03.03.2023

1- NAME OF THE PROJECT

“The Effect of Central Sensitization on the Treatment Success of Ultrasound-Guided Caudal Epidural Steroid Injection in Radicular Pain in Patients with Failed Back Surgery Syndrome”

2-QUALITY OF THE RESEARCH

Non-Pharmaceutical Prospective Observational Clinical Trial

3- IN MULTI-CENTER RESEARCH, CENTERS OUTSIDE THE INSTITUTION :

The research is not multicenter.

9-JUSTIFICATION / PURPOSE OF THE STUDY :

Low back pain is a very common clinical entity that has a tremendous social, financial and psychological impact on the patient's life. It is a worldwide problem, with a global incidence of 9.4%, and causes more disability than any other condition in the world. The percentage of adults who experience chronic low back pain throughout their lives varies between 51% and 84% (1). As the population ages, the incidence of surgery for low back pain increases dramatically; The number of lumbar fusions increased by as much as 170% from 1998 to 2008 (2). Failed back surgery syndrome (FBSS) has been reported to affect 10 to 40% of patients following spine surgery, but estimating the incidence of FBSS is difficult due to the broad scope of its definition and heterogeneous etiology (3). Failed back surgery syndrome (FBSS) is defined by the International Association for the Study of Pain as "lumbar spinal pain of unknown origin that persists despite surgical intervention or occurs after surgical intervention for pain in the same topographic area" (4). Pain may occur after surgery, as surgery may aggravate or fail to adequately heal existing pain. Patients with FBSS have long-standing chronic low back pain, with or without radicular symptoms, and have had one or more surgical interventions that do not treat the pain. Its etiology is complex and it is a condition with many factors that predispose patients to chronic pain. Epidural fibrosis, perineural scars, acquired stenosis, recurrent disc herniation or pain in the sacroiliac/facet joints are thought to play a role in the etiology of FBSS. Pain in the leg likely indicates nerve compression resulting from stenosis, epidural fibrosis, or disc herniation, while lower back pain is more common in facet joint arthropathy, sacroiliac joint problems, or myofascial etiologies . For the failed back surgery syndrome patient, physical examination is generally not useful

in determining a specific pain etiology, but may reveal several suggestive findings. Symptoms resulting from spinal stenosis are usually exacerbated by spinal extension and relieved by flexion. On the other hand, pain from disc herniation causes a positive straight leg raise test. Loss of strength or sensation in the lower extremities can help figure out which nerve roots are affected. Other tests may be used to elucidate the etiology of failed back surgery syndrome and differentiate it from other causes of low back pain. Erythrocyte sedimentation rate and C-reactive protein can be used to evaluate possible infection, especially in patients with constitutional symptoms or a predisposition to infection. Diagnostic nerve blocks can diagnose specific etiologies of FBSS, such as facet joint arthropathy (medial branch blocks), sacroiliac joint pain (lateral branch blocks and intra-articular injection), and foraminal stenosis (transforaminal epidural and selective single-level blocks) and roots associated with the patient's symptoms. can define. MRI with and without gadolinium contrast remains the gold standard imaging modality for failed back surgery syndrome due to its excellent ability to detect soft tissue abnormalities such as epidural fibrosis and disc herniation. Contrast is especially indicated in patients with a history of disc herniation surgery. An international panel of spine surgeons, neurosurgeons and pain specialists with a special interest in FBSS established the Chronic Low Back and Leg Pain (CBLP) network to address challenges and barriers in the clinical management of FBSS patients by creating a common interdisciplinary structure. The definition of FBSS proposed by the CBLP network is based on the prediction that no further spine surgery is required after an appropriate somatic, radiological and psychosocial evaluation (5). The key elements for the definition of FBSS can be summarized in 4 aspects:

1. There is back and/or leg pain that has persisted for at least 6 months after the most recent spine surgery.

2.The patient has undergone a comprehensive clinical and radiological evaluation

3.There is no clear surgical target compatible with the symptoms revealed on clinical examination and imaging

4. There is an interdisciplinary consensus that additional surgical intervention (decompression and/or fusion) is not appropriate

