Neuromodulation in the Treatment of Postoperative Epidural Fibrosis: Comparison of the Extent of Epidural Fibrosis and the Effect of Stimulation

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Summary

The goal was to prove that when a cohort of patients is chosen precisely, dorsal column stimulation provides significant improvement to quality of life. We studied a cohort of 50 patients with the history of failed back surgery syndrome coupled with epidural fibrosis (EF). A percutaneous implantation technique was used in each of the 50 patients. The study group was composed of 20 women and 28 men aged 26-67 years (mean age 49). A prospective observational questionnaire-based study was used. According to the methods, Ross's classification was adjusted to four degrees of scar size for our study objective. Despite this adjustment, it was not possible to statistically evaluate our research, due to very similar results in Groups I, III and IV. Patients without epidural fibrosis were assigned to Group 0, and patients with EF of different ranges were assigned to Group 1. The mean change in visual analogue scale **Δ**VAS after our division into Group 0 was 4.82; for Group 1 it was 6.13. Evaluation of EF and **Δ**VAS correlation by paired *t*-test shows a statistically higher effect of spinal cord stimulation (SCS) in the epidural fibrosis group, compared to group 0 without postoperative epidural fibrosis ($p=0.008$). The extent of epidural fibrosis is an important factor for Failed back surgery syndrome (FBSS). FBSS is the basis for the existence of neuropathic pain after lumbar spinal surgery. There is clear evidence of a correlation between patients with epidural scar formation on MR scan and the effect of dorsal column stimulation.

Key words

Epidural fibrosis • Neuromodulation • VAS • FBSS

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Introduction

Epidural fibrosis (EF) is defined as a non-physiological scar formation, usually on the site of the neurosurgical access into the spinal canal, in the intimate vicinity to and around the origin of the radicular sheath. (LaRocca *et al.* 1974) From the very onset, EF behaves as a reparative inflammation causing, as a rule, symptoms of characteristic nature and clinical course (pain). (McCarron *et al.* 1987) According to the findings of the aforementioned studies, the presence of epidural fibrosis can potentially cause pain and be the cause of the origin of Failed back surgery syndrome (FBSS) (Bartynski *et al.* 2007, Bokov *et al.* Maroon *et al.* 1999, Robertson 1996, Ross *et al.* 1996).

Treatment of epidural fibrosis causing a FBSS by the neuromodulation technique is very expensive but

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effective. 75 % of patients with refractory FBSS who were treated by spinal cord stimulation (SCS) were satisfied with the treatment results after 8.3 years. (Abeloos *et al.* 2011) The finding of suitable parameters for the indication of treatment is therefore very important.

The study is based on evidence of the importance of epidural fibrosis in the development of chronic pain. Research is also focused on the comparison of the range of fibrosis and the effect of SCS. The goal is to find a suitable selection factor for the indication of neuromodulation.

Methods

We studied a cohort of dorsal column stimulation in 50 patients with a history of failed back surgery syndrome coupled with epidural fibrosis. All patients suffered from a single root pain. A percutaneous implantation technique was used in 50 patients. The one-electrode technique was used in all patients. Two patients experienced no effective pain relief during the examination period and were excluded from the study. About 90 % of the pain area of both patients was covered, but without achieving a reduction in pain intensity. The duration of the examination was a minimum of 5 days. The study group (all the remaining patients) was composed of 20 women and 28 men aged 26-67 years (mean age 49). Table 1 shows a summary of the inclusion and exclusion criteria.

Table 1. Summary of the inclusion and exclusion criteria of the study.

