Effects of Systemic and Local Interferon Beta-1a on Epidural Fibrosis

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Study Design: Level 1 randomized controlled study.

Purpose: To investigate the effects of systemic and local interferon-beta-1a (IFN-β-1a) on prevention of epidural fibrosis using histopathological parameters.

Overview of Literature: Epidural fibrosis involves fibroblastic invasion of nerve roots into the epidural space. Formation of dense fibrous tissue causes lumbar and radicular pain. Many surgical techniques and several materials have been proposed in the literature, but no study has assessed the effect of IFN-β-1a on prevention of epidural fibrosis.

Methods: Forty-eight adult female Sprague-Dawley rats were divided into six groups of eight: sham group, control group, systemic 44 μg IFN-β-1a group and 22 μg IFN-β-1a group (after laminectomy and discectomy, 0.28 mL and 0.14 mL IFN-β-1a applied subcutaneously three times for a week, respectively), local 44 μg IFN-β-1a group (laminectomy and discectomy, followed by 0.28 mL IFN-β-1a on the surgical area), and local 22 μg IFN-β-1a group (laminectomy and discectomy, followed by 0.14 mL IFN-β-1a on the surgical area). All rats were sacrificed after 4 weeks and groups were evaluated histopathologically.

Results: Compared with sham and control groups, significantly less epidural fibrosis, dural adhesion, and fibroblast cell density were observed in the local and systemic 44 μg IFN-β-1a groups. No other differences were evident between the local and systemic groups.

Conclusions: IFN-β-1a is effective in preventing epidural fibrosis with systemic and local application.

Keywords: Fibrosis; Interferon beta-1a; Laminectomy

Introduction

Failed-back syndrome develops in 20% of the surgically treated lumbar disc herniation patients [1]. Epidural fibrosis is one of the main factors in failed-back syndrome [1]. Many surgical techniques and several materials have been proposed in various experimental research models to prevent epidural fibrosis. These materials free or pedicle fat graft [2], dermis [3], ligamantum flavum [4], dura mater [5], amniotic membrane [6], gelatin foam sponge [7], microfibrillar collagen [7], hemostatic agents [8,9], carboxymethylcellulose [10-12], polyethylene oxide [10,12], sodium hyaluronan [9,13], topical high-molecular-weight hyaluronan [9,13-15], methylprednisolone, triamcinolone, prednisolone, dexamethasone [16-19], anti-inflammatory agents [7,16], CO_2 laser [20], and low-dose external beam

radiation [21].

Interferon-beta-1a (IFN-β-1a) is an approved treatment for multiple sclerosis (MS). It improves the disease course by reducing the relapse rate as well as the persistent neurological deficits. The immunomodulatory effects of IFN-β-1a are well characterized in MS and experimental autoimmune encephalomyelitis (EAE) [22]. IFN-β-1a reduces the proliferation and cytokine secretion of autoimmune T-cells and decreases blood–brain barrier permeability [22]. This diminishes inflammatory infiltration within the central nervous system (CNS) [22].

Although IFN-β-1a has been commonly used in MS, there has been no study on the use of IFN-β-1a in spinal surgery. The aim of our study was to elucidate whether IFN-β-1a can prevent postoperative adhesions and epidural fibrosis formation.

Materials and Methods

1. Surgical procedure

Forty-eight, 12-week-old, 250–300 g body weight, white Sprague-Dawley rats were used. The care and use of the rats was approved by the Ethical Committee of Animal Resources (September 25th, 2012; 2012-11/04).

For prophylaxis, a single dose of 20 mg/kg cephasoline sodium (Cefozin, Bilim İlaç, Istanbul-Turkey) was injected intraperitoneally 30 minutes prior to the operation. Intramuscular anesthesia was induced with 70 mg/kg ketamine hydrochloride (Ketalar, Parke-Davis, Eczacıbaşı, Istanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Rompun, Bayer, Istanbul, Turkey). The rats were fixed in the prone position and the surgical field was prepared by scrubbing with 4% chlorhexidine soap (Klorheksol Scrub, Drogsan Pahrmaceuticals, Ankara, Turkey) for 8 minutes and disinfecting with povidone iodine solution (Isosol, Merkez Lab., Istanbul, Turkey). The operation area was covered with sterile blankets and draped. A midline skin incision was made to expose the spinose processes from L4 to L7, and the L5–6 level was determined. Bilateral paraspinous muscles were dissected. A dorsal total laminectomy at the lumbar 5–6 level was performed using an Opmi I operative microscope (Carl Zeiss, Jena, Germany) with a Micromot 50/E drill (Proxxon, Föhren, Germany). After exposing the posterolateral aspect of the right L5–L6 disc a 22-gauge needle was inserted to create a disc injury. In the sham group, laminectomy and disc injury were performed

