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Original Research Article

A Randomized, Multicenter, Double-Blind, Parallel Pilot Study Assessing the Effect of Mechanical Adhesiolysis vs Adhesiolysis with Corticosteroid and Hyaluronidase Administration into the Epidural Space During Epiduroscopy

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Abstract

Objective. Epiduroscopy is a proven method of diagnosis and treatment for chronic radicular pain after spinal surgery, which is known as failed back surgery syndrome (FBSS). The aim of the study was to compare the efficacy of drugs (the enzyme hyaluronidase and corticosteroid DEPO-Medrol) administrated into the epidural space during epiduroscopy, performed within the ventral and ventro-lateral epidural space with a focus on releasing foraminal adhesions.

Methods. Forty-eight patients with diagnosed FBBS were randomized into two groups before epiduroscopy. Group A received the standard treatment—mechanical lysis of fibrotic tissue in the epidural space. Group B received hyaluronidase and corticosteroid methylprednisolone acetate during the procedure. Subjects were followed for six and 12 months via scheduled double-blinded examinations by pain physicians. Leg and back pain intensity was assessed by an 11-point numerical rating scale, and patients' functional disability was assessed by the Oswestry Disability Index (ODI).

Results. Study subjects showed a significant decrease in ODI score in both groups ($P < 0.05$). Significantly lower pain scores for leg pain ($P < 0.05$) and back pain ($P < 0.05$) were also recorded after the six-month follow-up. However, the one-year follow-up showed a return to the baseline ODI values of most monitored pain scores in both groups ($P > 0.05$). Improvement was only noted on the NRS for back pain at one-year follow-up ($P < 0.05$).

Conclusions. A significant improvement of leg and back pain was found in both groups after six

months. ODI was significantly improved only in group B in both the six- and 12-month intervals. Back pain at one-year follow-up was only improved in group B.

Key Words. Adhesiolysis; Back Pain; Epiduroscopy; Failed Back Surgery Syndrome; Hyaluronidase

Introduction

Medical experts and researchers have investigated various types of optical visualization of human cavities for decades, with varying degrees of success [1]. Epiduroscopy is a relatively new technique used in the evaluation and treatment of low back pain via advancements in optical fiber technology. As a minimally invasive, endoscopic technique, it allows for direct endoscopic imaging of the epidural space and helps with pain management for patients suffering from post–lumbar surgery syndrome (PLSS) and other causes of low back pain and radiculopathy [2]. Epiduroscopy, the direct visualization of the epidural space with a flexible endoscope, has been performed in some places for years, but its significance is still questionable. For example, it has been shown to be more sensitive than magnetic resonance imaging (MRI) in detecting epidural fibrosis. According to literature, in patients with failed back surgery syndrome, MRI showed epidural fibrosis in 16.1% of patients whereas epiduroscopy showed epidural fibrosis in 91% of patients [3]. A systematic review of the literature regarding the effectiveness of spinal endoscopic adhesiolysis in managing chronic intractable pain from PLSS indicated an evidence level of II-1 or II-2 based on the US Preventive Services Task Force (USPSTF) criteria, and one randomized trial gave it a recommendation of 1 C/strong [4]. The authors of this study have been using epiduroscopy for a number of years, and they see a potential for this method to enable physicians to perform a detailed examination of the spinal canal with optic visualization of the particular structures. This type of examination will provide detailed information about the presence of postoperative fibrosis, adhesions, inflammatory changes, or any other pathological change within the epidural space. The current technique also allows the utilization of optical visualization for targeted therapeutical interventions in the epidural space, such as the removal of adhesions and fibrotic changes, or targeted administration of medication. According to the literature, in patients with failed back surgery syndrome (FBSS), epidurally applied corticosteroids reach the intended level in only 26% of cases [3]. Anterior epiduroscopy and epiduroscopic laser neural decompression (ELND) have recently been introduced in the treatment of herniated disc decompressions and chronic low back and radicular pain, respectively [2]. Recent publications describe the use of Fogarty catheters and resablation to remove adhesions attached to the dura [3].