Despite its adverse effects on patients and its relative prevalence in the population undergoing spine surgery, there are few high-quality randomized trials investigating the treatment of FBSS. (6). Treatments for FBSS are generally divided into conservative (physical therapy or drug therapy) and aggressive (interventional or surgical) management. Conservative treatment should always be the first choice before invasive techniques in patients who do not have an indication for urgent surgery (7). Various studies have shown that caudal ESI (CESI) is an effective method in patients with FBSS who do not respond to conservative pain-relieving treatments (8). Çelenlioğlu A. et al. In a prospective randomized study comparing the treatment success of TFESI and CESI in patients who developed FBSS after single-level discectomy, both CESI and TFESI (transforaminal epidural steroid injection) were

found to be effective and safe in treatment. CESI has been shown to be the safest and simplest ESI with a low rate of complications, including dural puncture and other side effects, compared to other injection methods (9). Yoon et al. (10) reported the success rate of US-guided caudal blockade as 94% (11). In a study conducted by Akkaya et al. (12), comparing ultrasound and fluoroscopy-guided caudal epidural steroid injection (CESI) in patients with FBSS, a decrease in both pain and ODI scores was achieved in both groups at 3-month follow-up, and CESI was found to be effective in the treatment of FBSS. has been reported. In a prospective randomized controlled study comparing the treatment success of caudal epidural steroid injection guided by ultrasonography (USG) and fluoroscopy in postlaminectomy patients, no difference was found in terms of complications between the two groups, while patients in the fluoroscopy group felt more pain during the intervention than patients in the USG group. Despite accurate needle localization and drug injection under fluoroscopic guidance, radiation is still a serious risk for both the patient and the interventionalist. The use of USG in caudal epidural injections protects against radiation exposure and is a safe and rapid method to locate the sacral hiatus and guide the needle (9). Color Doppler USG can visualize intravenous injections. Tsui et al. (13) reported that the color Doppler feature of US can confirm whether the injected drug diffuses into the caudal area. Injection of fluid into the epidural space causes turbulent flow, which appears as a burst of color, whereas intrathecal injection shows the absence of color flow Doppler signal. Although the exact pathophysiological process of FBSS remains unclear, increasing evidence suggests that the symptoms of diffuse pain distribution, hyperalgesia, and disproportionate pain intensity, which are also common in other chronic pain-related diseases (e.g., fibromyalgia, tension-type headache, and nonspecific chronic low back pain), are a potential pain disorder. predicts that central sensitization may develop (14). The International Association for the Study of Pain (IASP) defined CS in 2011 as “the increased response of nociceptive neurons in the central nervous system to normal or subthreshold afferent input.” Anxiety about pain, limitation of daily activities, quality of life and related stress lead to depression over time, thus beginning a vicious "pain-anxiety-depression" cycle. Altered central pain modulation may be involved in the pathogenesis of FBSS. Unfortunately, only a few studies have investigated the presence of central sensitization in patients with FBSS, although it may guide treatment. Central amplification of pain may contribute to both chronic low back pain intensity and disability in FBSS patients. Therefore, targeted treatments should take into account functional changes in the central nervous system of FBSS patients, and treatment modalities that can attenuate central sensitization (e.g., cognitive targeted exercise therapy, pharmacotherapy, spinal cord stimulation) may be useful in the treatment of FBSS. Our aim is to reveal the relationship between FBSS and central sensitization proportionally, to prevent the formation of a vicious circle of chronic pain with early detection and treatment, keeping in mind that central sensitization may develop in postspinal surgery patients with ongoing pain, and also to prevent the formation of a vicious cycle of chronic pain with USG-guided caudal epidural steroid injection, as there is no radiation exposure and it is advantageous and beneficial. Since it is a reliable

method, we aim to determine its effectiveness in patients with FBSS. To our knowledge, such a study has not been reported before in the literature. We hope to contribute to the literature.

10-APPROACHES AND METHODS TO BE APPLIED :

Among the patients who applied to Marmara University Pendik Training and Research Hospital, Physical Medicine and Rehabilitation and Algology outpatient clinics with complaints of low back pain, were diagnosed with FBSS by Algology after clinical, physical examination and radiological imaging and were planned for caudal epidural steroid injection, which is a treatment option applied in routine clinical practice. Those who meet the exclusion criteria will be included in the study after detailed information about the research is given and their verbal and written consent is obtained. These patients will not undergo additional treatment, any imaging methods or laboratory tests. Patients diagnosed with or in contact with Covid-19 will not be processed until the quarantine period expires. Patients will be reminded to comply with the mask and distance rules in the waiting area before the procedure and in the observation area after the procedure, not to touch any surfaces in the hospital unless necessary, and to frequently disinfect their hands. During the evaluations, the patient and the physician; will comply with mask, distance and hand hygiene rules. After the procedure, a waiting area will be allocated for patients in accordance with distance rules.

