EXPERIMENTAL STUDY

Acta Orthop Traumatol Turc 2013;47(3):193-200
doi:10.3944/AOTT.2013.2792

The effect of oophorectomy on epidural fibrosis after laminectomy: an experimental study in rats

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Objective: The aim of this study was to examine the effect of oophorectomy in the formation of epidural fibrosis in a rat laminectomy model.

Methods: Thirty-six 12-month-old adult female Sprague-Dawley rats were used in this study. Rats were evenly divided into two groups; oophorectomized and sham-operated. Bilateral oophorectomy was performed on the 18 rats in the oophorectomized group. Three weeks after oophorectomy, rats in both groups underwent complete bilateral laminectomy at the L2 and L3 vertebral levels. Rats were divided into 3 equal groups and sacrificed in groups of 4 at the 4th, 8t, and 12th weeks postoperatively and the lumbar spine excised en bloc, fixed and decalcified. Sections were stained with hematoxylin and eosin and Masson's trichrome were used to evaluate epidural fibrosis, acute inflammation, chronic inflammation, and vascular proliferation.

Results: The mean histological sum grade of the epidural fibrosis was greater in the oophorectomized group ($p>0.05$).

Conclusion: Endogenous estrogen could have an effect on epidural fibrosis formation after lumbar laminectomy in rats.

Key words: Epidural fibrosis; histological comparison; laminectomy; estrogen; rat.

Lumbar epidural fibrosis is increasingly recognized as a cause of persistent back pain. The reported incidence of postoperative epidural fibrosis ranges from 10 to 75%.[1] Approximately 10 to 24% of all cases of failed back surgery syndrome are the result of epidural fibrosis.[2,3] Epidural fibrosis is a multi-factorial process; during surgery, spinal epidural hematoma may occur. Once the hematoma is absorbed, it is gradually replaced by granulation tissues that mature into dense fibrous tissue. This process, called epidural fibrosis, can develop after a laminectomy, in which it replaces the bone that has been removed and binds the dura mater to the overlying muscle.[4-7]

It is well known that women are more likely than men to sustain soft tissue injuries. Many studies reveal that injury rates in the musculoskeletal injury differ

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Submitted: December 10, 2011 **Accepted:** November 25, 2012

Available online at
www.aott.org.tr
doi:10.3944/AOTT.2013.2792
QR (Quick Response) Code:

according to the sexes.[8] *In vitro* studies reveal that estrogen has an inhibiting effect on collagen formation and wound healing.[9,10] The presence of estrogen can also lead to elevation of inflammatory response.[11,12]

The implication of gender or estrogen related differences is obvious, but previous studies have not clearly stated the importance of estrogen on the rate of epidural fibrosis.

The aim of this study was to examine the effect of endogen estrogen in the formation of epidural fibrosis and epidural scar formation in a rat laminectomy model.

Materials and methods

Approval was obtained from our local ethical committee and adult female Sprague-Dawley rats were provided by the Medical and Surgical Research Center of our University. Rats were acclimatized to caged laboratory conditions and fed with a standard diet and water *ad libitum*. Room temperature and humidity were maintained at 20 to 24°C and 50 to 60%, respectively. The light cycle was fixed at 12 hours.

The study included 36 rats (mean age: 12 months, mean weight: 300±49 grams). All rats were divided randomly into two groups: oophorectomized (estrogen deficient, n=18) and sham-operated (estrogen maintained, n=18). Rats underwent total laminectomy at the L2 and L3 vertebral levels (two levels per rat) three weeks after the oophorectomy. Although more limited laminotomies are currently more common, we performed total laminectomy as it is a simple surgical technique easy to standardize in rats. Rats were then randomly divided into 3 equal groups and sacrificed at 4, 8, and 12 weeks postoperatively.

