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Comparison of Histopathological Analysis of Autologous Fat Tissue, Cerebrospinal Fluid and Sodium Hyaluronate for Preventing Epidural Fibrosis

Burak Bilal Balci[1], Mevlüt Özgür Taskapilioglu[2], Özlem Özmen[3] & Hakan Salci[1]

ABSTRACT

***Background*:** Decompressive surgery is an operative procedure performed to prevent the compression to the spinal cord or the other neural tissues. Laminectomy as a decompressive technique is applied to widening the spinal canal resulted from secondary to fractures, tumors, abscesses and deformities. Epidural fibrosis (EF) is a progressive formation. While the epidural hematoma in the spinal region is absorbed, it gradually occurs the granulation tissue and then this turns into the fibrous tissue. This fibrous tissue replaces the bone excised in laminectomy and attaches to the muscles overlying the dura mater. EF compress to the surrounding neural tissues and nerve roots, and cause to neuronal atrophy and axonal degeneration. This study aims to compare histopathological results of autologous fat tissue, cerebrospinal fluid (CSF) and sodium hyaluronate for preventing epidural fibrosis (EF).

***Materials, Methods & Results*:** Totally, 20 (n=20) Wistar Albino rats were randomly selected and the study was carried out in 4 groups with equal numbers of rats (5) in each group. Under general anesthesia, laminectomy was performed on L3 vertebral lamina in all groups. Biomaterials applicated to the laminectomy area were saline in GRI, autologous fat tissue in GRII, 0.1 mL CSF in GRIII and 0.1 mL sodium hyaluronate in GRIV. Lateral and ventrodorsal lumbar radiographs were taken from all rats before and after surgery. Tarlov's motor function tests were scored in groups pre- and postoperatively. At postoperative 45 day, the L2-4 spine segments of the rats were en-bloc removed and the prepared slides were stained with hematoxylin and eosin. Microscopically, fibroblastic density, EF, arachnoid fibrosis and inflammatory cell infiltration were evaluated. The obtained data were evaluated statistically. On control days, all rats gait was normal in GRI, GRIII and GRIV; however, In GRII, Tarlov's score was 2 in a rat. There was no significant difference in terms of measurement times of Tarlov's motor function scoring within and between groups ($P > 0.05$). Fibroblastic density, EF, arachnoid fibrosis and inflammatory cell scores were the most severe and dense in GRI. These were less in GRII and GRIV, and fibroblastic and inflammatory cell findings were the least in GRIII. Statistically significant differences were found between GRI and GRIII in terms of fibroblast density ($P = 0.002$), epidural fibrosis ($P = 0.002$), arachnoid fibrosis ($P = 0.001$) and inflammatory cell infiltration ($P = 0.003$). There was no statistically significant difference between the other study groups ($P > 0.05$).

***Discussion*:** Clinically, the presence of pain in patients who have undergone laminectomy is scored and neurological findings are evaluated with functional tests. Macroscopic examination of the dura mater and surrounding tissues is not sufficient to determine the degree of epidural adhesions and therefore experimental histopathological studies are required. Although easily obtained, the positive effect of autologous fat grafts in preventing EF is still controversial. Compared to plasma, the low potassium concentration of CSF appears to play a role in preventing fibrosis by suppressing the ability of fibroblasts to attach and spread. Exogenously applied hyaluronic acid inhibits fibroblast proliferation and reduces fibrosis and scar formation in the early stages of tissue healing. However, considering the data of this study, CSF was the most effective biomaterial in reducing fibroblastic density and preventing EF in the laminectomy area.

Keywords: EF, CSF, laminectomy, biomaterial, epidural fibrosis, motor function test, histopathology, Wistar Albino rats.

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[1]Department of Surgery, Faculty of Veterinary Medicine, Bursa Uludağ University, Bursa, Turkey. [2]Medicabil Hospital, İstanbul Yeniyüzyıl University, Bursa. [3]Department of Pathology, Faculty of Veterinary Medicine, Burdur Mehmet Akif Ersoy University, Burdur, Turkey. CORRESPODENCE: H. Salci [hsalci@uludag.edu.tr] Department of Surgery, Faculty of Veterinary Medicine, Bursa Uludağ University. 16059 Nilüfer/Bursa, Turkey.