and no treatment was used. In the control group, laminectomy and disc injury were performed and 0.1 mL of saline was applied to the epidural space. In the systemic 44 μg IFN-β-1a group (S_{44}), nothing was applied to the epidural space, however 0.28 mL of IFN-β-1a was applied subcutaneously (sc) three times for a week. In the systemic 22 μg IFN-β-1a group (S_{22}), 0.14 ml of IFN-β-1a was applied sc three times for a week after the surgical procedure. In the local 44 μg IFN-β-1a group (L_{44}), 0.28 ml of IFN-β-1a was applied to the epidural space, covering the laminectomy defects. In the local 22 μg IFN-β-1a group (L_{22}), 0.14 mL of IFN-β-1a was applied to the surgical area. The wounds were closed in layers in a routine manner after hemostasis control. After the procedure all rats were housed individually at normal room temperature and were monitored closely using the Basso Beattie Bresnahan (BBB) scale to grade histological and locomotor outcomes [23,24].

2. Preparation of specimens

Four weeks after surgery, all rats were sacrificed by the intraperitoneal administration of a high dose (75–100 mg/kg) of tiopental sodium (Pentothal Sodium, Abbott, Roma, Italy). The spinal column was removed en bloc between the L1 to L7 level. The specimens were fixed in 10% buffered formaldehyde solution. After 2 days for decalcification, they were immersed in Decal solution comprising equal volumes of 10% formic acid and 8% HCl for 3 days. After decalcification, the specimens were cut down to the laminectomy site transverse to the spinal cord, with a thickness of 2 mm. The tissues were routinely processed. Serial sections 3 μm in thickness were obtained from paraffin blocks using a model RM 2145 microtome (Leica, Wetzlar, Germany). Sections were stained with haematoxylin-eosin and Masson-Trichrome. Any animal with an intraoperative dural tear, nerve root injury, or postoperative infection and/or hematoma was excluded.

3. Histopathological examination

All tissue samples were evaluated by two blinded experienced histopathologists. Upon light-microscopy examination, samples were scored for extent of fibrosis, dural adhesion, foreign-body reaction, granulation tissue, inflammation, medulla spinalis retraction, and density of fibroblasts. The dural adhesion parameters were evaluated according to previously established criteria [18]. Epidural

fibrosis extention, foreign-body reaction, granulation tissue, inflammation, and medulla spinalis retraction were evaluated according to the established criteria [25]. Fibroblast cell density was calculated in each field at ×400 magnification according to a previously detailed classification [26] (Fig. 1).

4. Statistical analysis

Frequency with related percentage values were used for expressing variables. Fisher-Freeman-Halton test was used to determine statistical significance of the epidural fibrosis extention, foreign-body reaction, granulation tissue, inflammation, medulla spinalis retraction, dural adhesion, and fibroblast cell density among groups. Statistical analysis was performed with use of the IBM SPSS ver. 20 software (IBM Co., Armonk, NY, USA). Statistical significance was defined as $\alpha=0.05$.

Results

The final evaluation was done using 48 adult female Sprague-Dawley rats. All the animals were active, ambulatory, and showed no BBB scale neurological deficit at the time of sacrifice. No clinical signs of infection or side effects were encountered in the skin, fascia, and muscle layers. All wounds healed uneventfully after surgery. However, alopecia did develop in some rats in the systemic IFN-β-1a groups. Significant concordance was achieved between the two observers for all parameters.