On the first day of the study, the backs of the rats were shaved and aseptically prepared with povidone-iodine. All rats were anaesthetized with an intraperitoneal injection of 40 mg/kg ketamine (Ketalar®; Pfizer Ltd, Sandwich, Kent, UK) and 5 mg/kg xylazine (Rompun®; Bayer HealthCare AG, Leverkusen, Germany). Bilateral oophorectomies were performed for rats in the oophorectomy group. In the sham-operated group, the ovaries were exposed only. The fascia and skin were closed using absorbable 3-0 monocryl sutures (Ethicon Inc, CA, USA). An intraperitoneal injection of 10 mg/kg of enrofloxacin (Baytril-K, Bayer HealthCare AG, Leverkusen, Germany) was used for pre- and postoperative antibiotic prophylaxis. Analgesia was induced postoperatively by intraperitoneal injection of 0.02 mg/kg of fentanyl (Fentanyl; Janssen-Cilag Pty Ltd, North Ryde, Australia).

Laminectomy was performed 3 weeks following the oophorectomy. Estrogen has a half-life of between 3 and 8 hours and this time is sufficient for endogenous estrogen deficiency to occur.

Preoperative preparations were performed as described above. Rats were placed under general anesthesia and fixed on a small arched table. A midline incision of 4 cm was made along the spinous process of the lumbosacral area. Using a surgical microscope of x2.5 magnification (OPMI 9-FC; Carl Zeiss AG, Oberkochen, Germany), dissection of the subcutaneous tissue, fascia, and muscle was performed. Laminae of the lumbar vertebrae L4-L1 were successively approached and complete bilateral laminectomy was performed at the L2 and L3 vertebral levels (Fig. 1). The underlying dura mater and the nerve roots were exposed. The incision was closed with the usual surgical method after careful hemostasis. Antibiotic prophylaxis and analgesia were performed according to the previously described protocol.

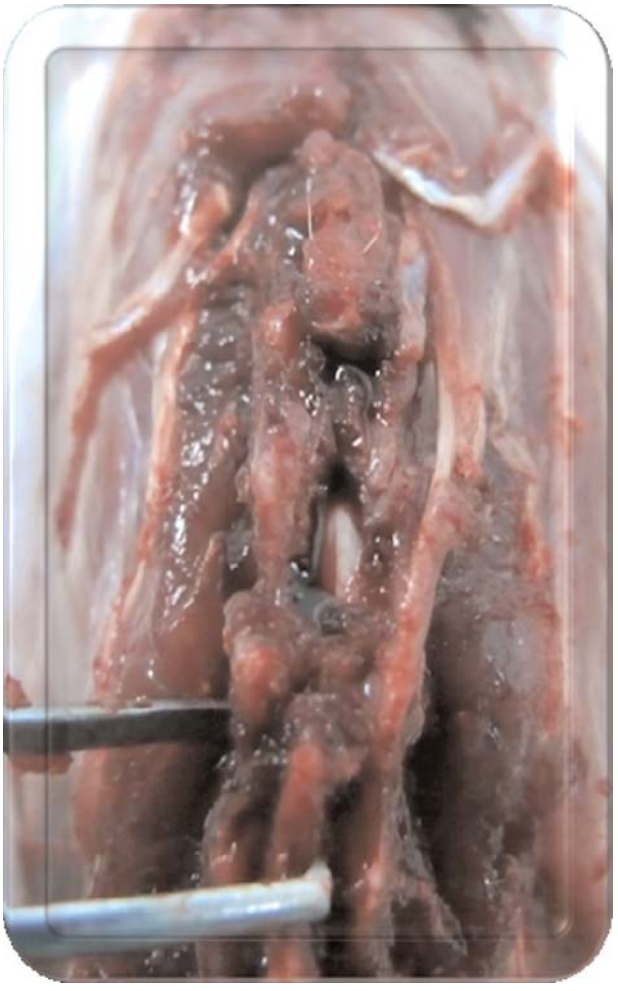

Fig. 1. Laminectomy at the L2 and L3 vertebral levels. [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

Rats were randomly divided into 3 equal groups of 12. The animals were sacrificed using an intraperitoneal injection of 100 mg/kg ketamine (Ketalar®) in groups of 4 at the 4th, 8th, and 12th weeks after laminectomy. Each rat was carefully dissected and the lumbar spine was excised en bloc (Fig. 2).

