduce the development of EF. Although antifibrotic medications have been studied, EF is still not always preventable. Decreased tissue cellularity and increased deposition of extracellular matrix components are two characteristics contributing to the etiopathogenesis of EF.^[5,6] Previously, barriers composed of polyethylene oxide and carboxymethylcellulose were examined to limit the formation of epidural adhesions in rabbit laminotomy and laminectomy models, and these barriers were found to reduce epidural fibrosis.^[5] Despite the use of medications such as anti-inflammatory agents, steroids, and hyaluronan, there is currently no effective preventive method for EF.^[7,8]

Nintedanib is a potent second-generation intracellular tyrosine kinase inhibitor that effectively targets a specific group of growth factor receptors, including fibroblast growth factor receptors, platelet-derived growth factor receptors, and vascular endothelial growth factor receptors.^[9] Nintedanib inhibits the proliferation and migration of lung fibroblasts and the growth of endothelial cells within tumor tissue. It helps reduce the ongoing fibrotic process and delays the onset of permanent damage.^[10] In vitro studies have demonstrated that nintedanib exerts antifibrotic effects on primary lung fibroblasts, muscle fibroblasts from patients with Duchenne muscular dystrophy, and skin fibroblasts from individuals with systemic sclerosis. Additionally, its antifibrotic properties have been confirmed in vivo using animal models of various fibrotic diseases.^[11-14]

In preclinical disease models, nintedanib has demonstrated remarkable antifibrotic effects in animal studies of pulmonary fibrosis. This has been evidenced by significant reductions in total lung collagen and a marked decrease in fibrosis observed in histological analyses. Additionally, nintedanib exhibited potent anti-inflammatory properties, as illustrated by substantial reductions in lymphocyte and neutrophil counts in bronchoalveolar lavage fluid. Furthermore, it led to decreased levels of

inflammatory cytokines and a notable reduction in inflammation and granuloma formation in histological examinations of lung tissue. These findings underscore nintedanib's potential as a promising treatment for pulmonary fibrosis.^[11,15]

The importance of early treatment and prevention of epidural scar adhesions is evident, as many patients remain dissatisfied with clinical outcomes. Given the clinical consequences associated with epidural fibrosis, adopting a preventive approach may significantly improve the success of lumbar surgery. Therefore, this study aimed to investigate the effects of nintedanib, administered both topically and systemically, on the formation of epidural fibrosis in a rat model following laminectomy.

MATERIALS AND METHODS

Study Design

This experimental study was conducted in accordance with the highest ethical standards and received approval from the Local Animal Ethics Committee at Van Yüzüncü Yıl University (Decision Number: 2021/07-06; Decision Date: 29/07/2021). All experimental procedures were performed in accordance with the guidelines of the National Institutes of Health (NIH) for the Care and Use of Laboratory Animals, ensuring the humane and responsible treatment of all animals. The principles of the Declaration of Helsinki were also adhered to in this study.

The study included 32 Wistar albino rats weighing between 250-350 g and aged over six months, selected without regard to sex. The animals were housed under controlled environmental conditions with temperatures maintained at 20-24°C, humidity of 50±10%, and a 12-hour light/dark cycle. The rats were randomly divided into four equal groups (n=8 per group) and were provided unrestricted access to food and water throughout the study.

Experimental Groups

Laminectomy Group (Group 1) (n=8): L1-L2 laminectomy was performed without any topical or systemic treatment.

Sterile Saline Group (Group 2) (n=8): L1-L2 laminectomy was performed followed by irrigation with sterile saline.

Topical Nintedanib Group (Group 3) (n=8): L1-L2 laminectomy was performed followed by perioperative topical administration of nintedanib^[11] (30 mg/kg dose diluted with 2 cc sterile saline).

Systemic Nintedanib Group (Group 4) (n=8): L1-L2 laminectomy was performed followed by a single systemic dose of nintedanib^[11] (1/6 of a 30 mg/kg dose).

All animals were sacrificed 30 days after the procedure according to the protocols described below.

