Eur Spine J (2006) 15: 959–964
DOI 10.1007/s00586-005-0959-6

ORIGINAL ARTICLE

Murat Bezer
Kemal Gokkus
Baris Kocaoglu
Osman Guven

The influence of vertebral instability on peridural circulation and concomitant peridural fibrosis formation

Received: 30 November 2004
Revised: 23 February 2005
Accepted: 21 April 2005
Published online: 29 December 2005

M. Bezer · K. Gokkus
B. Kocaoglu (✉) · O. Guven
Department of Orthopaedic Surgery,
Marmara University Hospital,
Sirmaperde Sok. Altunizade
Konutlari no/69 f blok/2 altunizade,
34662 Istanbul, Turkey
E-mail: bariskocaoglu2000@yahoo.com
Tel.: +90-533-7615690
Fax: +90-216-3254582

Abstract An animal model of vertebral instability was used to analyze the effect of chronic lumbar instability on the peridural vasculature and fibrosis formation. Fifty mature male domestic rabbits were divided into five equal groups. The vertebral instability was performed by excision of supra and interspinous ligaments between L2-L3 and L3-L4, excision of transverse and spinous processes and making bilateral laminectomies and facetectomies in groups I, II, III and IV. In group V only para vertebral muscle dissection was performed without vertebral instability. The simulation of the long term effects of overuse model on unstable spines (chronic instability) were performed with the use of Electrical Neuromuscular Stimulator to simulate cyclic flexion–extension movement in groups I, II. The rabbits in group I and III were sacrified for the histological evaluation at postoperative fifth day. The rabbits in groups I II, IV and V were sacrified at postoperative 21st day. There was no peridural venous endothelial injury or stasis but there was an increased amount of polymorph nuclear leukocytes in both group I (unstable-overuse) and group III (unstable-no overuse) after sacrification at postoperative fifth day. Peridural fibrosis and also vascular changes with different grades were seen in group II, VI and V after sacrification at postoperative 21th day. The grade of the venous changes and the mean amount of peridural scar formation were prominently higher in group II (unstable-overuse) than in group IV (unstable-no overuse) and V (control group). There was no difference between group IV and V for peridural scar formation and vascular changes. In conclusion, the instability of the lumbar spine with overuse could be a cause of peridural venous circulatory impairment, resulting in fibrosis formation.

Keywords Adhesion · Fibrosis · Instability · Peridural scar · Venous dilatation

Introduction

Postoperative peridural fibrosis is a common occurrence after lumbar spinal surgery and is one of surgeons' most challenging problems. In some cases, pain recurrence occurs after an initial pain free period of spinal surgery. This may be related to the formation of peridural fibrous tissue. Peridural fibrosis could cause traction on dura mater or nerve roots or on both, resulting in low back pain [5, 11, 19]. Although peridural fibrosis is defined as a normal post surgical biologic response, it is one of the major contributing factor in suboptimal patient outcome [3, 7, 9, 19].

Numerous materials and methods have been investigated to prevent peridural fibrosis formation after

spinal surgery [3–5, 8, 9, 13, 15, 22]. However, concerns about the etiology have been subject to less attention. A variety of causes for the development of peridural fibrosis have been suggested including retained surgical swab debris, compression of epidural veins, surgical manipulation, bleeding and defective fibrinolysis [1, 2, 16, 19]. Although instability of the lumbar spine and concomitant venous obstruction have been implicated as a causes of peridural fibrosis, the relation in between has not been thoroughly investigated in the literature [17]. Peridural venous impairment due to vertebral instability and overuse may be responsible for the development of peridural fibrosis. This current study investigates the effect of lumbar instability on peridural venous structures and the effect of this impairment on peridural fibrosis formation in rabbits.

Materials and methods

Animals and groups

Fifty domestic male rabbits, aged 7 months, weighing an average of 2,800 g (min: 2,500, max: 3,000, SD: 149, 9) were used in the experiment. The rabbits were divided into five equal groups. One group of ten rabbits constituted a control group.

Animal experiment permission: permission was given to the use of laboratory animals by Research Ethic Commission for animal experiments. Animal care complied with the guidelines of the authors' institution and the National Instutes of Health and national law on the care and use of laboratory animals.

Operative procedure

The rabbits were anesthetized by a mixture of ketamine (35 mg/kg) and Xylazine hydrochloride (5 mg/kg) that were administered intraperitoneally. Cephasoline sodium with 100 mg/kg I.V was given to each rabbit for infection prophylaxis. The rabbit was fixed on a small arched table and the lumbar area was shaved with a standard animal clipper. The surgical field was disinfected with povidone–iodine solution and draped in a standard fashion. The magnification was not used during the operation.

