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Basic Science

Evaluation of topical application and systemic administration of rosuvastatin in preventing epidural fibrosis in rats

Bora Gürer, MD[a,*], Ramazan Kahveci, MD[b], Emre Cemal Gökçe, MD[c], Huseyin Ozevren, MD[b], Erhan Turkoglu, MD[d], Aysun Gökçe, MD[e]

[a]*Department of Neurosurgery, Ministry of Health, Fatih Sultan Mehmet Education and Research Hospital, 34752, Ataşehir, Istanbul, Turkey*
[b]*Department of Neurosurgery, Ministry of Health, Kirikkale Yüksek Ihtisas Hospital, Baglarbasi mh. Lokman Hekim cd., Kirikkale, Turkey*
[c]*Department of Neurosurgery, Faculty of Medicine, Turgut Ozal University, Ayvali mh., Gazze cd., No:7 Etlik, Kecioren, Ankara, Turkey*
[d]*Department of Neurosurgery, Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Irfan Bastug cd., Diskapi, Ankara, Turkey*
[e]*Department of Pathology, Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Irfan Bastug cd., Diskapi, Ankara, Turkey*

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Abstract

BACKGROUND CONTEXT: Epidural fibrosis is a major challenge in spine surgery, with some patients having recurrent symptoms secondary to excessive formation of scar tissue resulting in neurologic compression. One of the most important factors initiating the epidural fibrosis is assumed to be the transforming growth factor-1β (TGF-1β). Rosuvastatin (ROS) has shown to demonstrate preventive effects over fibrosis via inhibiting the TGF-1β.

PURPOSE: We hypothesized that ROS might have preventive effects over epidural fibrosis through the inhibition of TGF-1β pathways.

STUDY DESIGN: Experimental animal study.

METHODS: Forty-eight adult male Wistar Albino rats were equally and randomly divided into four groups (laminectomy, spongostan, topical ROS, and systemic ROS). Laminectomy was performed at the L3 level in all rats. Four weeks later, the extent of epidural fibrosis was assessed both macroscopically and histopathologically.

RESULTS: Our data revealed that topical application and systemic administration of ROS both were effective in reducing epidural fibrosis formation. Furthermore, the systemic administration of ROS yielded better results than topical application.

CONCLUSIONS: Both topical application and systemic administration of ROS show meaningful preventive effects over epidural fibrosis through multiple mechanisms. The results of our study provide the first experimental evidence of the preventive effects of ROS over epidural fibrosis.

Keywords: Epidural fibrosis; Laminectomy; Rat; Rosuvastatin; Systemic; Topical

Introduction

Laminectomy is widely accepted choice of treatment in lumbosacral disorders, such as lumbar disc herniation. Unsatisfactory results may occur after laminectomy. Failed-back surgery syndrome is characterized by long-term unsatisfactory relief or recurrence of symptoms in patients who had laminectomies performed [1,2]. About 8% to 48% of patients who underwent lumbar disc surgery suffered from failed-back surgery syndrome [3–5].

Epidural fibrosis is a major challenge in spine surgery, with some patients having recurrent symptoms secondary to excessive formation of scar tissue resulting in neurologic compression [6,7]. The formation of epidural fibrosis causes compression and stretching of the associated nerve roots, leading to persistent back and leg pain [8,9]. Furthermore, postoperative epidural fibrosis may result in increased complications in revision surgeries, such as inadvertent dural lacerations, nerve root injuries, and epidural bleeding [10,11]. There is

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Conflict of interest: None.

* Corresponding author. S.B. Fatih Sultan Mehmet Egitim ve Arastirma Hastanesi, Beyin Cerrahi Servisi, 34752 Ataşehir, Istanbul, Turkey. Tel.: (90) 506-316-4201; fax: (90) 216-578-3000.

E-mail address: boragurer@gmail.com (B. Gürer)

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no way of predicting the patients who will develop symptomatic epidural fibrosis; once the condition occurs, there is no effective treatment [1].

The underlying mechanisms causing epidural fibrosis are complex. Epidural fibrosis results in a reduction of the tissue cellularity and excessive deposition of extracellular matrix (ECM) components such as collagen, fibronectin, and dermatan sulfate [12,13]. One of the most important factors initiating the epidural fibrosis is assumed to be the transforming growth factor-1β (TGF-1β) formation [11,14,15].