INTRODUCTION

Laminectomy as a decompressive technique is applied to widening the spinal canal resulted from secondary to fractures, tumors, abscesses and deformities [23]. After laminectomy, fibrosis and scar tissue formation in the operation area may lead to recurrent gait disorders and pain caused by epidural fibrosis (EF) [19,21,22]. EF compress to the neural tissues and nerve roots, and cause to neuronal atrophy and axonal degeneration [2,4,13]. In order to prevent the EF, several methods are recommended such as using anti-inflammatory drugs, minimal invasive surgical approach and placing a barrier between the epidural space and other tissues covering it in the laminectomy area [8,16,17,19,21,22]. Some materials including xenoderm, autologous free or pedicle fat grafts, omental grafts, heterogeneous bone grafts, absorbable gelatin sponge, polyglactin 910 mesh, carbohydrate polymers, thrombin impregnated collagen gel, polylactic acid membrane, methyl methacrylate, hyaluronic acid (HA) and fibrin glue are used as a barrier [18,22]. Additionally, mitomycin-c, adcon-l, curcumin, glucocorticoids and nonsteroidal anti-inflammatories are also applied locally or systemically [2,12,22].

Although many studies have reported that biological materials are more effective to prevent EF [10,17], it is still questioned which method is the most effective and superior to the others [8,11,19]. Thus, this study aims to compare histopathological findings of locally applied autologous fat tissue, cerebrospinal fluid (CSF) and sodium hyaluronate in preventing the EF in rats and to reveal which method is superior.

MATERIALS AND METHODS

Materials and study design

A total of 20 (n = 20) adult healthy Wistar Albino rats weighing approximately 300 g, without gender discrimination, were used in the study. CFS was also collected from 5 rats. All rats were kept in a 22°C environment, 12 h a day and night, and fed ad libitum. Rats were randomly selected for surgery and the study was carried out under 4 groups. Laminectomy was performed on the L3 vertebral lamina of the rats in all groups.

After laminectomy, saline in group I (GRI) [n = 5], autologous fat tissue in group II (GRII) [n=5], 0.1 mL CSF in group III (GRIII) [n = 5] and 0.1 mL sodium hyaluronate in group IV (GRIV) [n = 5] were locally applicated to the laminectomy sites (Figure 1).

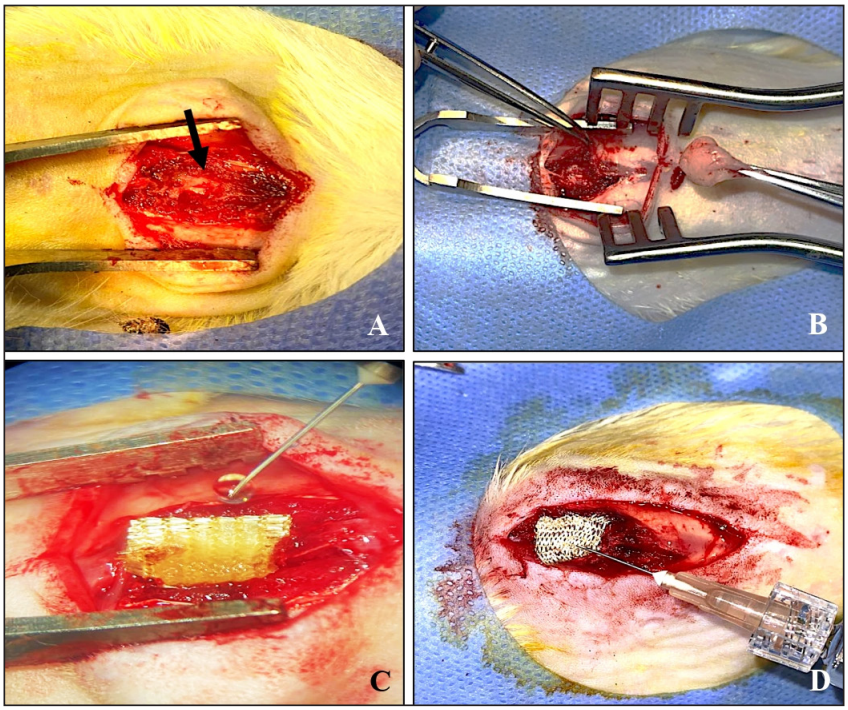

Figure 1. A- Appearance of the operation site after L3 laminectomy (arrow) in GRI. B- Application of autologous fat graft to the laminectomy site in GRII. C- Impregnation of CSF into the surgicel placed in the laminectomy site in GRIII. D- Impregnation of sodium hyaluronate into the surgicel placed in the operation site in GRIV.