A midline longitudinal incision was made along the spinous processes of the lumbar area. After dissection of the subcutaneous tissue and fascia, the muscles were dissected and retracted bilaterally with a self-retaining retractor. The paraspinous muscles were stripped away from the laminae and spinous processes. The L3 lamina was identified by counting up from the sacrum. Excision of supra and interspinous ligaments between L2-L3 and L3-L4, excision of transverse and spinous processes of L3 and bilateral laminectomies and facetectomies at L3 level were performed with a small rongeur. The underlying dura mater and the nerve roots were exposed in groups I, II, III and IV [14]. Only paravertebral muscle dissection was made without forming any spinal instability in group V (control group), (Table 1). Homeostasis was obtained with a bipolar electrocautery.

Table 1 Analysis of groups

	Group 1	Group 2	Group 3	Group 4	Group 5
Instability	+	+	+	+	–
Overuse by EMS	+	+	–	–	–
Sacrification	5th day	21st day	5th day	21st day	21st day

The incisions were closed with usual surgical methods using interrupted 3–0 Vicryl sutures for closing the fascia and subcutaneous layers, 3–0 Dexon sutures for subcuticular layer and staples for skin.

Overuse model

The simulation of the long term effects of overuse model on an unstable spine (chronic instability) was performed with the use of Electrical Neuromuscular Stimulator (EMS 8000). It was used to simulate cyclic flexion–extension movement in group I and II for 20 days and started the day after surgery [20]. While the rabbits were still anesthetized, the electrodes were implanted perioperatively into their lumbar paravertebral muscles. The rabbits returned to their cages, and cyclic extension–flexion movement was applied to their lumbar spines without any anesthesia. The total number of cyclic loads was approximately 6,000 cycles/day, the frequency of the stimulation was 10 cycles/min, and the average time of loading was 10 h/day.

Histological examination

The animals were killed on the fifth and 21st days after the surgery with a concentrated solution of pentobarbital (60 mg/kg). The lumbar spine with paravertebral muscles were excised en bloc and immersed in Bouin's solution for fixation and decalcification at room temperature. The specimens were than dehydrated and embedded in paraffin after decalcification was complete. Ten transversal sections of 10 μm were made through the L3 vertebra, every millimeter from the L2-L3 to the L3-L4 intervertebral disc. The sections were stained with Gomori's trichrome. All sections were examined by a light microscope (Olympus BX-50). All histological observations were made by the same pathologist who was blinded for the study groups.

Qualitative histologic analysis

It consisted in subjective evaluation of the extent of fibrous tissue and the venous changes, the relation of the scar tissue with the dura mater and nerve roots.

Venous change

Venous changes were evaluated qualitatively. The veins were counted by a light microscope per field and graded as follows:

Grade 0. No vein.
Grade 1. One vein with or without dilatation.
Grade 2. Two or more veins with significant dilatation.

Extent of adhesions

Extent of adhesions was graded qualitatively according to the following classification which was named as 'Gross analyzing scoring system' [6]:

Grade 0. The dura mater was free of the scar tissue.
Grade 1. Only thin fibrous bands between the scar tissue and dura mater were observed.
Grade 2. Continuous adherence was extending to the nerve roots or severe thickening at the dura was presented.

The grade of adhesion was determined for each slide, then for all slides of each group.

Quantitative histologic analysis

It was performed using a semiautomatic image analysis system by a personal computer (Intel Pentium III, 800 MHz, Matrox Meteor vision card). This system comprised a microscope (Olympus), a color camera fixed on a microscope, a computer with a Zeiss Vision KS400 version 3.0 analysis programs and a high definition color monitor. The system was tested before the experiment using micrometry procedure to determine the ratios between the screen and different microscopic magnifications. The thickness of dura mater was measured by this ocular micrometer [11].

Thickness of dura mater

The thickness of dura mater was calculated quantitatively. The thickest area of duramater was taken for the measurement and further evaluation.

Statistical analysis

Comparison of dural thickness between the groups was analyzed by ANOVA. Bartett's test was used to check the differences among the SDs. For non-parametric ANOVA, Kruskal-Wallis test was used. Comparison of venous dilatation, extent of adhesion and also association between them were analyzed by chi-square test. Association between dural thickness and venous dilatation was evaluated by unpaired t-test. A p value of less than 0.05 was considered significant for all statistical tests.

Results

Postoperative complications

The general condition of all rabbits was good. There was no case of paralysis or infection. Subcutaneous hematoma was found five days after operation in six rabbits. Two of the rabbits were in the group II; the other four were in the group V.