Inclusion criteria	Exclusion criteria
Failed back surgery syndrome diagnosis	Multiple root pain
Single root pain	No effective pain relief
Percutaneous implantation technique	Other neuromodulation techniques
One-electrode technique	
5-days of test SCS period	

A prospective observational questionnaire-based study was used. Informed consent for the inclusion of anonymous data in the National Neuromodulation Database was signed by the patients. The National Neuromodulation Database contains many questions, but we only used the visual analogue scale (VAS) (Williamson *et al.* 2005) for our simpler statistical processing. The results were processed relative to the clinical finding, the subjective intensity of complaints rated on VAS (the difference between input and output VAS is equal to **Δ**VAS), and the graphic finding (degrees of epidural fibrosis – Ross classification). Our patients were labelled only by initials in the National Neuromodulation Database and thus no closer identification was possible. Our monitoring of patients' clinical findings and pain intensity was conducted over a period longer than 3 years.

The MRI findings were researched by another physician without his knowledge of patients' clinical signs. At the end of our study, all data were pooled by an independent statistician. Ross's classification was adjusted for our study objective. (Ross *et al.* 1999, Ross *et al.* 1998) The fourth degree of Ross´s classification was combined with the fifth degree of Ross's classification to the fourth degree (the fourth degree was 50-100 % of a quadrant filled with scar). Four degrees of scar size were obtained, to make it preferable for our statistical processing (Fig. 1). A new MRI based on the epidural fibrosis classification system was used for scar localization (Sen *et al.* 2005). Patients were divided into different groups based on VAS and Ross's classification. Details of the process are presented in the results section.

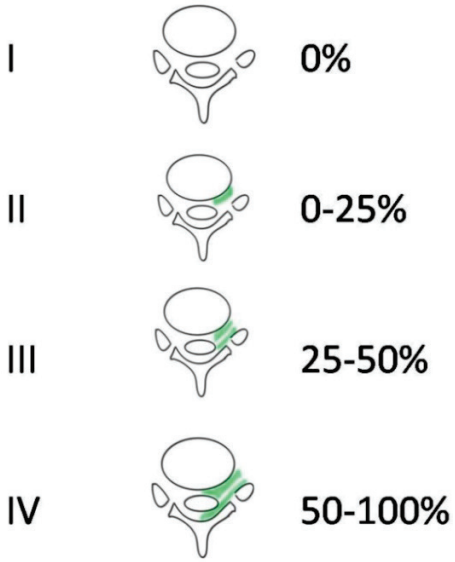

Fig. 1. Four degrees classification of scar size.

Our statistical processing was performed in STATISTICA 12 CZ software (StatSoft ČR, s.r.o.). Fisher's exact test was used to compare categorical data. The *t*-test was used to compare the averages of the continuous variables, and a one-way ANOVA was used if more than 2 groups were compared. A p-value of 0.05 was considered to be a level of statistical significance.

Results

According to the methods, Ross's classification was adjusted to four degrees of scar size for our study objective. Despite this adjustment, it was not possible to statistically evaluate our research, due to very similar results in Groups I, II, III and IV (Fig. 2a). The mean ΔVAS for Group I was 4.8, for Group II 6.2, for Group III 6.1, and for Group IV 6.0 (Table 2) So we had to merge groups II, III and IV into one group, and split the whole group into two subgroups. Patients without epidural fibrosis were assigned to Group 0, and patients with epidural fibrosis of different ranges were assigned to Group 1. The mean ΔVAS after our division into Group 0 was 4.82; for Group 1 it was 6.13 (Fig. 2b).

Evaluation of EF and ΔVAS correlation by paired t-test shows a statistically higher effect of SCS in the epidural fibrosis group, compared to group 0 without postoperative epidural fibrosis (p=0.008) (Table 3).