There is some controversy regarding the theory behind the role of postoperative fibrosis and epidural adhesions in the etiology of FBSS. This is a syndrome in which patients do not experience an improvement in their clinical status after successful back surgery or, after a minor improvement, their status deteriorates without any correlations with MRI. The formation of scar tissue near the nerve root is a common occurrence after back surgery and is called epidural fibrosis: Scar tissue might be a major cause of postoperative pain, commonly called FBSS. This epidural scarring can cause pain for many reasons; for example, the nerves may be trapped by scars, while veins in the epidural space press down upon the nerves and become enlarged, putting pressure on them [5]. The decreased nourishment of nerve tissue and traction of epidural adhesions on the dural sac can also contribute to the etiopathogenesis of the complex pain syndrome in FBSS. Stenosis of the spinal canal by fibrosis is also a justifiable factor in the worsening of the clinical prognosis in a patient after back surgery. If the aforementioned statements do have a clinical foundation, the removal of fibrosis and adhesions should lead to an improvement in the clinical state of the patient even without the administration of anti-inflammatory medications, depomedrol, and hyaluronidase.

On the other hand, it has been scientifically proven that hyaluronidase inhibits cellular recruitment, edema formation, and pro-inflammatory mediator production, resulting in decreased adherence of leukocytes to blood vessels and tissue infiltration [6].

The goals of our study are to evaluate the changes in the clinical state of patients with FBSS after the endoscopic removal of fibrosis and adhesions and to compare between an exclusively mechanical intervention and a mechanical intervention with targeted administration of depot corticosteroids and hyaluronidase.

Methods

A randomized controlled trial with a parallel group study design was used. The present study was approved by the Ethics Committee of Louis Pasteur University Hospital in Košice (approval number 75/EK/15) and registered at clinicaltrials.gov with registration ID NCT02459392. Written informed consent was obtained from all participants. All patients with failed back surgery syndrome who were indicated to undergo an epiduroscopy procedure were recruited from one of the three pain clinics in Bratislava, Bardejov, and Košice in the Slovak republic. Inclusion criteria were age 18 years or older, written informed consent, symptoms of FBSS, permanent low back pain with dominant (more than 60%) radiation to lower extremities despite previous epidural corticosteroid injections, current magnetic resonance imaging (no older than three months) without serious spinal stenosis and serious radicular compression. Exclusion criteria were the presence of annihilating phenomena (loss of sensitivity of the skin, loss of coordination of the lower extremities, problems with urination