Collection and application of the biomaterials

Before laminectomy, autologous fat tissue was taken from the inguinal region of each rat under general anesthesia in a sterile manner as reported previously [6,10,14]. The fat tissue was cut to 5x5 mm in size to lay on laminectomy area for all rats and then applied locally in GRII (Figure 1).

Five rats were placed in the dorsoventral position under general anesthesia for the collection of CSF. The area from the back of the cranium to the middle of the cervical vertebra was shaved and prepared aseptically for surgery. A 24-gauge sterile cannula was inserted to the cisterna magna at a 45° angle and a total of 1 mL of CSF was collected into a sterile syringe [19]. After CSF was impregnated with an absorbable hemostat[1] [Surgicel®], it was applied on the laminectomy area in GRIII (Figure 1).

Sodium hyaluronate[2] [Crownflex® - 20 mg] were also impregnated an absorbable hemostat[1] [Surgicel®] and applied to laminectomy area in GRIV (Figure 1).

Experimental procedures

Lateral and ventrodorsal lumbar radiographs were taken from all rats before and after surgery. Surgical procedures were performed under general anesthesia. Xylazine HCl[3] [Alfazine® - 10 mg/kg, IM] and ketamine HCl[3] [Alfamine® - 60 mg/kg, IM] were administered for preanesthetic and induction, respectively.

The rats were placed in the dorsoventral position and a 2 cm skin incision was made over the spinal process from the lumbar vertebral median line. The paraspinous muscles were separated by blunt dissection and the L2-4 dorsal laminar region was exposed. Dorsal laminectomy was performed on L3 vertebral lamina using an operating microscope and no surgical procedure was carried out on the dura mater. After the materials determined for the groups were applied to the laminectomy area, bleeding control was performed and the muscle and subcutaneous tissues were routinely closed.

In the postoperative period, only cefazolin Na[4] [Cefozin® - 20 mg/kg, twice daily, IM for 7 days] was applied to all rats as an antibiotic, and neither glucocorticoids nor non-steroidal anti-inflammatory drugs were applied to the rats. The rats were sacrificed by decapitation on the 45th postoperative day, and the laminectomy site on L2-4 lumbar spine was en-bloc removed.

Tarlov's motor function evaluation

The motor functions of the extremities of rats in all groups were monitored preoperatively and on postoperative days 1, 7, 15, 30 and 45 using the scale previously described by Tarlov [20]. Motor functions were scored as 1: no movement in the extremities, 2: partial movement in the joints, 3: movement in the hind extremities but unable to step on 4 extremities, 4: able to step on 4 extremities but unable to walk normally, and 5: able to walk normally.

Histopathological examinations

The segmental part of L2-4 spine, which was en-bloc removed without damaging the surgical area, was embedded in 10% neutral formalin solution. It was fixed for 2 days and then kept in separate containers in decalcification solution for 7 days. A 5 µm thick sections were taken from the vertebrae and surrounding tissues, passing through the laminectomy area. The sections were placed on the slide and the preparations were stained with hematoxylin and eosin (H&E). The preparations were examined blindly under a light microscope and were evaluated in terms of fibroblastic density, epidural fibrosis, arachnoid fibrosis and inflammatory cell infiltration. Fibroblastic density and inflammatory cell infiltration were scored: 1; less than 100 cells in each area at 400x, 2; 100-150 cells in each field at 400x, 3; more than 150 cells in each field at 400x. Epidural fibrosis was scored as follows; 0: no scar formation, 1: presence of only thin fibrous bands between scar tissue and dura mater, 2: continuous adhesions filling less than 2/3 of the laminectomy area, 3: adhesions filling more than 2/3 of the laminectomy area and/or spreading to the nerve roots. Arachnoid fibrosis was scored as; 0: none, 1: minimal, 2: moderate, 3: severe [11].

Statistical analysis

A package program[5] [GraphPad Prism 9.0.1®] was used for analysis of Tarlov's motor function scoring and histopathological data. The conformity of the data to normal distribution was assessed with the "Shapiro-Wilk" test. In between-group comparison of data that did not conform to normal distribution, the "Kruskal Wallis" test was used. Multiple comparisons of variables found to be significant were made with

the "Dunn test". The "Friedman test" was used for within-group comparisons. The significance level was accepted as $P < 0.05$.