Statistically significant differences were evident between groups in terms of medulla spinalis retraction ($p=0.019$). Various grades of epidural fibrosis were observed in all rats. The sham and control groups had dense epidural fibrosis, while IFN-β-1a groups had less and varying degrees of epidural fibrosis. Animals treated with local and systemic IFN-β-1a showed discrete hyposignal space between the dura mater and the surrounding muscle tissue and nevre roots. In the S_{44}, S_{22}, and L_{44} groups, epidural fibrosis was statistically significantly less than sham ($p=0.001$, $p=0.001$, and $p=0.014$, respectively) and control groups ($p=0.001$, $p=0.001$, and $p=0.010$, respectively).

Inflammation and fibroblast cell density were significantly different among various groups (both $p<0.001$). Inflammation and fibroblast cell density were higher in the control and sham groups when compared with the S_{44}, S_{22}, L_{44}, and L_{22} groups (Table 1).

Distribution of foreign-body reaction was significantly different among the groups ($p=0.035$). Foreign-body reaction in the L_{44} and L_{22} groups was less than the control group ($p=0.026$ and $p=0.007$, respectively). Distribution of granulation tissue was also significantly different among groups ($p=0.018$), with less granulation tissue in rats of the L_{22} group compared with the control and S_{22} groups ($p=0.077$ and $p=0.007$, respectively).

Distribution of dural adhesion was significantly different among the groups ($p<0.001$), and was being significantly less in the S_{44}, S_{22}, L_{44} groups compared with the
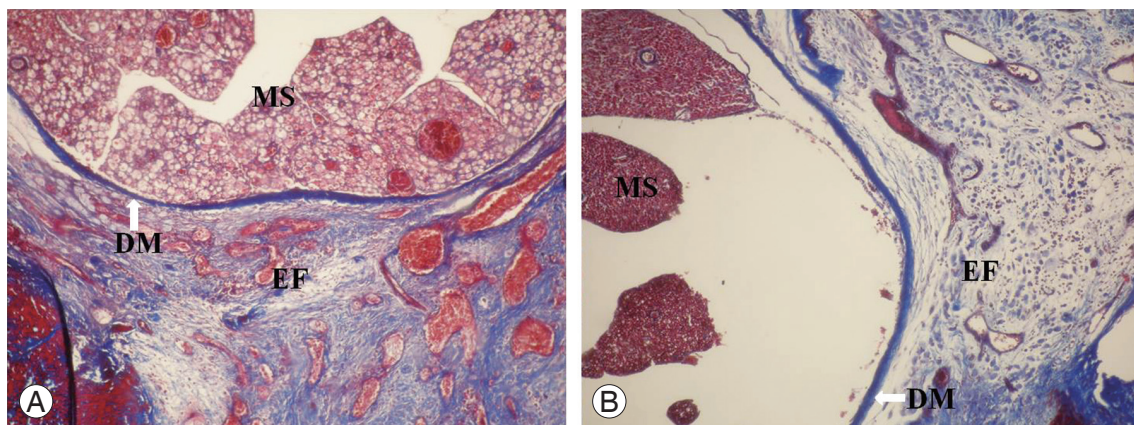

Fig. 1. Epidural fibrosis and dural adhesion in the groups of rats. **(A)** Grade 3 epidural fibrosis and dural adhesion is shown in the control group stained with Masson-Trichrome (MT)×100. Dense epidural fibrosis, dural adhesion, and medulla spinalis retraction are seen in the laminectomized area. **(B)** Grade 1 epidural fibrosis and dural adhesion is shown in the S_{44} group stained with MT×100. Note that less epidural fibrosis, fibroblast cell density, and only thin fibrous bands between dura mater and scar tissue are observed in the laminectomized area. DM, dura mater (white arrow); EF, epidural fibrosis; MS, medulla spinalis.