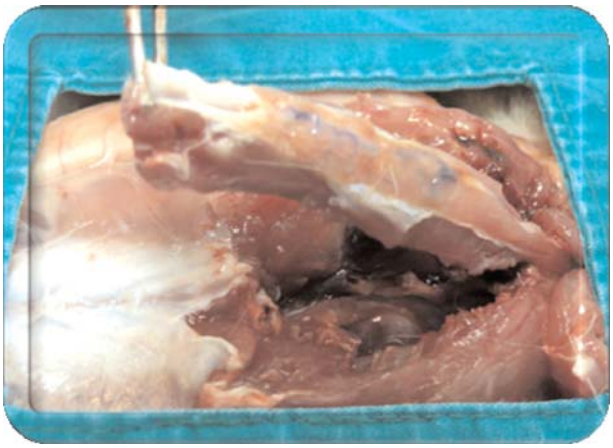

Fig. 2. En bloc dissection of the lumbar spine. [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

Tissue samples were fixed in a 10% neutral buffered formalin solution then dehydrated with alcohol. The fixed tissue was processed, embedded in paraffin, and sectioned at 3 µm. Tissue sections were stained with hematoxylin-eosin according to standard protocols for evaluations of acute and chronic inflammation and vascular proliferation. Histologic analysis was performed on a 5-point grading system according to the following scale: (0) indicates the laminectomy defect was free of the parameter; (1) indicates a parameter of less than 25% of the laminectomy defect; (2) indicates a parameter of 50% of the laminectomy defect; (3) indicates a parameter of 75% of the laminectomy defect; and (4) indicates a parameter covering the entirety of the laminectomy side.

Masson's trichrome staining was used to investigate epidural fibrosis. The extent of epidural fibrosis was graded according to the following classification; (0) when the dura mater was free of the scar tissue; (1) when only thin fibrous bands between the scar tissue and dura mater were observed; (2) when continuous adherence was observed in less than one-third of the laminectomy defect; (3) when scar tissue adherence was large but in less than two-thirds of the laminectomy defect, and/or extended to the nerve roots; and (4) when scar tissue adherence covered the entire laminectomy defect.[13]

For each staining technique, slides were examined by the same pathologist under a light microscope (Olympus Bx50) and read blindly.

Data were evaluated using SPSS statistical software package 16.0 for windows (SPSS Inc., Chicago, IL, USA). Descriptive analyses were calculated. The Mann-Whitney U test was applied to compare 2 groups and the Kruskal-Wallis test to compare 3 or more groups. Dunn's post test was applied for multiple comparisons. The results were accepted as being statistically significant at $p<0.05$.

Results

The general condition of all rats was good, with no cases of paralysis, dural tear or infection noted after laminectomy. The distributions of the histological grades of the groups, without statistical analysis, are shown in Table 1.

The mean histological grade and standard deviation and median value of the groups are shown in Table 2. Sham-operated groups and oophorectomized groups were analyzed separately. Histological grades were analyzed according to study weeks. There were statistically significant differences between the oophorectomized and sham groups for all parameters ($p<0.05$; Table 2).

The most acute inflammation response was seen at 4 weeks in both sham-operated and oophorectomized groups. Inflammatory response decreased in the following week. More acute inflammatory responses were found in sham-operated groups at 4 and 8 weeks.

Similar results were found in chronic inflammatory response. The most severe chronic inflammatory response was seen at 4 weeks for both groups and was followed by a decrease in inflammatory response. The sham-operated group showed more chronic inflammatory response both at 4 and 8 weeks.

The oophorectomized group showed more vascularity response than the sham-operated groups at the 4th week and results were the same in both groups in subsequent weeks. Thus, the follow-up time affected the vascularity response.