RESULTS

Tarlov's motor function results

In the preoperative period, all rats in the groups had normal gait and the Tarlov's score was recorded as 5. On postoperative days 1, 7, 15, 30 and 45 in GRI, GRIII and GRIV; all rats could stand on their four extremities and their gait was normal; the Tarlov's score was 5. In GRII, only 1 rat had restricted movement in the joints of its hind extremity, and the Tarlov's score of this rat was recorded as 2. The other 4 rats could stand on their four extremities and walked normally. The Tarlov's score of these 4 rats was 5. There was no significant difference in terms of measurement times of Tarlov's motor function scoring within and between groups ($P > 0.05$).

Histopathological results

Histopathological findings score of all groups are given in Table 1. In GRI; there was a significant increase in connective tissue in the laminectomy region and adhesions were observed. Fibroblast density, epidural fibrosis and inflammatory cell infiltration scores were 3 in 3 experiments and 2 in 2 experiments. Arachnoid fibrosis scores were 3 in 4 experiments and 2 in 1 experiment (Figure 2).

In GRII; there was less connective tissue in the laminectomy region and adhesions were observed to be even less compared to GRI. Fibroblast density scores were 2 in 4 experiments, 1 in 1 experiment and epidural fibrosis scores were 2 in 5 experiments. Arachnoid fibrosis scores were 2 in 2 experiments and 1 in 3 experiments, while inflammatory cell infiltration scores were 2 in 2 experiments and 1 in 3 experiments (Figure 2).

In GRIII; connective tissue development was limited in the laminectomy region. Epidural fibrosis was almost non-existent. Fibroblast density scores were 1 in all experiments. Epidural fibrosis and inflammatory cell infiltration scores were determined as 1 in 4 experiments and 0 in 1 experiment. Arachnoid fibrosis scores were as 1 in 3 experiments and 0 in 2 experiments (Figure 2).

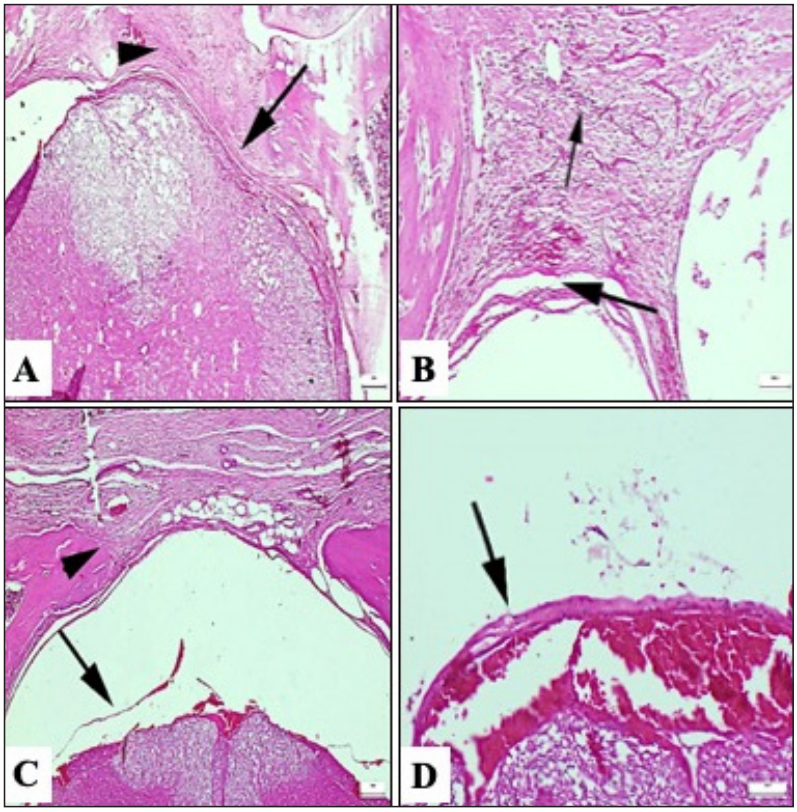

Figure 2. Microscopic appearances of laminectomy sites in groups (H&E). A- In GRI, adhesion of dura mater to bone and spinal cord (arrow), connective tissue development in the laminectomy site (arrow head) [bar= 200 µm]. B- In GRII, very thin adhesions with decreased connective tissue increase (thick arrow), mild inflammatory cell infiltration (thin arrow) [bar= 100 µm]. C- In GRIII, limited connective tissue development (arrow head), dura mater without any adhesion (arrow) [bar= 200 µm]. D- In GRIV, dura mater without any adhesion (arrow) [bar = 50 µm].