Surgical Procedure

Anesthesia was induced using ketamine (60–100 mg/kg, Keta-

sol, Richter Pharma, Austria) and xylazine (5 mg/kg, BIOVETA PLC, Czech Republic), administered intravenously. To prevent surgical site infections, an intramuscular injection of cefazolin (20 mg/kg) was administered prior to the procedure. Body temperature was maintained at 37°C using a heating pad and a rectal probe. The rats were positioned prone on the surgical table. After shaving the lower back region, the surgical area was disinfected with povidone. Following sterile preparation, a longitudinal midline skin incision was made between the L1 and L3 levels. The lumbosacral fascia was incised to expose the L2 laminae, and the paravertebral muscles were dissected subperiosteally. A laminectomy was performed at the L2 level to expose the dura mater and epidural space. Subsequently, the ligamentum flavum and epidural fat tissue were removed from the surgical site. Bipolar cautery, bone wax, and other hemostatic agents were intentionally not used during the procedure. Following topical drug administration in the local therapy group, the wounds were closed anatomically using 4-0 Prolene polypropylene sutures. No topical treatment was administered in either the laminectomy or systemic therapy groups. All procedures were performed under a surgical microscope to protect neurological structures.

In the second group, after laminectomy, the dura mater was irrigated with 10 mL of 0.9% sodium chloride, and the surgical site was closed in anatomical layers using 4-0 polypropylene sutures. In the third group, following laminectomy, a cotton pad soaked with nintedanib at a dose of 30 mg/kg diluted in 2 cc of sterile saline was placed on the exposed dura mater. After 10 minutes, the pad was removed and the area was irrigated with 10 mL of saline before closure. In the fourth group, a single oral dose of nintedanib, corresponding to one-sixth of the 30 mg/kg dose, was administered, after which the incision was closed in anatomical layers to promote healing and reduce complications.

The rats were euthanized by cardiac exsanguination under deep anesthesia with ketamine (80 mg/kg) and xylazine (20 mg/kg). All animals were ambulatory at the time of euthanasia. No infections, hematomas, or cerebrospinal fluid leakage were observed at the surgical site. The entire lumbar vertebral column, including the surgical region, was carefully removed and fixed in 10% neutral formaldehyde for 48 hours to preserve tissue integrity. Subsequently, the specimens were decalcified in 10% formic acid for three days to enable histological evaluation. Following standard tissue processing procedures, the samples were embedded in paraffin for further examination.

Biochemical Evaluation

Blood samples were collected into ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 3,000 × g for 10 minutes at 4°C to obtain plasma. The separated plasma samples were stored at -80°C until analysis.

Plasma levels of several biomarkers were measured using solid-phase sandwich enzyme-linked immunosorbent assay

(ELISA) methods, ensuring precise and reliable results that underscore their significance in clinical assessments. The evaluated biomarkers included matrix metalloproteinase-9 (MMP-9) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0322), interleukin-6 (IL-6) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0136), vascular endothelial growth factor (VEGF) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0660), transforming growth factor beta-1 (TGF-β1) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0780), tumor necrosis factor-alpha (TNF-α) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0765), hydroxyproline (HYP) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0512), and myeloperoxidase (MPO) (Sunred Rat Immunoassay Kit, Cat. No: 201-11-0575). This rigorous approach underscores the significance of these biomarkers in understanding underlying physiological processes and their potential implications for research.

Histopathological Examination

Four-micron-thick sections were cut from the paraffin blocks using a microtome (Thermo-Fisher Scientific, Germany) and stained with hematoxylin and eosin (H&E). The stained slides were examined blindly by a histopathologist using a Nikon Eclipse 80i light microscope (Nikon, Germany) at 10× magnification and evaluated for fibrosis intensity and dural thickness. ImageJ analysis software (version 1.52; National Institutes of Health, MD, USA) was used for morphometric analysis.

According to the definition of He et al.,^[8] histological epidural fibrosis was graded as follows:

- Grade 0: No scar tissue is present on the dura mater.
- Grade 1: Only thin fibrous bands are present between the dura mater and scar tissue.
- Grade 2: Continuous adhesion involving less than two-thirds of the laminectomy defect.
- Grade 3: Extensive scar tissue adhesion covering more than two-thirds of the laminectomy defect or extending to the nerve roots.

The thickness of the dura mater was measured at the midpoint of the laminectomy defect, as well as 2 mm to both the right and left sides of the midline. These measurements were analyzed to obtain mean values for statistical evaluation.^[16] Additionally, fibroblast density within the scar tissue was assessed at the same locations. Cells were counted in three distinct regions (the two borders and the central point of the laminectomy defect) to calculate an average value.