Table 1. Results of histopathologic evaluation

Variable	S$_{44}$ (n=8)	S$_{22}$ (n=8)	L$_{44}$ (n=8)	L$_{22}$ (n=8)	Sham (n=8)	Saline (n=8)
Multiple sclerosis retraction						
Absent	7 (87.5)	8 (100.0)	8 (100.0)	8 (100.0)	5 (62.5)	4 (50.0)
Mild	1 (12.5)	0	0	0	3 (37.5)	4 (50.0)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Epidural fibrosis						
Absent	0	1 (12.5)	0	0	0	0
Mild	8 (100.0)	7 (87.5)	7 (87.5)	5 (62.5)	1 (12.5)	1 (12.5)
Moderate	0	0	1 (12.5)	3 (37.5)	5 (62.5)	7 (87.5)
Severe	0	0	0	0	2 (25.0)	0
Inflammation						
Exist	7 (87.5)	8 (100.0)	8 (100.0)	7 (87.5)	3 (37.5)	2 (25.0)
No	1 (12.5)	0	0	1 (12.5)	5 (62.5)	6 (75.0)
Foreign body reaction						
Absent	2 (25.0)	2 (25.0)	4 (50.0)	5 (62.5)	1 (12.5)	0
Mild	6 (75.0)	5 (62.5)	3 (37.5)	2 (25.0)	7 (87.5)	8 (100.0)
Moderate	0	1 (12.5)	1 (12.5)	1 (12.5)	0	0
Severe	0	0	0	0	0	0
Dural adhesion						
0	5 (62.5)	8 (100.0)	5 (62.5)	0	3 (37.5)	0
1	3 (37.5)	0	2 (25.0)	8 (100.0)	1 (12.5)	1 (12.5)
2	0	0	1 (12.5)	0	1 (12.5)	1 (12.5)
3	0	0	0	0	3 (37.5)	6 (75.0)
Granulation tissue						
Exist	1 (12.5)	2 (25.0)	1 (12.5)	4 (50.0)	8 (100.0)	2 (25.0)
No	7 (87.5)	6 (75.0)	7 (87.5)	4 (50.0)	0	6 (75.0)
Fibroblast cell density						
<100	7 (87.5)	8 (100.0)	8 (100.0)	7 (87.5)	0	1 (12.5)
100–150	1 (12.5)	0	0	1 (12.5)	5 (62.5)	4 (50.0)
>150	0	0	0	0	3 (37.5)	3 (37.5)

Dural adhesions was graded on the basis of the scheme devised by He et al. [18]: grade 0, the dura is free of scar tissue; grade 1, thin fibrous bands are observed between the scar tissue and dura; grade 2, continuous adherence is observed in less than two-thirds of the laminectomy defect; and grade 3, scar tissue adherence is large, affecting more than two-thirds of the laminectomy defect, or the adherence extends to the nerve roots. The fibroblast and inflammatory cell densities were graded as follows: grade 1, less than 100 fibroblasts/ inflammatory cells per 400× field; grade 2, 100 to 150 fibroblasts/inflammatory cells per 400× field; grade 3, more than 150 fibroblasts/inflammatory cells per 400× field.

L$_{22}$ group (p=0.026, p<0.001, and p=0.007, respectively) (Table 2).

Discussion

Epidural fibrosis is an inevitable consequence of spinal laminectomy and one of the causative factors in failed back syndrome after spinal surgery. Fibrosis tissue can cause adhesions among adjacent tissues; dense fibrotic tissue can lead to compression on adjacent anatomical structures, dural tethering, immobility, and distortion on the spinal nerve root, resulting in susceptibility of the spinal root. However, there is no consensus for the role of epidural fibrosis in lingering back pain or its efficacy on

Table 2. Intergroup comparisons of parameters followed by overall comparisons as p-values

Groups	MS retraction (p=0.019)	Epidural fibrosis (p<0.001)	Inflammation (p<0.001)	Foreign-body reaction (p=0.035)	Dural adhesion (p<0.001)	Granulation tissue (p=0.018)	Fibroblast cell density (p<0.001)
S_{44}–S_{22}	1.000	1.000	1.000	1.000	0.200	1.000	1.000
S_{44}–L_{44}	1.000	1.000	1.000	0.315	1.000	1.000	1.000
S_{44}–L22	1.000	1.000	1.000	0.132	**0.026**	0.282	1.000
S_{44}–Sham	**0.041**	**0.001**	0.119	1.000	0.160	**0.041**	**0.001**
S_{44}–control	0.119	**0.001**	**0.041**	0.467	**0.001**	**0.001**	**0.010**
S_{22}–L_{44}	NP	1.000	NP	0.782	0.200	1.000	NP
S_{22}–L_{22}	1.000	0.200	1.000	0.429	**<0.001**	0.608	1.000
S_{22}–Sham	**0.007**	**0.001**	**0.026**	0.569	**0.026**	0.132	**<0.001**
S_{22}–control	**0.026**	**0.001**	**0.007**	0.200	**<0.001**	**0.007**	**0.001**
L_{44}–L_{22}	1.000	0.569	1.000	1.000	**0.007**	0.282	1.000
L_{44}–Sham	**0.007**	**0.014**	**0.026**	0.119	0.393	**0.041**	**<0.001**
L_{44}–control	**0.026**	**0.010**	**0.007**	**0.026**	**0.002**	**0.001**	**0.001**
L_{22}–Sham	**0.041**	0.119	**0.026**	**0.041**	**0.001**	0.608	**0.001**
L_{22}–control	0.119	0.119	**0.007**	**0.007**	**0.001**	0.077	**0.010**
Sham–control	1.000	0.713	1.000	1.000	0.256	0.467	1.000