Histological observation

At the end of the sacrification at postoperative fifth day in group I (unstable-overuse) and III (unstable-no overuse), increased number of PNL was seen without any peridural venous endothelial injury. There were capillaries and granulation tissue, including fibroblasts and inflammatory cells which were extended over the dura mater and nerve roots. After sacrification at postoperative 21th day, peridural fibrosis and venous changes with different grades were seen in group II (unstable-overuse) and IV (unstable-no overuse). Fibrocytes replaced the fibroblasts, the inflammatory cells and some muscle fibers had a degenerative fibrous aspect.

Venous changes

The amount and grade of venous changes were more prominent in group II (unstable-overuse) than those in group IV (unstable-no overuse) and V (control group), ($P < 0.001$), (Fig. 2). There was no difference between group I and group III and also between group IV (unstable-no overuse) and V (control group) (Table 2).

Extent of adherence

Adhesions were observed on all slides of group II (Table 2). The amount and grade of peridural fibrosis formation and extent of adherence in group II were more than that in group IV and V (control group), qualitatively ($P < 0.0001$). There was no difference between group IV and V. Venous changes and peridural fibrosis scores were also in correlation statistically ($P < 0.05$) (Fig. 1).

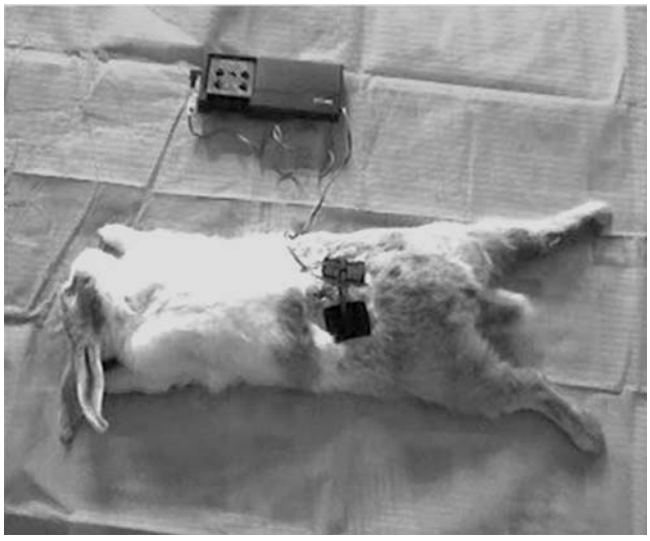

Fig. 1 The simulation of the long term effects of overuse model on an unstable spine (chronic instability) were performed with the use of Electrical Neuromuscular Stimulator (EMS 8000)

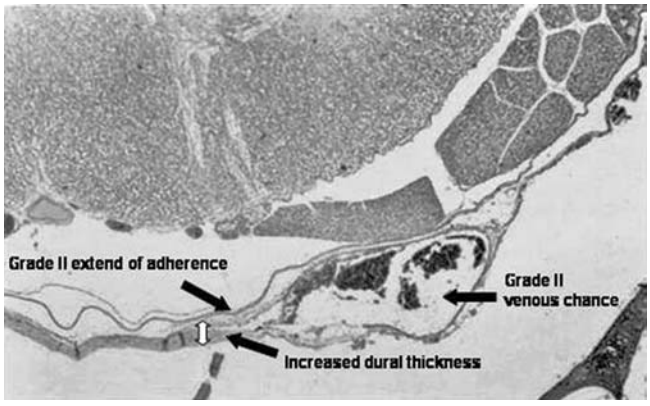

Fig. 2 Grade II peridural fibrosis formation, increased dural thickness and vascular dilatation were seen in a section which was taken from group II (Grocott-Gomori's methenamine-silver nitrate staining, light microscope, original magnification, ×40)

Thickness of dura mater

The thickness of dura mater in group II was more than that in group IV and V quantitatively ($P < 0.05$), (Table 3). There was no difference between group IV and V. There was also association between venous changes and dural thickness statistically ($P < 0.05$).

The amount and grade of peridural fibrosis formation, extent of adherence and thickness of dura mater in group II were more than those in group IV and V, both qualitatively and quantitatively. Higher grades of vascular changes were prominent in group II. Statistically there was also an association between venous changes, peridural fibrosis formation and dural thickness. Whenever, there was a venous change, fibrosis and dural thickening were more prominent (Table 4).