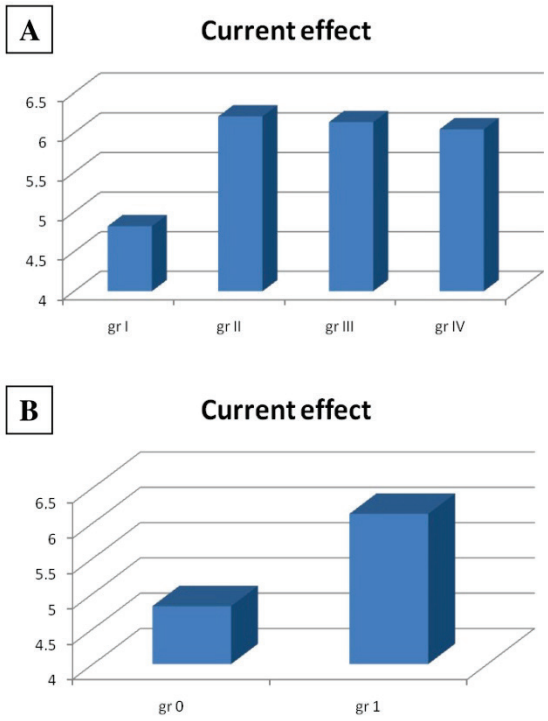

Fig. 2. (**A**) Evaluation of EF and ΔVAS – group I-IV. (**B**) Evaluation of EF and **Δ**VAS – group 0 and 1.

Table 2. Evaluation of EF and **Δ**VAS – group I-IV.

Group	N	ΔVAS mean [±SD]	ΔVAS -95.00 %	ΔVAS +95.00 %
Total	48	5.75 [±1.59]	5.29	6.21
EF group I	14	4.82 [±2.39]	3.44	6.20
EF group II	12	6.21 [±0.87]	5.66	6.76
EF group III	11	6.14 [±1.14]	5.37	6.90
EF group IV	11	6.05 [±0.79]	5.52	6.58

Table 3. Statistically higher effect of spinal stimulation (SCS) in patients with EF (Group 1) compared with the patients without EF (Group 0).

	Group 1 (n=14)	Group 0 (n=34)	p value
ΔVAS	6.132353	4.821429	0.007998

To eliminate the effect of multiple method failure (implantation of neuromodulation with low efficiency) in group 0, a two-dimensional delta VAS table was used. When we divided the patients as a percentage between VAS lower than 5 and higher than 5, we found that there was not a statistically significant proportion of patients with an inferior stimulation effect in the non-epidural fibrosis group, however approaching 5 % level of significance (p=0.067).

When we further narrowed the criteria and searched for a statistical incidence of patients with ΔVAS below 4 (stimulation was almost ineffective), then we had a higher number of patients with treatment failure in the epidural fibrosis group (p=0.002).

When we divide patients into patients with a lower incidence of failure and a higher incidence of failure (group with ΔVAS below 6 and group with ΔVAS above 6), there is no statistical significance found.

Discussion

FBSS is major cause of chronic neuropathic pain after peripheral nerve injury (IASP ICD-11). (Scholz *et al.* 2019) FBSS affects more than 40 % of patients who undergo spinal surgery for low back pain. (Lad *et al.*

2014) The relationship between EF and FBSS has been widely discussed in the algesiological literature. In particular, the role of EF in the development of FBSS is discussed, similarly to its prevention and its treatment. According to literature clinically significant EF is described in between 5 % and 33 % (Cinotti *et al.* 1998, Fritsch *et al.* 1996).

The authors have clearly shown the relationship between epidural fibrosis formation and radicular pain in clinical results – a statistically significant correlation between the presence of EF and patients' subjective rating (difference between input and output visual analogue scale) was found (Masopust *et al.* 2009). The presence of scar tissue around the nerve roots increases the incidence of radicular pain up to 3.2 times (Ross *et al.* 1996). Epidural scar tissue formation after microdiscectomy due to disc extrusion or sequestration is the cause of recurrent pain in 12.3 % of patients with FBSS (Bokov *et al.* 2011). There is a significant relationship between peridural scar formation and persistent low back pain after discectomy (Maroon *et al.* 1999). In many cases, but not always, MR imaging findings correlate with the clinical presentation. (Bartynski *et al.* 2007). The pathophysiology of scar formation was described by LaRocca and Macnab in 1974 (LaRocca *et al.* 1974).