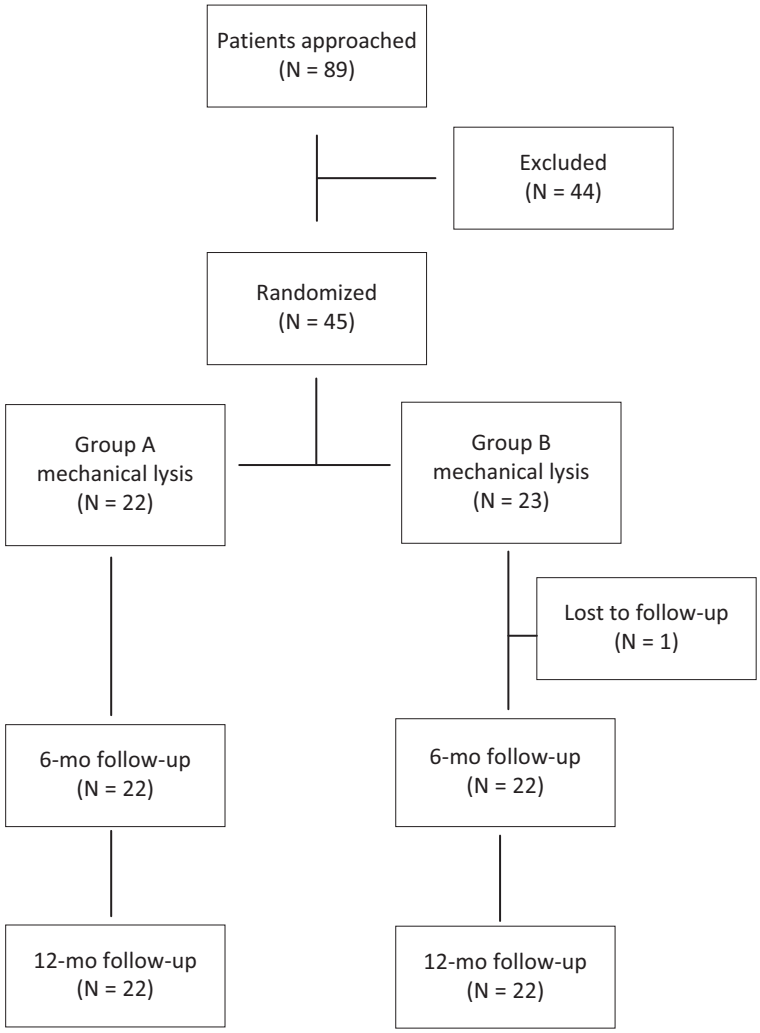

Figure 1 Flow chart of patient selection, enrollment, and follow-up in the study.

or defecation), presence of infection, neoplasms, and lack of patient approval.

All eligible patients were approached. After written informed consent was obtained, participants were allocated into study groups according to computer randomization software. Each patient had obtained a unique clinical trial ID number, which was generated by computer software before epiduroscopy. Blinding at the time of randomization was maintained with a sealed envelope given to the anesthesiologist managing the patient. The anesthesiologist was not involved in data collection. Study outcome measurements were obtained by an independent research team from the Medical Faculty, Pavol Jozef Šafárik University in Košice. Study continuance was maintained by an independent clinical study coordinator from the East Slovak Institute of Cardiovascular Disease in Košice, and the report was prepared in accordance with the Consolidated Standards of Reporting Trials (the "CONSORT statement"). All data were assembled in a protected and encrypted database accessible only to the study coordinator including statisticians from an independent statistical institution and local study site coordinators.

Patients diagnosed with failed back surgery syndrome (FBSS) were enrolled in the study. Patients underwent at least one previous back surgery with ongoing pain radiating to the lower extremities with or without back pain, which was still present after periradicular therapy or caudal blockade (less than 50% visual analog scale [VAS] relief of pain 30 days after intervention) performed by a pain management specialist. A patient who had met the inclusion criteria was informed by the examining doctor about the study and given the opportunity to participate. They were informed about the intervention procedure, epiduroscopy performed by a flexible fiber-optic endoscope with a video-guided catheter (Myelotec, Inc., Roswell, GA, USA), strictly within the ventral and ventro-lateral epidural space with focus on

releasing foraminal adhesions. Consequently, in the case of agreement, the patient signed the informed consent documents about the interventional procedure, epiduroscopy, and their informed consent to participate in the study.