Discussion

We have described a model of vertebral instability in the rabbit to analyze the effect of chronic lumbar instability on the peridural vasculature and concomitant fibrosis formation [3, 7, 9, 11, 19]. Post operative peridural fibrosis is a common occurrence after lumbar spinal surgery. Fibrosis can cause compression and tethering of the nerve root that has been implicated as one of the factors that contribute to recurrent radicular or low back pain after a successful operation. In literature, fibrosis may be the underlying cause in failed back surgery syndrome. Re-operation with the intention of excising the fibrous tissue often produces a poor surgical result and further scarring [3, 7, 9, 19].

As it was mentioned by other studies, there is no correlation between scar formation and bad outcome in patients undergoing spinal surgery. Even if the scar is not the only point in failed back syndrome, it is the one of the major factors which were known [6, 7, 8, 18]. For this reason many materials and methods have been investigated to prevent post laminectomy scar formation. Dogs, rabbits and rats have been used in experimental models for mostly the treatment and prevention of this entity [3, 5–7, 9–11, 19, 21]. A large variety of materials, implanted onto dura mater in animal models but the results of these studies have demonstrated only moderate success in the inhibition of peridural fibrosis. According to our knowledge there is no experimental study which evaluates the underlying etiology and defines the relationship between peridural fibrosis, peridural venous changes and lumbar instability.

Table 2 The analysis of venous changes and extent of peridural fibrosis

	Group 2										Group 4										Group 5									
Animal no	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
Grade of venous change	1	2	2	2	1	2	2	2	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Extent of adhesion	1	2	2	2	1	2	2	2	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dural thickness (μm)	45	75	70	80	45	80	75	78	50	70	28	15	45	17	15	25	25	25	30	25	35	10	12	20	10	12	15	12	5	12

Table 3 Analysis of dural thickness

Groups	N	Minimum	Maximum	Mean	Std. error	Std. deviation	95% confidence nterval for mean	
							Lower bond	Upper bond
Group 2	10	45.0	80.0	66.8	4.5	14.4	56.5	77.1
Group 4	10	15.0	45.0	25.0	2.8	8.8	18.7	31.3
Group 5	10	5.0	35.0	14.3	2.6	8.2	8.4	20.2
Total	30	5.0	80.0	35.4	4.6	25.3	25.9	44.8

Table 4 Statistical Analysis

Comparison between groups	Statistical test	Group II and IV,V (*P* value)	Group IV and V (P value)
Verous change	χ^2	<0.001	$>0{,}050$
Extend of adhesion	χ^2	<0.001	>0.050
Dural thickness	Anova	<0.050	>0.050
Association		Statistical test	Group 2 (*P* value)
Verous dilatation–extend of adhension		χ^2	< 0.050
Verous dilatation–dural thickness		χ^2	<0.050
Extend of adhension–dural thickness		Unpaired t-test	<0.001

In the current study, we formed an instability model and used Electrical Neuromuscular Stimulator (EMS 8000) for the simulation of the long term effects of overuse on an unstable spine which meant that we performed chronic instability [14, 20]. There is no study to relate this overuse model with the daily activities of an unstable human spine. However, we assume that this model is sufficient for the formation of overuse as it was performed before in the literature [20].

In this study, Preceding peridural vascular changes and peridural fibrosis formation were more evident in groups where the instability and overuse exists. Venous proliferation and dilatation due to obstruction were more prominent in group II (unstable-overuse) than in group IV (unstable-no overuse) and V (control group). Also the grade of peridural fibrosis formation, extent of adherence and thickness of dura mater in group II (unstable-overuse) were more than those in group IV (unstable-no overuse) and group V (control group), both qualitatively and quantitatively. Statistically, there was an association between venous changes, peridural fibrosis formation and dural thickening. Whenever, there was a higher grade of venous change, fibrosis and dural thickening were more prominent. Venous proliferation and dilatation which were seen in higher grades demonstrated that there was a venous circulatory impairment. This indicates that, instability of the lumbar spine with overuse (chronic instability) could be a cause of peridural venous circulatory impairment.

Indeed, studies on peripheral nerves have shown that neural ischemia as a cause of circulatory impairment results in intraneural microvascular damage and localized demyelization. Microvascular damage results in an increased permeability and hence endoneural edema may develop [12]. The exudates are cleared slowly, thus prolonging contact with the tissue and predisposing the nerve to reactive fibrosis. It has been recognized that pain, parasthesis, sensory deficits and motor weakness are clinical manifestations of neural ischemia with or without mechanical deformation and that the neural response to such injury in time is neural fibrosis [12].

The etiology of peridural fibrosis is not clear and sometimes we can see post operative fibrosis and pain in patients after diskectomy who neither have instability nor overuse. For this reason, future studies in larger animal models will be necessary to further define the etiology and the association between chronic instability, venous impairment and peridural fibrosis formation.