Values in boldface are statistically significant.
MS, multiple sclerosis; NP, not performed: analyses could not be performed due to insufficient sample size.

bad clinical outcomes, but it can cause difficulty for re-exposure of operative areas during second surgery that may lead to complications [27].

Multiple factors are involved in the pathogenesis of epidural fibrosis formation. These include individual variability, postoperative haematoma, laminectomy techniques, amount of bone removed, and species and race differences [28]. In our study, laminectomy and discectomy (annular fenestration) performed on male Sprague-Dawley rats 12-weeks-of-age and 250–300 g in body weight was done to provide relevance with other studies [29].

Animal and clinical studies have sought to prevent epidural fibrosis [2,4]. Although significant results have been reported in a number of studies, peridural fibrosis remains a substantial problem in spinal surgery [1]. Most of these studies are expensive, and the findings are unsuitable for human use.

Fibrogenic pathologies are a characteristic feature of a systemic disease. Generation of specific cytokine patterns by immune and structural cells, and interactions among these cells mediate many of the key events involved in fibrogenesis [1]. The imbalance between Type 1 Type 2 cytokine responses that cues an abnormal response to the injury is an important hypothesis of the pathogenesis of fibrogenesis [1].

The observed pathologies with regard to epidural fibrosis suggest the onset of inflammatory processes after the surgery. IFNs are proteins that are made in and released by host cells in response to the presence of pathogens that include viruses, bacteria, and parasites, and tumor cells. They allow for communication between cells to trigger the protective defenses of the immune system, activate immune cells including natural killer cells and macrophages, and increase recognition of infection or tumor cells by up-regulating antigen presentation to T-lymphocytes.

The immunomodulatory effects of IFN-β were studied in detail in MS and EAE [22]. IFN-β diminishes inflammatory infiltration within the CNS [22]. IFN-β-1a is a glycoprotein produced in mammalian cells using the natural human gene sequence. In an experimental model, the histopathological analysis of the spinal cord after IFN-β-1a immunization revealed a significantly lower MS lesion load in comparison with vehicle treated controls [22]. Topical application of low-dose IFN-gamma (γ) is an effective and safe method of preventing peridural fibrosis [1].

The T-cellular immunomodulatory effects of IFN-β are mediated by antagonizing the pro-inflammatory properties of IFN-γ secreted by CD4-positive T-helper cells [28], and inhibition of T-cell proliferation [30]. Despite the widespread use and well documented immuomodulator effects of IFN-β-1a no published study has investigated its efficacy on epidural fibrosis.

Compared to the sham and control groups, epidural fibrosis, dural adhesion formation, inflammation, and fibroblast cell density were statistically less in the S_{44} and L_{44} groups, demonstrating that the systemic or local use of IFN-β-1a may prevent epidural fibrosis formation after spinal surgery. There were no statistical differences between S_{44} and L_{44} groups, allowing us to conclude that we can use IFN-β-1 locally or systemically to prevent epidural fibrosis.

Fibroblast cell density was significantly less in all IFN-β-1a groups compared to sham and control groups, proving that IFN-β-1a is an effective medication to prevent migration of fibroblasts. Fibrosis tissue will have alooser conformation.

Conclusions

Local or systemic use of 44 μg IFN-β-1 is an effective and promising material in prevention of epidural fibrosis and reduction of fibrotic tissue density. However, the efficacy of this agent should also be supported with further experimental and clinical studies.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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