The mechanical adhesiolysis itself was performed by three different tools: laser, radiofrequency probe, or a balloon catheter. The choice of the instrument was made by the surgeon according to his clinical preference. The total volume of our standard pharmacological mixture was 30 mL per foraminal level (20 mL of the mixture bupivacaine 0.5%, 5 mL methylprednisolone, 80 mg saline, and 150 I.U. of hyaluronidase, Hylase "Dessau", in 10 mL saline). The maximum volume injected was never more than 60 mL. Patients were randomly split into two groups (Figure 1). The first group (Group A) underwent epiduroscopy (5 mL of 0.5% bupivacaine was injected; the total volume injected was supplemented up to 20 mL with saline), during which only a mechanical lysis of the epidural fibrotic attachments was performed by either laser (four patients), radiofrequency (15 patients), or the balloon technique (three patients). The second group (Group B) underwent epiduroscopy, during which mechanical lysis of the epidural fibrotic attachments was performed by laser (five patients), radiofrequency (16 patients), or the balloon technique (four patients), as in group A (5 mL of 0.5% bupivacaine). At the same time, a solution of hyaluronidase (Hylase "Dessau" 150 I.U. in 10 mL of saline) and injectable corticosteroid methylprednisolone acetate (DEPO-Medrol) 80 mg were administered to the patient into the place of conflict (the depression in the spinal root by fibrosis). After completing the first protocol of the preoperative examination, this protocol was sent to the coordinator of the study as well as the researcher in charge of processing study data. The coordinator of the study planned the first postoperative examination six months after the procedure and the second postoperative examination after 12 months following the procedure. The first and second postoperative examinations of the patient were performed by a different physician (not the one performing the actual procedure), or at a different pain management clinic. They performed a pain assessment of the patient while blinded to which procedure they had undergone (endoscopy only including mechanical lysis or with the administration of the drugs) and completed the pain management protocol of the study. Primary outcomes were pain intensity spreading in the back and legs and also evaluation of the Oswestry Disability Index (ODI). Patient Status Score (PSS) is a grading scale from 0–4, where 0 means the patient is without pain, has a normal life, normal job, is able to exercise; and 4 means the patient needs help to take care of themselves and is bed-ridden. The Patient Self-Content Score (PSCS) is evaluated on a scale from 0 to 10, where the patient describes his satisfaction with the procedure at six- and 12-month follow-up (0 being the worst and 10 being the best). There were no important changes to the methods after the study commenced.

Table 1 Characteristics of patients in groups divided according to the performed procedure

	Group A (Min–Max) Med	Group B (Min–Max) Med
Participants, No.		
Before procedure	22	23
6-mo follow-up	22	22
12-mo follow-up	22	22
Age, y	(35–70) 54	(33–69) 46.5
Sex (F/M)	10/12	12/11
ASA	(1–3) 2	(1–3) 2
BMI	22	20
Pain in dermatomes according to examination before procedure		
L2	0	1
L3-L4	1	0
L4-L5	4	5
L5	2	6
L5-S1	5	3
S1	4	4
Mechanical therapeutic intervention		
Balloon	3	4
Laser	4	5
Radiofrequency	15	16

Descriptive statistical methods were used to evaluate the results (mean, median, maximum, minimum, and SD). Examination of the distributional form for score and time data was determined by box plots. Each box plot indicated minimal value, lower quartile (lowest 25% of data), median, upper quartile (highest 25% of data), and maximal value. Normality of data distribution was assessed by the Shapiro-Wilk test. Homogeneity of variances was estimated using the Levene test. Differences between continuous variables were analyzed by a nonparametric Kruskal-Wallis one-way test. A paired Student *t* test was used to assess the statistical significance of changes within each treatment group. *P* values of less than 0.05 were considered significant. Statistical analysis was performed with the SPSS version 11.0 statistical software package.

Results

Of the 86 admitted patients with FBSS, 45 fulfilled the selection criteria and were randomized into two groups (Group A—mechanical lysis, Group B—mechanical lysis and drugs) and then underwent epiduroscopy. One patient from group B was lost during follow-up. There were no unexpected side effects. The baseline demographic and characteristic values are summarized in Table 1 and were similar in both groups.