Although greater fibroblast density was seen in the oophorectomized groups at both 4 and 8 weeks, fibroblast density was higher in the sham-operated groups at Week 12. Fibroblast density level was higher at 8 weeks than at 4 and was lower at 12 weeks than 8 in both groups (Figs. 3-5).

Statistical analysis showed a correlation within each category between the oophorectomized and sham-operated groups for all weeks (Table 3). Only acute inflammation was significant at 12 weeks in the

Table 1. The distributions of the histological grades of the groups.

Oophorectomized group	**Four weeks**					**Eight weeks**					**Twelve weeks**				
	(n=6)					**(n=6)**					**(n=6)**				
Histological grade	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Acute inflammation			6			1	5				2	4			
Chronic inflammation		1	5			1	5				2	4			
Vascularity	2	1	3			5	1					6			
Fibroblast density	1	2	2	1				1	4	1			5	1	
Sham-operated group	**Four weeks**					**Eight weeks**					**Twelve weeks**				
	(n=6)					**(n=6)**					**(n=6)**				
Histological grade	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Acute inflammation			4	2			4	2			6				
Chronic inflammation			5	1		1	3	2			3	3			
Vascularity	4	1	1			5	1					6			
Fibroblast density		5	1					3	2	1		1	3		2

oophorectomized group (p=0.01). Oophorectomized groups have more acute inflammation than sham-operated groups.

Mean histological sum grade, standard deviation and median values are shown in Table 4. The mean histological sum grade of the epidural fibrosis of the oophorectomized group was greater than that of the sham-operated group. No significant differences between the groups were found.

Discussion

Failed back surgery syndrome is a clinical condition in which patients experience persistent or recurrent lower back and leg pain following one or more surgical procedures for lumbosacral disease. Lumbar epidural fibrosis is increasingly recognized as a condition responsible for lower back pain although its role in failed back surgery continues to be debated, mainly due to the multiple factors involved in the pathogenesis of this condition.[5,6]

Postoperative epidural fibrosis is a manifestation of the normal process of wound repair following lumbar spine surgery. The exact pathogenesis of epidural fibrosis has not been established although several different theories exist.[14,15] Key and Ford[16] were the first to describe scar tissue entrapment of the nerve root after the lumbar laminectomy. They theorized that the annulus fibrosis was the source of the anteriorly located post-laminectomy scar tissue. In another experimental study, the authors showed that the endogen intervertebral disc material was embedded into the epidural space and that the epidural fat tissue was pen-

Table 2. The mean histological grade and standard deviation, median value of the groups.

	Sham-operated group				**Oophorectomized group**			
	Four weeks	**Eight weeks**	**Twelve weeks**		**Four weeks**	**Eight weeks**	**Twelve weeks**	
Histological grade	**(n=6)** Mean±SD (median)	**(n=6)** Mean±SD (median)	**(n=6)** Mean±SD (median)	p value*	**(n=6)** Mean±SD (median)	**(n=6)** Mean±SD (median)	**(n=6)** Mean±SD (median)	p value*
Acute inflammation	2.3±0.5 (2.0)	1.3±0.5 (1.0)	0.0±0.0 (0.0)	**p=0.001**	2.0±0.0 (2.0)	0.8±0.4 (1.0)	0.7±0.5 (1.0)	**p=0.001**
Chronic inflammation	2.1±0.4 (2.0)	1.2±0.8 (1.0)	0.5±0.5 (0.5)	**p=0.004**	1.8±0.4 (2.0)	0.8±0.4 (1.0)	0.7±0.5 (1.0)	**p=0.004**
Vascularity	0.5±0.8 (0.0)	0.2±0.4 (0.0)	1.0±0.0 (1.0)	**p=0.03**	1.2±1.0 (1.5)	0.2±0.4 (0.0)	1.0±0.0 (1.0)	**p=0.04**
Fibroblast density	1.2±0.4 (1.0)	2.7±0.8 (2.5)	2.5 ±1.2 (2.0)	**p=0.01**	1.5±1.1 (1.5)	3.0±0.6 (3.0)	2.2±0.4 (2.0)	**p=0.02**

*Kruskal-Wallis test. Significant p values are written in bold.