The histopathological density of epidural fibrosis was graded based on the fibroblast predominance according to the criteria described by Hinton et al.^[17] In this classification, grade 1 corresponds to fewer than 100 fibroblasts, grade 2 to 100–150 fibroblasts, and grade 3 to more than 150 fibroblasts. Fibroblasts were counted in three regions using a light microscope at 40× magnification to obtain the mean value (Fig. 1). This approach highlights the significance of our findings for

understanding epidural fibrosis and its implications.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 27 (Statistical Package for the Social Sciences, New York, USA) to ensure a rigorous and reliable interpretation of the data. Frequency tables and descriptive statistics were used to summarize the data. For measurement data that followed a normal distribution, parametric methods were applied. Specifically, the analysis of variance (ANOVA) test (F value) was used to compare measurement values among three or more independent groups. For measurement data that did not follow a normal distribution, non-parametric methods were used. The Kruskal-Wallis H test (χ^2) was applied to compare three or more independent groups, reinforcing the integrity and depth of our analysis. When the analysis of variance showed statistical significance, the Mann-Whitney U test with Bonferroni correction was used to determine group differences. Data are expressed as mean±standard deviation, and a p value <0.05 was considered statistically significant.

RESULTS

Biochemical Evaluation

Plasma MMP-9, IL-6, VEGF, TGF- β 1, TNF- α , and HYP levels were significantly lower in Group 3 and Group 4 compared to Group 1 and Group 2 ($p<0.05$) (Table 1). Plasma MMP-9, IL-6, VEGF, TGF- β 1, TNF- α , and HYP levels were lower in Group 4 compared to Group 3; however, this difference was not statistically significant ($p>0.05$) (Table 1). Plasma MPO activity remained unchanged in the study groups following nintedanib treatment ($p>0.05$) (Table 1).

Histopathological Evaluation

In the laminectomy group, two rats exhibited grade 2 fibrosis (25%), while six rats showed grade 3 fibrosis (75%). Ex-

tensive epidural fibrotic tissue, marked dural thickening, and fibrotic tissue adhesion were observed. Numerous irregular blood vessels adhered to the dura on the laminectomy side, resulting in spinal cord compression (Figs. 1, 2). The level of fibrosis in Group 2 (sterile saline [SF] group) was similar to that observed in Group 1, with two rats presenting grade 2 fibrosis and six rats exhibiting grade 3 fibrosis. In the topical nintedanib group, three rats showed grade 1 fibrosis, four rats showed grade 2 fibrosis, and one rat showed grade 3 epidural fibrosis. In the oral nintedanib group, five rats exhibited grade 1 fibrosis and three rats showed grade 2 fibrosis. Notably, no rats in this group displayed grade 3 fibrosis.

In both the control and SF groups, the majority of the rats displayed grade 3 epidural fibrosis. The laminectomy defects were entirely covered by fibrotic tissue adherent to the dura mater (indicated by an arrow), affecting nearly two-thirds of each defect. In contrast, rats treated with topical nintedanib frequently developed grade 2 fibrosis, with less than two-thirds of the laminectomy defect showing continuous adhesion of the dura mater (arrow) to the fibrous tissue. Only thin fibrous bands between the loose fibrous tissue and the underlying dura mater (arrow) were indicative of grade 1 epidural fibrosis, which was present in the majority of animals in the oral nintedanib group (scale bar: 100 μ m).

The differences in epidural fibrosis levels among the groups were statistically significant ($\chi^2=19.871$; $p<0.001$). Bonferroni-corrected pairwise comparisons were conducted to identify the groups responsible for this significant difference. The epidural fibrosis values in Group 1 were found to be significantly greater than those of Groups 3 and 4. Similarly, Group 2 also showed significantly higher epidural fibrosis values compared to Groups 3 and 4. A striking disparity was identified between animals in Group 2 and those in Groups 3 and 4, with Group 2 demonstrating significantly higher levels

Table 1. Plasma levels of matrix metalloproteinase-9 (MMP-9), interleukin-6 (IL-6), vascular endothelial growth factor, transforming growth factor beta-1, tumor necrosis factor-alpha, hydroxyproline), and myeloperoxidase in all groups (mean±standard deviation)