Table 1. Scores of fibroblast density, epidural fibrosis, arachnoid fibrosis, and inflammatory cell infiltration findings for subjects in all groups of Wistar Albino rats.

Groups	Experiment	Fibroblastic density	Epidural fibrosis	Arachnoid fibrosis	Inflammatory cell infiltration
GRI	1	3	3	3	2
	2	3	3	3	3
	3	3	3	3	3
	4	2	2	2	3
	5	2	2	3	2
GRII	1	2	2	2	2
	2	1	2	1	1
	3	2	2	1	1
	4	2	2	1	1
	5	2	2	2	2
GRIII	1	1	0	0	0
	2	1	1	0	1
	3	1	1	1	1
	4	1	1	1	1
	5	1	1	1	1
GRIV	1	2	1	2	1
	2	1	1	2	1
	3	2	1	2	1
	4	2	2	1	2
	5	1	2	1	1

In GRIV; connective tissue development in the laminectomy region was less than in GRII. Epidural fibrosis was partially similar to GRIII. Fibroblast density and arachnoid fibrosis scores were determined as 2 in 3 experiments and 1 in 2 experiments. Epidural fibrosis scores were 2 in 2 experiments and 1 in 3 experiments. Inflammatory cell infiltration scores were 2 in 1 experiment and 1 in 4 experiments (Figure 2).

When all groups were evaluated comparatively; fibroblastic density, epidural fibrosis, arachnoid fibrosis and inflammatory cell scores were the most severe and dense in GRI. When compared to GRI, these findings were less in GRII and GRIV, and fibroblastic and inflammatory cell findings were the least in GRIII. The group with the least epidural and arachnoid fibrosis formation was again GRIII.

In the microscopic evaluation of all rats in the study groups, no significant difference was found in fibroblast density, epidural fibrosis, arachnoid fibrosis and inflammatory cell infiltration findings ($P > 0.05$). Statistically significant differences were found between GRI and GRIII in terms of fibroblast density ($P = 0.002$), epidural fibrosis ($P = 0.002$), arachnoid fibrosis ($P = 0.001$) and inflammatory cell infiltration ($P = 0.003$). There was no statistically significant difference between the other study groups ($P > 0.05$).

DISCUSSION

EF caused by healing tissue affects nerves, and when EF is removed during reoperation, new neuronal damage occurs [17]. Neurologic deficits may develop due to adhesion between the dura mater, spinal cord and dural sac after laminectomy [6,12,18]. Although many techniques have been applied to prevent EF, which method provides the best results is still being investigated [1,8,14,17]. Therefore, the presented study was planned to compare the effects of different biomaterials (autologous fat tissue, CSF and sodium hyaluronate), in preventing EF with histopathological findings and to determine the superiority of biomaterials over each other.

After laminectomy, EF develops in rabbit, rats and dogs [21]. Spinal muscles, annulus fibrosus, ligamentum flavum and longitudinal ligament contribute to the formation of EF [4,16,21,22]. Individual health status, breed and species differences, postoperative

hematoma formation of laminectomy area and surgical technic also effect the formation of EF [13]. In the study presented, adult, Wistar albino rats were used as an experiment, and after dorsal laminectomy was performed in the L3-4 vertebral segment of the rats. Basically, for the formation of EF, local inflammation and hemostasis in the postoperative process for the first 3-5 days, fibroblast proliferation and differentiation in the next 2-3 weeks, and then the tissue reconstruction that could last for months and years [16,17,19,22]. Furthermore, it is reported that the 6-week period is sufficient in the postoperative early assessment of EF [10]. In the presented study, the formation of EF in the laminectomy region was investigated on the basis of the literature information above. Considering the pathophysiological process of EF, the follow-up period in the presented study was determined as 45 days.