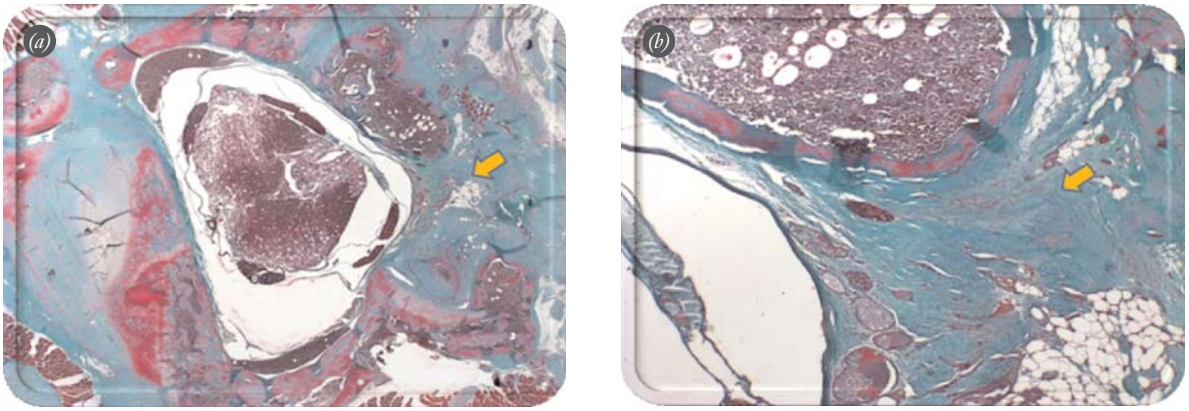

Fig. 3. **(a,b)** Fibroblast density in Stage 4 sham-operated group rat at 12 weeks (Masson's trichrome ×20 and ×100). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

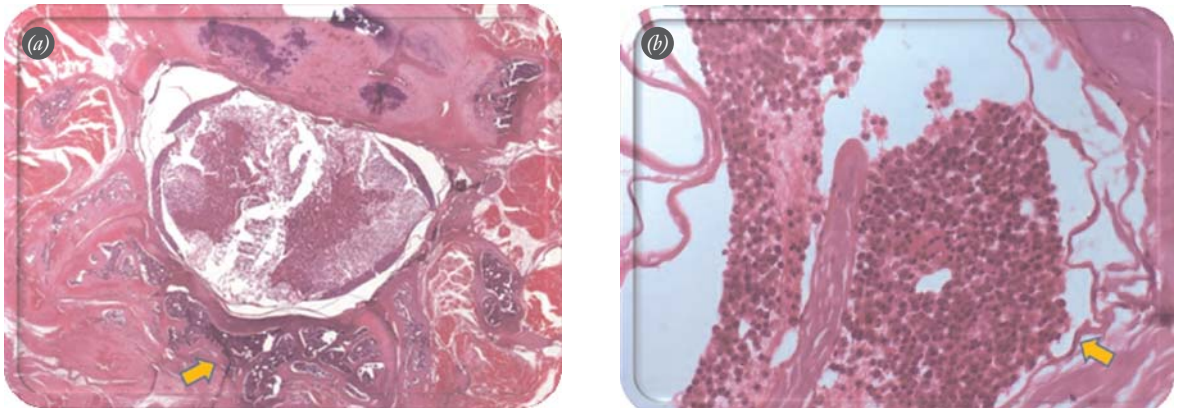

Fig. 4. **(a, b)** Acute inflammation in Stage 3 sham-operated group rat at 4 weeks (hematoxylin-eosin ×20 and ×400). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

etrated by newly formed vessels which caused an inflammatory reaction.[17] LaRocca and McNabb described a posteriorly located epidural fibrosis which may occur following surgical laminectomy.[18]