Parameters	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
MMP-9 (ng/mL)	1.43±0.23	1.41±0.13	1.40±0.13	1.28±0.22
IL-6 (pg/mL)	2.84±1.11	2.86±0.53	1.13±0.12	1.01±0.25
VEGF (ng/mL)	3.04±0.21	2.91±0.38	1.16±0.43	1.13±0.05
TGF- β 1 (ng/L)	2.20±0.51	1.98±0.23	1.04±0.22	1.03±0.16
TNF- α (ng/L)	2.14±0.28	2.23±0.27	1.45±0.13	1.37±0.38
HYP (ng/mL)	3.13±0.63	3.16±0.54	0.93±0.13	0.92±0.14
MPO(ng/mL)	2.98±0.96	3.18± 0.64	1.21±0.33	1.32±0.23

MMP-9: Matrix metalloproteinase-9; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor; TGF- β 1: Transforming growth factor beta-1; TNF- α 1: Tumor necrosis factor-alpha; MPO: Myeloperoxidase; HYP: Hydroxyproline.

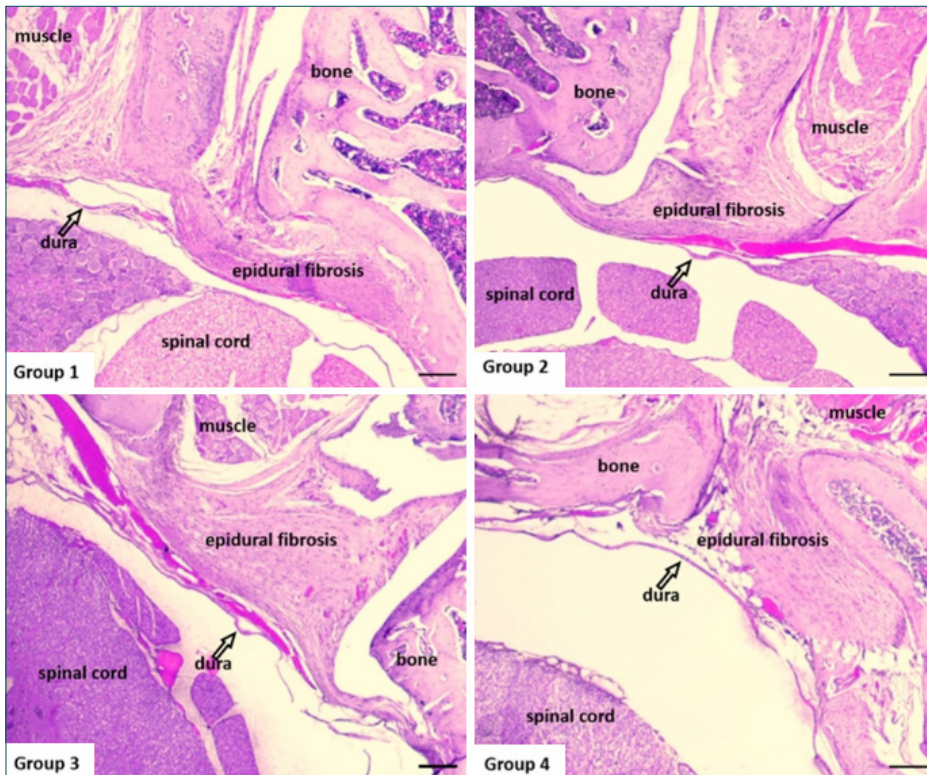


Figure 1. Photomicrographs of hematoxylin and eosin (H&E)-stained epidural adhesions on the laminectomy sides.

of epidural fibrosis compared to its counterparts.

Moreover, analysis of dural thickness at the midpoint revealed significant differences among the groups ($F=106.686$; $p<0.001$). Tukey pairwise tests conducted to evaluate variance homogeneity revealed a notable difference between Group 1 and Groups 3 and 4. Group 1 exhibited substantially greater midpoint dural thickness values, indicating a significant difference among the groups. Similarly, a significant difference was observed between animals in Group 2 and those

in Groups 3 and 4 (Fig. 3, Table 2).