In determining the degree of epidural adhesions, macroscopic examination of the dura mater and the surrounding tissues is not sufficient. Thus, histopathological examination of the cellular structures and EF formation of the tissues taken from the laminectomy area should be performed [14,15,17,22]. Clinically, myelography can be performed on patients who have undergone laminectomy [6], pain presence is scored [17] and neurological findings are evaluated with functional tests [6,13]. In the presented study, the operation area was checked radiologically before and after surgery and the laminectomy area was examined in terms of cellular structure and EF formation histopathologically. In addition, the motor function loss that may occur due to EF formation was evaluated with Tarlov's motor function scoring.

Autologous fat grafts are widely used to prevent EF by creating a physical barrier [14,16]. However, despite being easily obtained, the positive effect of autologous fat grafts in preventing EF is still controversial [16]. In a study where fat grafts were applied to the laminectomy area, it was reported that neurological deficits were gradually observed within 3-10 days postoperatively and that this was related to the migration of the graft to the spinal cord and epidural space [6]. In this study, a postoperative neurological deficit was determined in a GRII rat in which autologous fat graft was used, but this was not statistically significant in the within-group evaluation ($P < 0.05$). It is reported that 50% of dogs that received fat grafts to the operation area after laminectomy developed EF [6]. In the presented study, less connective tissue and adhesion were formed in GRII compared to the control group. Applying a fat graft larger than necessary to the laminectomy site may lead to nerve compression [10,14], and that a routine fat graft thickness of approximately 5 mm adequately protects the dura mater and prevents excessive fibrous tissue formation [6,10,14]. In the presented study, approximately 5x5 mm autologous fat grafts were taken from the inguinal region of each rat in GRII and placed on the laminectomy area, and after the rats were sacrificed on the 45th postoperative day, no fat graft tissue was seen microscopically. This situation can be interpreted as the locally applied fat grafts being resorbed from the region over time.

CSF has structural, hydrodynamics, metabolic and immunological task within the nervous system [3]. Compared to plasma, the low potassium concentration of CSF plays a role in preventing fibrosis formation by suppressing the binding and spreading abilities of fibroblasts. In an *in-vitro* study, it is reported that CSF prevents the formation of EF [9]. In this study, development of connective tissue in the laminectomy region was low CFS applied group (GRIII) and EF was almost non-existent. Statistically, in the comparisons between the groups, there was significant difference between GRI and GRIII in terms of fibroblast density ($P = 0.002$), epidural fibrosis ($P = 0.002$), arachnoid fibrosis ($P = 0.001$) and inflammatory cell infiltration ($P = 0.003$).

HA plays a regulatory role in many biological processes such as embryonic development, tissue organization, wound healing, and angiogenesis [5,13]. Exogenous HA inhibits fibroblast proliferation and reduces fibrosis and scar formation in the early stages of tissue healing [12,18]. HA generally used in the treatment of osteoarthritis, ophthalmology, rheumatology, treatment of ulcerative lesions and prevention of adhesions after surgical operations [7]. In studies using HA after laminectomy, it is stated that motor functions are normal and no neurological deficit occurs [12,13]. In this study, there was no loss of motor function abnormality in rats of sodium hyaluronate applied in GRIV. In studies where HA was used after laminectomy, it was reported that granulation tissue and fibrosis formation in the operation area was less [2,13] and fibroblast cell score was quite low [12]. In the presented study, fibroblastic density, inflammatory cell infiltration, epidural and arachnoid fibrosis scores were lower in GRIV compared to the control group.

CONCLUSIONS

Although Tavlov's motor function findings did not provide sufficient results to show the superiority of any group, on the basis of histopathological findings, it was determined that CSF was the most effective biomaterial in reducing fibroblastic density and preventing EF in the laminectomy area.

MANUFACTURERS

[1]Ethicon J&J. Raritan, NJ, USA.

[2]Miray Medikal. Bursa, Turkey.

[3]Alfasan, Egevet Ltd. İzmir, Turkey.

[4]Bilim İlaç Sanayii ve Ticaret A.Ş. İstanbul, Turkey.

[5]GraphPad Software. Boston, MA, USA.

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***Ethical approval*.** This study was approved from Bursa Uludağ University Animal Experiments Local Ethics Committee (Decision no: 2021-12/01).

***Declaration of interest*.** The authors declare that they have no conflicts of interest. All authors have worked together and provided critical feedback and helped shape the research.

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