Statins, structural analogs of 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase, are currently used for the treatment of hyperlipidemia and the prevention of cardiovascular disease [16]. Aside from their antilipidemic effects, statins have been suggested to have effects on preventing fibrosis [17–27].

Rosuvastatin (ROS), a relatively new HMG-CoA reductase inhibitor, has exhibited a more potent affinity to HMG-CoA reductase and has the longest half-life compared with other statins [28]. Transforming growth factor-1β plays an important role in the formation of epidural fibrosis and ROS has shown to demonstrate preventive effects over fibrosis via the inhibition of TGF-1β [21,23,24]. In the current literature, preventive effects of ROS have never been studied in the postlaminectomy epidural fibrosis model.

In the present study, we use a rat laminectomy model to examine the effects of both topical application and long-term systemic administration of ROS on the prevention of epidural fibrosis.

Materials and methods

Experimental groups

Animal care and all of the experiments adhered to the European Communities Council Directive of November 24, 1986 (86/609/EEC) related to the protection of animals for experimental use. All of the experimental procedures used in this investigation were reviewed and approved by the ethical committee of the Ministry of Health Ankara Education and Research Hospital. Forty-eight adult male Wistar albino rats weighing 250±60 g were used. The rats were randomly assigned to four groups with 12 rats per group.

The groups were as follows:

Group 1: Laminectomy (n=12); only a laminectomy was performed, as described in the next section.

Group 2: Spongostan (n=12); a spongostan (Ethicon; Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) was soaked with 2 cc/Kg saline solution and was left on the dura mater after laminectomy.

Group 3: Topical ROS (n=12); 20 mg/Kg ROS (AstraZeneca, Cheshire, UK) was applied with a spongostan soaked with 0.5 mL of saline solution and left on the dura mater after laminectomy.

Group 4: Systemic ROS (n=12); laminectomy was performed as described in the next section and 20 mg/Kg ROS was administered daily through an intragastric tube for 4 weeks starting the day after laminectomy.

Anesthesia and spinal cord injury procedure

All of the rats were kept in environmentally controlled conditions at 22°C to 25°C, with appropriate humidity and a 12-hour light cycle. The rats were granted free access to food and water.

The animals were anesthetized by an intraperitoneal injection of 10 mg/Kg xylazine (Rompun, Bayer, Turkey) and 50 mg/Kg ketamine (Ketalar, Parke Davis, Turkey) and allowed to breathe spontaneously. A rectal probe was inserted and the animals were positioned on a heating pad to maintain their body temperature at 37°C.

The rats were placed in the prone position. After their lower backs were shaved, the surgical sites were sterilized using povidone. All of the surgical procedures were performed by the same surgeon (BG). A longitudinal midline skin incision was performed over the L2–L4 levels. The lumbosacral fascia was incised, the paravertebral muscles were dissected subperiosteally, and the L2–L4 laminae were exposed. A total laminectomy was performed at the L3 level and then the ligamentum flavum and epidural fat tissue were cleared away from the surgical site. The dura mater was fully exposed and left intact. Hemostasis was achieved using cotton pads. After the application of the topical agents, the wounds were closed in anatomical layers using the same 4-0 prolen polypropylene sutures (Ethicon; Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA). There were no complications, no wound infections, or any adverse effects observed relevant to ROS. All of these procedures were performed carefully using a surgical microscope (Zeiss OPMI 1; Carl Zeiss Meditec, Oberkochen, Germany) so as not to injure the neural tissues.

Macroscopic assessment of epidural scar adhesion

Macroscopic assessment was performed after 4 weeks. Six rats were selected from each group and anesthetized by an intraperitoneal injection of 10 mg/Kg xylazine and 50 mg/Kg ketamine. The surgical sites were reopened carefully and epidural scar adhesion was evaluated by a professional neurosurgeon blinded to the treatment groups according to the Rydell classification [29]. This classification scheme includes the following grades: Grade 0: epidural scar tissue was not adherent to the dura mater, Grade 1: epidural scar tissue was adherent to the dura mater, but easily dissected, Grade 2: epidural scar tissue was adherent to the dura mater and dissected with difficulty without disrupting the dura mater, and Grade 3: epidural scar tissue was firmly adherent to the dura mater and could not be dissected.