A statistically significant difference was also detected in right-sided dural thickness values among the groups ($F=73.911$; $p<0.001$). As a result of Tukey pairwise comparisons performed by considering the homogeneity of variances to determine which group the significant difference originated from, a significant difference was detected between animals in Group 1 and those in Groups 3 and 4. It was determined that the dural thickness (right-sided) values of Group 1 were

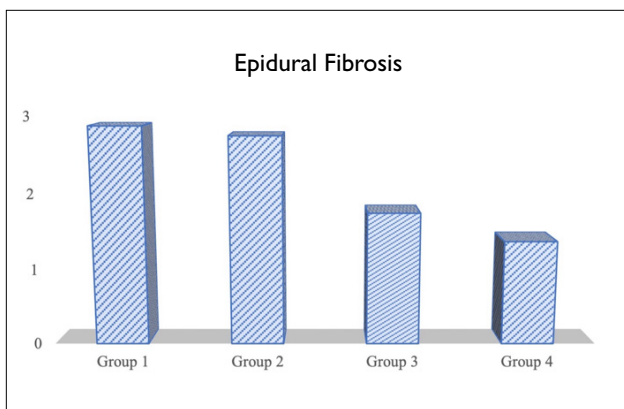


Figure 2. A line graph illustrating the distribution of epidural fibrosis across the study groups.

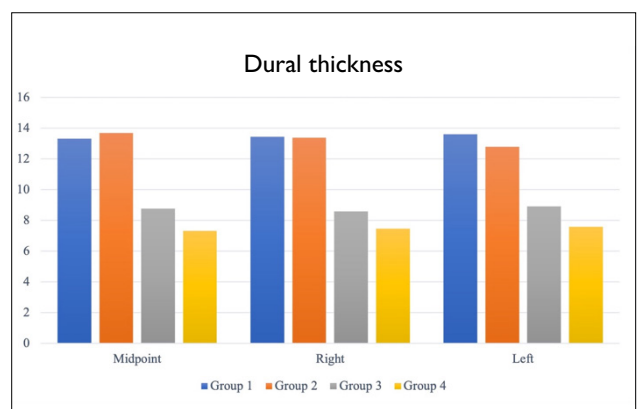


Figure 3. Line chart depicting dural thickness in all groups measured at the laminectomy areas—right side, midpoint, and left side.

Table 2. Comparison of epidural fibrosis and dural thickness values among the groups

Variable	Group 1 (n=8) (1)		Group 2 (n=8) (2)		Group 3 (n=8) (3)		Group 4 (n=8) (4)		Statistical analysis* Probability
	$\bar{X} \pm S.S.$	Median [IQR]	$\bar{X} \pm S.S.$	Median [IQR]	$\bar{X} \pm S.S.$	Median [IQR]	$\bar{X} \pm S.S.$	Median [IQR]	
Epidural fibrosis	2.87±0.35	3.0 [1.0]	2.75±0.46	3.0 [0.8]	1.75±0.71	2.0 [1.0]	1.38±0.51	1.0 [1.0]	$\chi^2=19.874$ $p<0.001$ [1-3,4] [2-3,4]
Dural thickness (midpoint)	13.32±0.78	13.6 [1.6]	13.69±0.89	13.4 [1.2]	8.77±0.94	8.8 [1.3]	7.32±0.89	7.2 [1.5]	$F=106.686$ $p<0.001$ [1-3,4] [2-3,4] [3-4]
Dural thickness (right)	13.45±1.19	13.6 [1.9]	13.39±1.27	13.5 [1.6]	8.59±0.79	8.4 [1.4]	7.47±0.77	7.5 [1.4]	$F=73.911$ $p<0.001$ [1-3,4] [2-3,4] [3-4]
Dural thickness (left)	13.62±0.94	13.6 [0.8]	12.79±0.88	12.7 [1.7]	8.91±1.02	9.1 [1.1]	7.59±1.15	7.7 [2.3]	$F=67.816$ $p<0.001$ [1-3,4] [2-3,4]

*The analysis of variance (ANOVA) test (F value) was used to compare measurement values among three or more independent groups when the data followed a normal distribution. The Kruskal-Wallis H test (χ^2 value) was used to compare measurement values among three or more independent groups when the data did not follow a normal distribution.

significantly higher than those of Groups 3 and 4. Likewise, a significant difference was detected between animals in Group 2 and those in Groups 3 and 4. The results indicated that the epidural fibrosis values in Group 1 were significantly higher than those in Groups 3 and 4. Similarly, a notable difference was found between Group 2 and both Groups 3 and 4, with the epidural fibrosis values in Group 2 also being significantly higher than those in Groups 3 and 4.