A significant improvement was recorded in ODI in both groups after six months ($P < 0.05$), which indicated

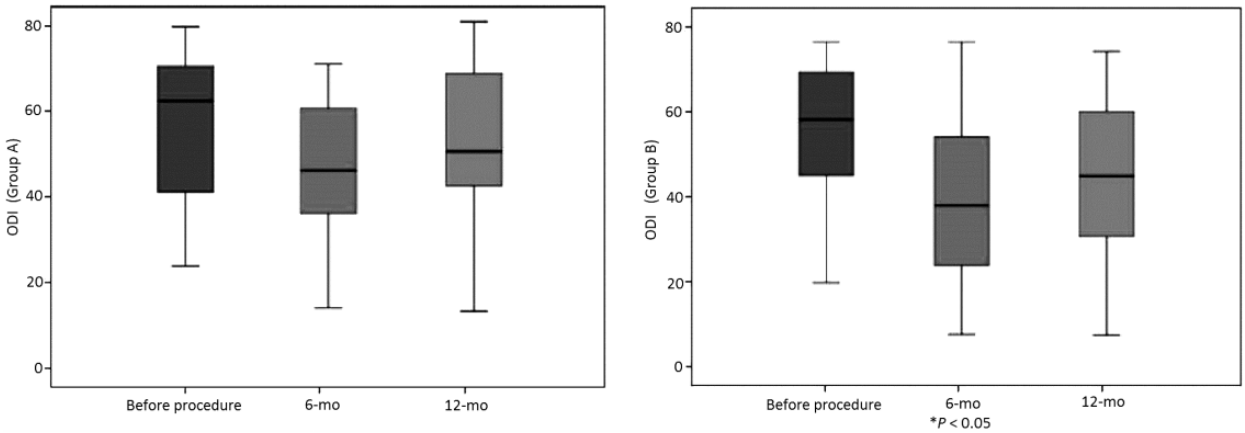

Figure 2 Evaluation of patient functional disability by the Oswestry Disability Index indicating significant improvement in comparison with baseline after six months, with return to baseline values after 12 months in both groups.

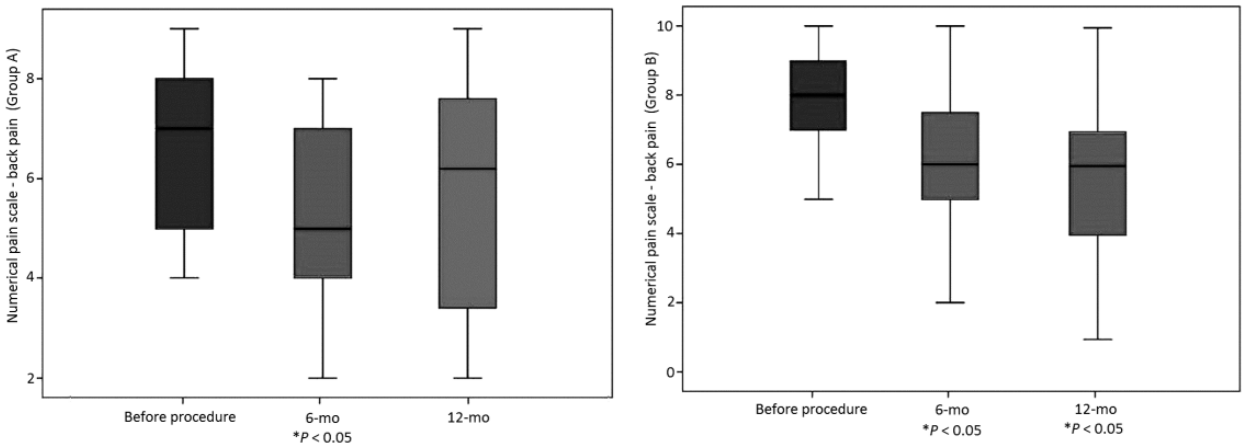

Figure 3 Evaluation of back pain intensity in patients indicating significant reduction in low back pain in both groups after six months, with persisting significant improvement after 12 months in group B.

that subjects had greater clinical improvement. After 12 months, the ODI score was the same as before the procedure, which showed a return to the previous state (Figure 2). A reduction in low back pain was recorded after six months in both groups ($P > 0.05$), but this did not persist until 12 months in Group A ($P > 0.05$) (Figure 3). A similar reduction in pain after six months was found on examination of leg pain ($P < 0.05$), but the level of pain in the legs had reverted to baseline after 12 months in both groups ($P > 0.05$) (Figure 4).