Epidural hematoma occurs during surgical dissection. The hematoma is absorbed and gradually replaced by granulation tissue within the deep surface of the paravertebral muscles originating from the

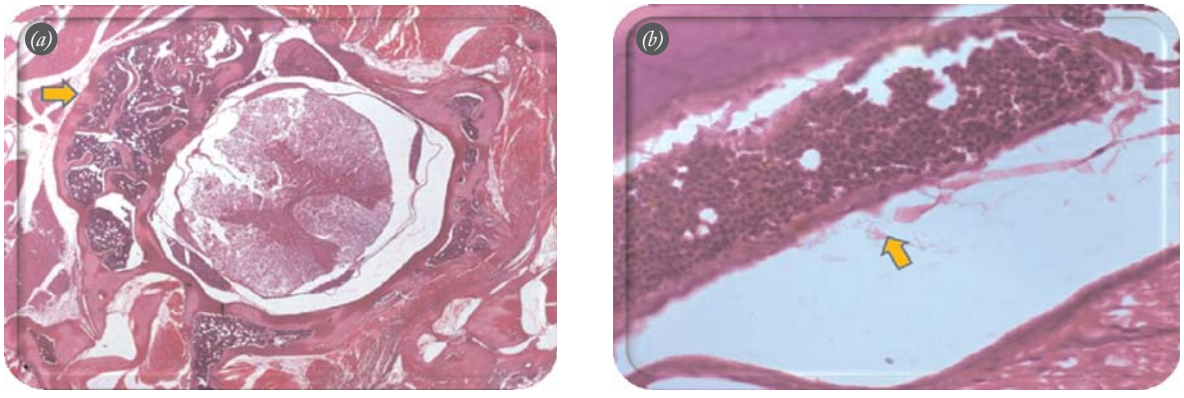

Fig. 5. **(a, b)** Chronic inflammation in Stage 2 oophorectomized group rat at 4 weeks (hematoxylin-eosin ×20 and ×400). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

Table 3. Statistical analysis of the histological evaluations.

	Intergroup evaluation		
	Four weeks	**Eight weeks**	**Twelve weeks**
p value*			
Acute inflammation	p=0.13	p=0.09	**p=0.01**
Chronic inflammation	p=0.17	p=0.33	p=0.57
Vascularity	p=0.22	p=1.00	p=1.00
Fibroblast density	p=0.47	p=0.38	p=0.77

*Mann-Whitney U test. Significant p values are written in bold.

fibrous layers of the periosteum. The granulation tissue matures into a dense fibrous tissue. The formation of fibrous tissue takes place from 6 weeks to 6 months after laminectomy.[7,18] The amount of fibrous tissue decreases during the first year after surgery but some fibrous tissue persists in most cases.[19]

Possible mechanisms of epidural fibrosis causing recurrent pain include nerve root irritation, nerve root entrapment, anoxia of perineural or intraneural fibrosis, direct neural compression, and restricted nerve mobility.[5,7,15] Diagnosis of epidural fibrosis is performed by contrast-enhanced magnetic resonance imaging.[20] There is currently no effective medical or surgical treatment for epidural fibrosis. Reoperation with the intention of excising this fibrous tissue often produces a poor surgical result and further scarring. The goal of treatment is to minimize epidural fibrosis.

For many years, the prevention of post-laminectomy fibrosis has been attempted using different mechanical barriers, chemicals and prevention of local hematomas. Most materials previously reported to be successful in decreasing scar formation remain as permanent foreign bodies that may increase the risk of infection.[18,21-24] Additionally, these materials are rigid, which can allow scar tissue to migrate around the margins of the material. Another potential pitfall in the use of a rigid material is impingement upon the spinal canal if the material is poorly fitted to the bone defect, causing compression of neural structures.[22] Fat grafts causing a clinically significant neural compression or subcutaneous seroma formation have also been reported.[25]