DISCUSSION

In this study, both local and systemic therapy with nintedanib resulted in a reduction of EF. Previous studies have demonstrated a strong correlation between epidural fibrosis and both collagen overproduction and fibroblast activation.^[18,19] Various materials and drugs have been investigated to prevent epidural fibrosis, including adipose tissue, hydrogel membranes, polytetrafluoroethylene membranes, polyvinyl alcohol, polylactic acid membranes, pentoxifylline, and Vicryl mesh, all of which act as physical barriers.^[8,16,17]

This study investigates the protective effects of nintedanib on epidural fibrosis using both histological and biochemical analyses. The findings demonstrate that nintedanib significantly reduces fibrosis formation in the epidural area, as shown in Figures 1-3. Notably, the midpoint dural thickness values in

Group 2 were significantly greater than those in Groups 3 and 4, highlighting the detrimental impact of fibrosis. Furthermore, a significant difference in dural thickness was observed between Groups 3 and 4, with Group 3 exhibiting greater thickness than Group 4. These results underscore the efficacy of nintedanib. Additionally, treatment led to an increase in bone regeneration areas in both Groups 3 and 4. These findings support the potential role of nintedanib as a therapeutic agent in the management of epidural fibrosis.

TGF- β plays a crucial role in fibrosis by stimulating the synthesis of collagen and fibronectin through fibroblasts.^[20-22] Additionally, TGF- β significantly influences the production of the extracellular matrix (ECM) by fibroblasts and inhibits the biosynthesis of proteases responsible for ECM degradation.^[20,22] According to several studies, TGF- β 1 levels increase in fibrosis, and inhibition of TGF- β 1 can prevent the production of fibrous tissue.^[23] Upon tissue injury, cellular proliferative and migratory factors are activated, leading to increased secretion of matrix metalloproteinases (MMPs), which facilitate remodeling. Growth factors and cytokines such as TGF- β 1, IL-6, and TNF- α further stimulate this process.^[24] MMPs degrade basement membrane matrices, enabling cell proliferation and migration.^[25] While most cytokines are pro-inflammatory, IL-6 also possesses strong anti-inflammatory effects, inhibit-

ing TNF- α -induced upregulation of endothelial adhesion molecules.^[26] Some studies have also shown that TNF- α 's role in collagen synthesis and fibrosis can be mitigated by specific agents.^[27]

In the current investigation, we found that Groups 3 and 4 had considerably lower plasma levels of MMP-9, IL-6, VEGF, TGF- β 1, and TNF- α than Groups 1 and 2. Furthermore, compared to Group 3, the plasma levels of these markers in Group 4 were lower; however, this difference was not statistically significant.

In preclinical models of systemic sclerosis (SSc), an immune-mediated rheumatic disease of uncertain etiology characterized by vasculopathy and fibrosis of the skin and internal organs, nintedanib has demonstrated antifibrotic properties.^[28] Nintedanib showed potent antifibrotic effects and significantly reduced fibroblast activation in two preclinical mouse models of SSc. Additionally, nintedanib improved the histological features of pulmonary arterial hypertension, destructive microangiopathy, and pulmonary and cutaneous fibrosis in another mouse model.^[13,29]

In the present study, nintedanib may improve fibrosis not only through its direct effects but also by reducing the levels of MMP-9, IL-6, VEGF, TGF- β 1, and TNF- α . Hydroxyproline rapidly accumulates in collagen during the wound-healing process. The degree of adhesion is negatively correlated with its concentration.^[23]

According to the findings, Groups 3 and 4 had significantly lower plasma HYP levels than Groups 1 and 2. Furthermore, the plasma HYP levels in Group 4 were lower than those in Group 3; however, this difference was not statistically significant.

We suggest that the systemic administration of nintedanib has the potential to effectively target multiple stages of inflammation simultaneously, rather than being limited to a single phase. Significant effects on both the inflammation and proliferation phases are indicated by the observed decrease in HYP levels. Notably, fibroblasts modified by reduced levels of pro-inflammatory cytokines become more prominent during the proliferation phase of inflammation, suggesting that this phase may be indirectly affected.

Extensive research has demonstrated that lowering the levels of key inflammatory markers such as TNF- α , IL-6, and TGF- β 1 can inhibit the proliferation and differentiation of fibroblasts and endothelial fibroblasts.^[30,31] In our current study, both systemic and topical administration of nintedanib resulted in a marked reduction in MMP-9, IL-6, VEGF, TGF- β 1, and TNF- α levels. These findings support the role of nintedanib as a powerful therapeutic option for managing complex inflammatory responses.