Corticosteroids can be used as prophylaxis. It has been hypothesized that the use of steroids will decrease pain by the prevention of epidural fibrosis and by limiting the degree of scar formation. In 2009 Häckel *et al.* published a study that found a statistically significant correlation between the degree of fibrosis and pain, but also reported that the application of epidural steroids was not associated with a lower incidence of scar formation or failed back surgery syndrome (Häckel *et al.* 2009). Based on the analysis of 17 studies assessing the use of epidural steroids after lumbar discectomy, there is some evidence that steroids may not significantly increase the rate of complications. However, there is good evidence that steroids reduce short-term pain and narcotic requirements after surgery (Akinduro *et al.* 2015). Paradoxically, results of the VAS 12 months post-surgery did not reach statistical significance between the group after and without perioperative corticosteroid administration (Häckel *et al.* 2009). Gelatin sponge could reduce the formation of epidural scar adhesion after laminectomy; the composite materials of dexamethasone gelatin sponge can promote this effect (Tian *et al.* 2015). The other technique which is being researched is to block the formation of epidural fibrosis. The selected compositions of biosynthetic, bioelastic polymers were safe and effective in the limiting of postlaminectomy epidural fibrosis in rabbits (Alkalay *et al.* 2003). Another study showed that oxidized regenerated cellulose could be used for epidural fibrosis prevention (Temel *et al.* 2006). The effectiveness of a poloxamer 407-based new anti-adhesive material was proved in a laminectomy model in rats (Yu *et al.* 2012). The effectiveness of acetylcysteine was also proved in a laminectomy model in rats (Güvenç *et al.* 2018). Haemostasis is also an important factor preventing epidural fibrosis but, according to meta-analysis, it is not useful in a wound blood drain in posterior spinal surgery (Erdogan *et al.* 2016, Liu *et al.* 2016).

There are many procedures to reduce the extension of epidural fibrosis post-surgery and to decrease the intensity of pain. For example, caudal epidural injection resulted in an improvement of functional status in 55 % and pain reduction in 60-70 % of patients (Manchikanti *et al.* 2008). The epidural administration of hyaluronidase is an effective method of treating epidural fibrosis in 52 % of patients 6 months after treatment and in 21 % of patients 12 months after treatment (Masopust *et al.* 2003). One-day adhesiolysis is recommended with a success rate in patients of 76.7 % (Hossieni *et al.* 2017). Re-operations for epidural fibrosis had less satisfactory results (29.1 % excellent and 12.9 % good) (Kayaoglu *et al.* 2003). In general, the results of the aforementioned methods are worse than in anaesthesiologists' methods.

One of the most important methods for the treatment of FBSS is spinal cord stimulation. The effectiveness of spinal cord stimulation, the significant increase in leg pain relief, quality of life, and functional capacity were demonstrated by a prospective randomized controlled multicenter trial (Kumar *et al.* 2008). Treatment of epidural fibrosis causing failed back surgery syndrome (FBSS) by the neuromodulation technique is very expensive but effective. 75 % of patients with refractory FBSS, who were treated by SCS, were satisfied with the treatment results after 8.3 years (Abeloos *et al.* 2011). SCS is a safe procedure (Kumar *et al.* 2008). Safety outcomes found that electrode migration (incidence of 15.1 %) and infection (incidence of 3.4 %) were the two most frequently reported complications of SCS (Cameron 2004). Longitudinal migration was already resolved in 2006 (Renard *et al.* 2006). Longitudinal migration is important in order to avoid

a progressive ejection of electrodes. Lateral migration was resolved in 2019 (Masopust *et al.* 2019).