Fibroblast, originating from the overlying soft tissue and following expansion of postoperative hematoma in the vertebral canal, causes epidural fibrosis.[13,14,18,26] Examination of biopsy specimens revealed marked collagen proliferation in presence of epidural fibrosis. Small areas of focal inflammatory cell infiltration and dilated veins were observed. Fibrous tissue contained high collagen fiber content per unit of the tissue volume. In their study, Nussbaum et al. reported that the severity of epidural fibrosis and the amount of collagen fiber is parallel.[23] *In vitro* studies have shown that estradiol has an inhibiting effect upon collagen formation.[9-11] Magnusson et al. revealed that women have a lower rate of new connective tissue formation.[27] Collectively, these data show that the absence of estrogen may cause greater susceptibility to the formation of fibrous tissue. Fibrous tissue is present in humans after the 4th postoperative week. Because the period of fibrosis formation is brief in rats,[28] our rats were sacrificed at 4, 8 and 12 weeks. In this study, more epidural fibrosis was observed in the oophorectomized group

Tablo 4. Histolojik toplam değer ortalama, standart sapma ve ortancaları.

	Sham-operated group	**Oophorectomized group**	
	(n=18) Mean±SD (median)	**(n=18) Mean±SD (median)**	**p value***
Acute inflammation	1.2±1.1 (1.0)	1.2±0.7 (1.0)	p=0.92
Chronic inflammation	1.3±0.9 (1.0)	1.1±0.7 (1.0)	p=0.53
Vascularity	0.6±0.6 (0.5)	0.7±0.7 (1.0)	p=0.37
Fibroblast density	2.1±1.1 (2.0)	2.2±0.9 (2.0)	p=0.50

*Mann-Whitney U test.

than in the sham-operated group 4 and 8 weeks after laminectomy.

Experiments indicate that withdrawal of endogen estrogen may negatively impact many tissues, which can lead to increased risk of diseases.[8] Inflammatory responses are attenuated in many females when levels of sex hormones are higher, such as in pregnancy.[12] Experimental studies have revealed that the presence of endogen estrogen in rats causes an increased inflammatory response during the tendon healing process.[11] In addition, previous studies demonstrated that supraphysiological levels of estrogen treatment decreased cell proliferation.[29] In this study, both acute and chronic inflammatory responses were greater in the presence of endogenous estrogen at 4 and 8 weeks. No acute inflammatory results were obtained at 12 weeks in the sham-operated groups. Although these results show statistical differences between the groups, they were not considered significant. Vascular proliferation was higher in the oophorectomized groups at 4 weeks, but there were no differences in subsequent weeks. In both groups, the acute inflammatory response decreased in succeeding study weeks with a significant difference at Week 12. This could be due to the greater inflammatory response in the sham-operated groups than in the oophorectomized group at 4 and 8 weeks or due to greater acute inflammatory response in the early period presence of the endogenous estrogen.

Although the rat is an easier model for applying laminectomy and develops epidural fibrosis at a faster rate than larger animals, it has been used infrequently as an experimental model for the study of post laminectomy membranes. Nussbaum et al.[23] examined dogs after laminectomy from 2 weeks to 6 months. They revealed that scar tissue formation was consistent over time following the laminectomy. In our study, there was less epidural fibrosis and inflammatory response in both groups at Week 12 than in previous study weeks. Epidural fibrosis was reduced in the last study weeks. Time to the resolution of the fibrous tissue also allows for enough time for fibrous tissue maturation in rats.

Psychosocial and cultural factors, personal habits such as alcohol and tobacco use as well as and the underlying cause for surgery may play a much larger role in the development of failed back surgery. Our data suggests that deficiency of estrogen may lead to more fibrosis.

A limitation of this study was that only one dependent variable was assessed and biomechanical or quantitative analyses were not evaluated. Therefore, we consider post-menopause state, during which spinal surgery is frequently performed, to be a risk factor increasing the formation of epidural fibrosis.

In conclusion, estrogen levels could be important in the formation of epidural fibrosis. Therefore, the solution may be estrogen replacement therapy in postmenopausal woman.

Conflicts of Interest: No conflicts declared.

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