The results demonstrate that rats treated systemically with nintedanib exhibited significantly lower grades of epidural fibrosis compared to those in the other groups. Moreover,

systemic nintedanib proved to be more effective in preventing epidural fibrosis than topical administration. This study highlights nintedanib's potent antifibrotic mechanisms, which not only directly inhibit TNF- α but also substantially reduce the levels of MMP-9, IL-6, VEGF, TGF- β 1, and HYP. These findings underscore the potential of systemic nintedanib as an effective approach to combating epidural fibrosis.

CONCLUSION

In conclusion, our study clearly demonstrates that the systemic administration of nintedanib significantly reduces the formation of epidural fibrosis in a rat model of laminectomy. Moreover, nintedanib shows promise as an effective intervention at various stages of inflammation, highlighting its potential as a powerful therapeutic agent for preventing epidural fibrosis. To fully harness its benefits, further research is needed to establish the optimal dosage and method of administration of nintedanib.

Ethics Committee Approval: This study was approved by Local Animal Ethics Committee at Van Yüzüncü Yıl University (Date: 29.07.2021, Decision No: 2021/07-06).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: O.O., A.T.; Design: A.A., A.T.; Supervision: O.O., Z.Y.; Resource: A.T., A.A.; Materials: A.C.G., Z.Y.; Data collection and/or processing: A.C.G., O.S.; Analysis and/or interpretation: O.S., A.T.; Literature review: O.S., A.Ç.G.; Writing: O.O., Z.Y., O.S.; Critical review: Z.Y., A.A.

Conflict of Interest: None declared.

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DENEYSSEL ÇALIŞMA - ÖZ

Şıçanlarda laminektomi sonrası oluşan epidural fibrozisi önlemede nintedanibin etkinliğini araştırma

AMAÇ: Nintedanibin topikal ve sistemik uygulanmasının, bir şıçan modelinde post-laminektomi epidural fibrozis gelişimi üzerindeki etkisini araştırmak.
GEREÇ VE YÖNTEM: Otuz iki şıçan, dört eşit gruba ayrıldı. L1-L2 laminektomi, standart mikrocerrahi tekniği kullanılarak gerçekleştirildi. Kontrol grubuna yalnızca laminektomi yapıldı; steril salin grubuna laminektomi sonrası steril salin ile yıkama yapıldı; topikal nintedanib grubuna laminektomi sonrası topikal nintedanib uygulandı; sistemik nintedanib grubuna laminektomi sonrası oral nintedanib verildi.

BULGULAR: Kontrol grubundaki iki şıçanda 2. derece ve altı şıçanda 3. derece epidural fibrozis gelişti. Steril salin grubundaki fibrozis seviyesi kontrol grubuna benzerdi. Topikal nintedanib grubunda üç, dört ve bir şıçan sırasıyla 1., 2. ve 3. derece epidural fibrozis geliştirdi. Sistemik nintedanib grubunda beş şıçanda 1. derece ve üç şıçanda 2. derece epidural fibrozis gözlemlendi. Plazma matris metalloproteinaz-9 (MMP-9), interlökin-6 (IL-6), vasküler endotelial büyüme faktörü (VEGF), transformasyon büyüme faktörü beta-1 (TGF-β1), tümör nekroz faktörü-alfa (TNF-α) ve hidrokspirolin (HYP) seviyeleri grup 3 ve grup 4'te, grup 1 ve grup 2 ile karşılaştırıldığında önemli ölçüde daha düşüktü ($p < 0.05$). Çalışma gruplarında plazma miyeloperoksidaz (MPO) aktivitesinin nintedanib tedavisinden sonra değişmediği gösterilmiştir ($p > 0.05$).

SONUÇ: Mevcut çalışmada histolojik ve biyokimyasal sonuçlar, nintedanibin post-laminektomi epidural fibrozisin tedavisi için potansiyel bir farmakolojik ajan olduğunu göstermektedir. Doz etkinliğini belirlemek için geniş popülasyon üzerinde ve aralıklı değerlendirme yapılan çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Epidural fibrozis; nintedanib; inflamasyon; hidrokspirolin; miyeloperoksidaz.

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