The changes between both groups are summarized in Table 2. No difference was found between Group A and Group B in ODI scoring values nor in the numerical pain scale for leg pain and back pain before the procedure (T0) or at six months (T1) and 12 months (T2) after procedure ($P > 0.05$) in all observed parameters. There was no difference in PSS between Group A and Group B. We found significant worsening of PSCS in Group A at $P < 0.05$, but not in Group B.

Discussion

Everything we do regarding success or failure in pain medicine is ultimately expressed at the cellular level and represents changes in electrical patterns, neurotransmitters, and metabolism. Epidural fibrosis has been described as a common phenomenon with a place among the major causes of continued pain after surgical intervention [7]. As Baber and Erdek [8] pointed out, scar formation is part of the healing process after spinal surgery, like any other surgical procedure, resulting in fibrosis within the epidural space. Epidural fibrosis can be

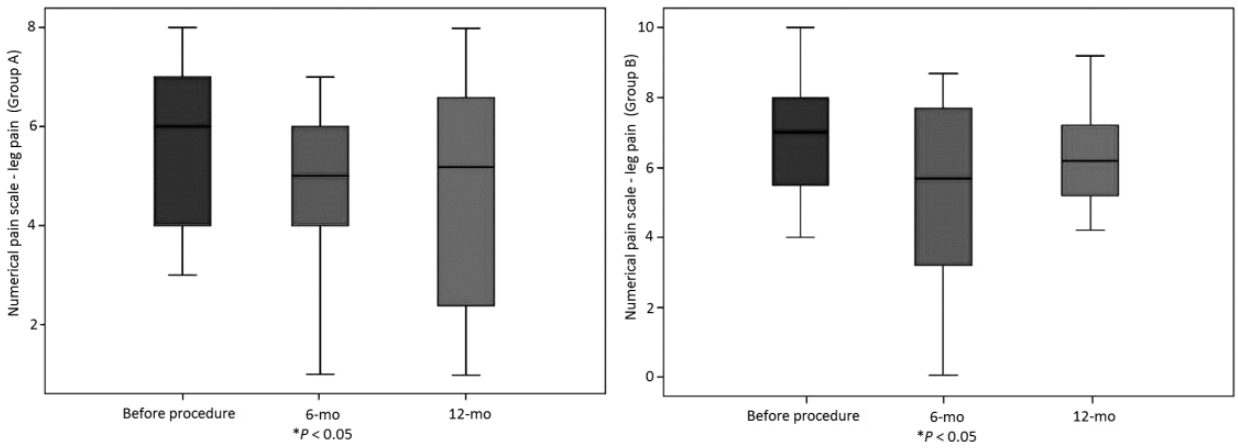

Figure 4 Evaluation of leg pain intensity in patients indicating significant reduction in leg pain in both groups after six months.

Table 2 Comparison of the mean values of recorded parameters between groups in the 6 and 12 months following the procedure