Effective pain relief due to spinal cord stimulation has been critically dependent on the overlap of chronically painful areas by stimulation-induced pleasant paresthesia. Our research is also based on classic stimulation by pleasant paresthesia. We know that new research is based on high-frequency stimulation, but our research was done at the time of classic paresthesia stimulation. Our research is not conducted to understand the absolute effect of the treatment, but to select patients for neuromodulation in general. Therefore our research was not affected by the frequency of stimulation. The first prospective randomized head-to-head study of SCS where these results were confirmed, reported that 10-kHz paresthesia-free stimulation was statistically and clinically superior to conventional SCS at both 12- and 24-month follow-up, with responder rates for back and leg pain of 77 % and 73 % at 2 years, respectively (Kapural *et al.* 2015, Kapural *et al.* 2016).

Despite moderate to high initial costs, spinal cord stimulation is a superior cost-effective treatment for a specific patient population (Manca *et al.* 2008, Taylor *et al.* 2010). SCS was found to be a dominant economic option compared with reoperation (SCS was less costly and more effective) by a randomized controlled trial at 3-year follow-up (North *et al.* 2007). The economic aspect is not everything, but is still important information for every insurance company. This fact was the reason to conduct research to improve the effectiveness of neuromodulation of FBSS, by the better selection of candidates for this treatment. Our research is based on more than 36 months of follow-up, prospective data collection and evaluation of MRI scans by an independent radiologist, without the knowledge of patients´ clinical symptoms. Four degrees of scar size (modified Ross´s classification) were used to make it preferable for our statistical processing. The national neuromodulation database contains not only MRI findings, but also extensive information on patients' pain intensity, pain localization, kind of pain, psychological and psychiatric findings and quality of life. Our outcome did not assume an evaluation of our neuromodulatory technique in the treatment of FBSS, but a comparison of groups of patients with different MRI findings. Therefore we statistically processed the data only using the pain intensity score. We did not find statistical correlations between groups because Groups II, III and IV had very similar results. This means that the extent of scars is not an important finding for the treatment of pain by neuromodulation. Good results were found in all groups of patients who developed epidural fibrosis. The average difference between input and output VAS was more than 6 in all epidural fibrosis groups. At this point, it is difficult to show the effectiveness of treatment better than using VAS. Objective evaluation is almost impossible, measurement of glycated products failed. (Rokyta *et al.* 2018).

The statistically higher effect of spinal stimulation (SCS) in the epidural fibrosis group was proven at a 1 % level of significance. To eliminate the effect of multiple method failure, a two-dimensional delta VAS table was used. It was shown that there is a different effect of neuromodulation, depending on the presence or absence of fibrosis in the treatment of pain. In the group with epidural fibrosis, the fixed and altered spine root was treated. In this case, we refer to this neuromodulatory treatment as treating neuropathic pain. In fact, the difference between typical neuropathic pain and pain with an unclear background is discussed here. Neuropathic pain is associated with a change in mediator levels – increase in substance P and serotonin, decrease in gamma-Aminobutyric acid (GABA). Neuromodulation stabilizes the levels of these mediators and also lowers glutamate, aspartate, and acetylcholine levels (Cui *et al.* 1997, Linderoth *et al.* 1999, Song *et al.* 2009, Stiller *et al.* 1996). These results are typical of neuropathic pain. Group 0 is also included as patients with neuropathic pain, but the characteristics are slightly different. We have to consider another cause of pain origin in Group 0. In Group 0, other factors are important, whether psychological, psychiatric or socio-economic. This is important to be assessed when the patient is selected for neuromodulatory treatment, which is confirmed by our conclusions. In Group 0 without epidural fibrosis, more attention should be paid to patient selection.

Conclusions

The extent of epidural fibrosis is an important factor for FBSS. FBSS is the basis for the existence of neuropathic pain after lumbar spinal surgery. There is clear evidence of a correlation between patients with epidural scar formation on MRI scan and the effect of dorsal column stimulation. Stimulation in patients without postoperative epidural fibrosis is less effective. This is an important factor for the indication of patients for spinal cord stimulation.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

ΔVAS – change in visual analogue scale, EF – epidural fibrosis, FBSS – Failed back surgery syndrome, GABA – gamma-aminobutyric acid, SCS – spinal cord stimulation.

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