As a conclusion, we found an association between venous changes, peridural fibrosis formation and chronic instability. We assumed that the instability of the lumbar spine with overuse could be one of the causes of peridural fibrosis formation. Moreover, treatment of chronic instability may inhibit peridural fibrosis formation by preventing peridural circulatory impairment. At the light of this, performing safe spinal instrumentation and fusion may improve outcome and stop new fibrosis formation especially for patients who undergo re-operation for recurrent low back pain after a successful lumbar spinal surgery.

References

1. Abitbol JJ, Lincoln TL, Lind BI et al (1994) Preventing postlaminectomy adhesion: a new experimental model. Spine 19:1809–1814
2. Barbera J, Gonzalez J, Esquerdo J et al (1978) Prophylaxis of the laminectomy membrane: an experimental study in dogs. J Neurosurg 49:419–424
3. Barr JS (1951) Low-back and sciatic pain. J Bone Joint Surg 33(A):633–649
4. Benoist M, Ficat C, Baraf P et al (1980) Post-operative lumbar epiduro-arachnoiditis: diagnosis and therapeutic aspects. Spine 5:432–436
5. DiFazio FA, Nichols JB, Pope MH et al (1995) The use of expanded polytetrafluoroethylene as an interpositional membrane after lumbar laminectomy. Spine 20:986–991
6. Einhaus S, Robertson J, Dohan C, Wujek J, Ahmad S (1997) Reduction of peridural fibrosis after lumbar laminectomy and diskectomy in dogs by areabsorbabl gel (ADCON-L). Spine 22(13):1440–1447
7. Fritsch EW, Heisel J, Rupp S (1996) The failed back surgery syndrome. Reasons, intraoperative findings, and long-term results: a report of 182 operative treatments. Spine 21:626–633
8. Gerszten P, Moossy J, Bahri S, Kalend A, Martinez J (1999) Inhibition of peridural fibrosis after laminectomy using low-dose external beam radiation in a rat model. Neurosurgery 44(3):597–603
9. Greenwood J Jr, McGuire TH, Kimbell F (1952) Study of causes of failure in herniated intervertebral disc operation: analysis of 67 reoperated cases. J Neurosurg 9:15–20
10. Guven O, Bezer M, Gokkus K, et al (2001) Transpedicular decancellation osteotomy in the treatment of peridural fibrosis. Arch Orthop Trauma Surg 121:517–520
11. He Y, Revel M, Loty B (1995) A quantitive model of post laminectomy scar formation, effects of a nonsteroidal anti-inflammatory drug. Spine 20(5):557–563
12. Hoyland JA, Freemont AJ, Jayson MIV (1989) Intervertebral foramen venous obstruction. A cause of periradicular fibrosis? Spine 14:558–568
13. Jacobs RR, McClain O, Neff J (1980) Control of postlaminectomy scar formation. An experimental and clinical study. Spine 5:223–229
14. Kaigle AM, Holm SH, Hansson TH (1995) Experimental instability in the lumbar spine. Spine 20(4):421–430
15. Keller JT, Dunsker SB, McWhorter JM et al (1978) The fate of autogenous grafts to the spinal dura. J Neurosurg 49:412–418
16. Langenskiold A, Kiviluoto O (1976) Prevention of epidural scar formation after operations on the lumbar spine by means of free fat transplants; a preliminary report. Clin Orthop 115:92–95
17. Quist J, Dhert W, Meij B, Visser W, Oner C et al (1998) The prevention of peridural adhesions: a comparative long term histomorphometric study using biodegradable barrier and a fat graft. J Bone Joint Surg 80(3):520–526
18. Richter HP, Kast E, Tomczak R, Besenfelder W, Gaus W (1995) Results of applying ADCON-L gel after lumbar discectomy: the German ADCON-L study. J Neurosurg Spine 95(2):179–189
19. Sakurai M, Miyasaka Y (1986) Neural fibrosis and the effect of neurolysis. J Bone Joint Surg Br 68(3):483–488
20. Wada E, Ebara S, Sahito S, Ono K (1992) Experimental spondilosis in rabbit spine, overuse could accelerate spondylosis? Spine 17:421–430
21. Warejcka DJ, Mei Y et al (1995) Inhibition of epidural scar formation after lumbar laminectomy in the rat. Spine 20:564–570; discussion 79–80
22. Yong-Hing K, Reilly J, Korompany V et al (1980) Prevention of nerve root adhesions after laminectomy. Spine 5:59–64