Parameters	Time Interval	Group A (Min–Max) Med	SD	Group B (Min–Max) Med	SD	Mean Difference	95% CI	*P* Value
Oswestry Disability Index	Before procedure	(31–80) 65	15.57	(20–76) 58	18.46	−5.192	−15.485 to 5.101	0.313
	6-mo follow-up	(12–76) 47	18.63	(8–76) 38	21.77	−8.921	−21.090 to 3.248	0.148
	12-mo follow-up	(18–82) 54	17.78	(12–74) 48	19.14	−8.591	−19.833 to 2.651	0.131
Numerical pain scale– back pain	Before procedure	(4–9) 7	1.64	(0–10) 8	2.19	1.022	−0.150 to 2.194	0.086
	6-mo follow-up	(2–8) 5	1.97	(0–10) 6	2.85	0.561	−0.921 to 2.043	0.449
	12-mo follow-up	(4–9) 7	1.63	(1–10) 6	2.33	−0.727	−1.951 to 0.496	0.237
Numerical pain scale–leg pain	Before procedure	(3–8) 6	1.72	(4–10) 7	1.54	0.868	−0.071 to 1.806	0.069
	6-mo follow-up	(1–7) 5	1.56	(0–9) 6	2.78	0.887	−0.476 to 2.251	0.193
	12-mo follow-up	(3–8) 6	1.54	(1–9) 6	2.11	−0.045	−1.254 to 1.163	0.940
Patient status score	Before procedure	(1–4) 3	0.728	(1–4) 3	0.700	0.197	−0.239 to 0.632	0.367
	6-mo follow-up	(0–4) 2	0.976	(0–3) 2	0.839	−0.47	−0.604 to 0.632	0.864
	12-mo follow-up	(1–4) 2	0.728	(1–4) 3	1.071	−0.054	−0.620 to 0.512	0.848
Patient self-content Score	6-mo follow-up	(0–10) 7	3.171	(0–10) 7	2.864	0.329	−1.583 to 2.240	0.73
	12-mo follow-up	(0–10) 5	3.092	(0–10) 6	4.025	1.560	−0.722 to 3.841	0.171

CI = confidence interval.

caused by chronic inflammatory changes also from chronic spinal cord injury. The pathophysiological background of epidural fibrosis is the inflammatory reaction of the arachnoid mater [9]. The pain is a characteristic manifestation of inflammation there [10]; however, fibrotic adhesions themselves cause back and leg pain by compressing nerve roots, decreasing the range of motion in the back and introducing pain with movement [11]. Despite multiple studies, the relationship between fibrosis and pain is still not entirely resolved [12]. In earlier studies, active signs of root inflammation were seen in only six patients from the 20 studied [13], or none [7]. Therefore, we did not focus on following the signs or markers of inflammation in fibrosis during epiduroscopy.

This study concerns an initial evaluation of an initial group of patients over a one-year period after a spinal endoscopic procedure. In our study, an attempt was made to show that the targeted destruction of postoperative fibrosis and adhesions has the potential to improve the patient's clinical condition in cases of FBSS

Table 3 Comparison of patients' pain intensity, self-content score, patient status score, and functional disability inside the groups in the 6- and 12-month postoperative examination periods

Parameters	Groups	Before Procedure Mean	6-mo Follow-up Mean	Mean Difference	95% CI	*P* Value	12-mo Follow-up Mean	Mean Difference	95% CI	*P* Value
Oswestry Disability Index	A	59.41	49.18	10.227	−0.117 to 20.676	0.055	53.68	4.331	−5.857 to 14.520	0.400
	B	54.22	40.26	13.957	1.960 to 25.953	0.024*	45.09	9.126	−2.191 to 20.444	0.111
Numerical pain scale–back pain	A	6.50	5.09	1.409	0.078 to 2.285	0.037*	6.45	−0.182	−1.175 to 0.811	0.714
	B	7.52	5.65	1.870	0.357 to 3.382	0.017*	5.73	1.794	0.431 to 3.158	0.011*
Numerical pain scale–leg pain	A	6.05	4.59	1.318	0.320 to 2.317	0.011*	5.77	0.136	−0.856 to 1.129	0.783
	B	6.91	5.48	1.435	0.101 to 2.768	0.036*	5.73	1.095	−0.22 to 2.211	0.061
Patient status score	A	2.57	1.96	−0.609	−1.120 to −0.097	0.021*	2.43	−0.130	−0.563 to 0.302	0.546
	B	2.76	2.32	−0.853	−1.340 to −0.366	0.067	2.38	−0.111	−0.463 to 0.102	0.181
Patient satisfaction score	A		6.57				4.19	2.381	0.427 to 4.334	0.018*
	B		6.90				5.75	1.150	−1.086 to 3.386	0.305

CI = confidence interval.
*statistical significance at $P < 0.05$

diagnosis. Clinical effectiveness of spinal endoscopy with adhesiolysis from prospective trials [13,14], retrospective trials [15–18], and case reports showed evidence for moderate short-term pain relief and limited evidence for long-term pain relief. Moreover, Manchikanti et al. [7] have shown that the targeted injection of local anaesthetic and steroid can be significantly effective for patients as short-term pain relief. The study by Kim et al. [19] has aided in the increase of knowledge in this area, the conclusions of which show the long-term benefits of the application of hyaluronidase along with a steroid. This study was therefore aimed to compare the effectiveness of the mechanical removal of fibrosis with mechanical intervention and targeted administration of corticosteroids and hyaluronidase in pain relief.

Our results show improvement in pain relief in group B at 12 months, with group A demonstrating an improvement only up to the six-month follow-up. Because of the interval of improvement and a consecutive return to the original state, we assume that either new fibrotic changes might develop or a repeated attempt is required to achieve better clinical improvement. In some patients, there was a significant improvement with a long-term effect, and this improvement lasted even after the 12-month follow-up. At this stage, we can hypothetically suggest an improved selection of patients suitable for an epiduroscopy procedure with a higher chance of significant clinical improvement. However, based on empirical relations between the clinical outcome of epiduroscopies and the number of open spinal surgical interventions, it seems logical that a higher number of open surgical interventions in the spinal canal will lead to increased formation of fibrosis and worsening of the prognosis for an epiduroscopy procedure. Mild-to-moderate fibrosis, in conjunction with local pain reproduction, was an indicator of a more favorable outcome than severe fibrosis [20]. The amount of nerve root damage, where the pain is distributed in the corresponding dermatomes, should also be considered an important parameter. Severe damage to the nerve roots gives only a small chance of a good clinical prognosis in an epiduroscopy procedure, and it might be more effective to implant a spinal cord stimulator. This theory has not yet been completely proven in an adequate amount of studies. In conclusion, information obtained through lumbosacral epiduroscopy has significant diagnostic and prognostic value and may be helpful in the management of patients with low back pain and/or leg pain in general [21]. Even more detailed knowledge of the anatomy, histology, and pathology of both the intact and pathological epidural space will improve our ability to understand the pathophysiology of back and leg pain. The question is whether this potential should also be implemented in routine diagnostics and treatment of all patients with back pain, as it is in the diagnosis and treatment of joint diseases and diseases of the abdominal cavity.

Conclusion

Forty-four patients with six- and 12-month follow-up intervals were evaluated in the initial phase of our study. It concerned patients after a minimum of one back surgery without a satisfying clinical result regarding pain relief in the back and the lower limbs. In the first group of patients, the main goal was to remove, under endoscopic guidance, the postoperative fibrosis or adhesions in the vicinity of nerve roots, where pain is distributed in the corresponding dermatomes. A radiofrequency probe, laser, or balloon was used to work in the anterior epidural space. Subsequently, the posterior epidural space was always examined endoscopically, and in the case of visible adhesions fixated on the dural sac, an attempt was made to remove them. The same procedure was performed in the second group of patients, with the additional administration of hyaluronidase and a mix of Depo-Medrol with a local anaesthetic after mechanical intervention. An improvement was observed at six-month follow-up in both groups, regarding back and lower limb pain. At 12-month follow-up, the effect of pain relief in the lower limbs was insignificant in both groups. Pain relief in the low back was only seen after 12 months in the group of participants who had received medication. ODI was significantly improved only in group B at six-month follow-up. A limitation of the study was the relatively small sample size. The continuation will be the enrollment of a higher number of patients to collect and evaluate more data. Based on results of our study, epiduroscopy has great potential to become an effective and well-accepted diagnostic and therapeutic tool in the treatment of FBSS symptoms.

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