Patients who meet the Chronic Low Back and Leg Pain consensus group FBSS definition and meet the inclusion criteria will be included in the study. Before the patients are processed, data such as demographics, height, weight, which leg the pain is on, additional diseases, and medications used will be recorded. Before the procedure, patients will be evaluated with scales and methods such as Numeric Rating Scale (NRS), Oswestry Disability Index (ODI), Central Sensitization Inventory (CSI), Beck Depression Inventory (BDI), Douleur Neuropathic 4 (DN4) and a pressure algometer (baseline brand manual Quantitative sensory testing will be performed using algometer) . Those who score 40 and above on CSI will be included in Group 1 (those with CS), and those with lower scores will be included in Group 2 (those without CS). Homogeneity between groups will be ensured in terms of the surgical method applied (lumbar stabilization or microdiscectomy) and etiological cause (fibrosis and recurrent disc herniation). Patients in both groups will undergo CESI under USG guidance. Patients will be re-evaluated with NRS at 1 hour, 3 weeks and 3 months after the procedure, using the scales and methods mentioned above. A 50% or more reduction in NRS in the 3rd month will be considered treatment success.

Numeric Rating Scale (NRS) is a scale in which the patient gives a score between "0" and "10" for the back and leg pain felt, where "0" = no pain and "10" = the most severe, unbearable pain. is a scale. Turkish validity and reliability studies of the scales and surveys to be used in the study have been conducted and are stated in the references.

The Central Sensitization Inventory (CSI) includes 2 parts: part A, which evaluates symptoms thought to be related to CS, and part B, which quickly questions whether the patient has previously received a specific diagnosis. Part A contains 25 items that question the frequency of symptoms seen in SS syndromes and are scored between 0-100 points. Each symptom is defined as "never" (0 points) if the patient never experiences that symptom, "rarely" (1 point) if the patient experiences it rarely, "sometimes" (2 points) if he sometimes experiences it, "often" (3 points) if he frequently experiences it, "frequently" (3 points) if he always experiences it. It is recorded as “always” (4 points). As the patient's score increases, he or she is considered to have more symptoms related to CS.

Beck Depression Inventory (BDI) was created by Beck in 1961 to measure the characteristic attitudes and depression symptoms of patients. The survey consists of a total of 21 questions, each with four options. Each option is scored between 0-3 and the total score is calculated. In scoring, 0-9 is interpreted as normal, 10-18 as mild depression, 19-29 as moderate depression, and 30-63 as severe depression (15).

Oswestry Disability Index (ODI) consists of 10 items. Items question the severity of pain, self-care, lifting, carrying, walking, sitting, standing, sleeping, degree of pain change, travel and social life. There are 6 statements under each item, in which the patient ticks the one appropriate to his/her situation. The first statement is scored as “0” and the 6th statement is scored as “5”. When the total score is calculated, it is multiplied by 2 and expressed as a percentage. The maximum score is "100" and the minimum score is "0". As the total score increases, the disability level also increases.

Quantitative Sensorial Testing (QST) is widely used in human research to investigate the contributions of the peripheral and central nervous system to pain modulation. Pressure pain threshold (PPT) measurements are also a frequently used evaluation method among QST. PPT measurements will be measured using two different regions in each patient; areas with maximum pain at the waist for group 1 (those with CS), 3 cm adjacent to the L5 spinous process (local area) for group 2 (those without CS); and the dominant hand (approximately in the middle of the proximal transverse arch) for all subjects (far pain-free area). PPT will be evaluated three times in each region, with at least 60 seconds between stimuli, and the average of these 3 evaluations will be recorded as the PPT value for this region. If patients fail to report pain to a pressure of 10 kg/cm2, the test will be stopped and this value will be recorded as PPT.

Douleur Neuropathic 4 (DN4) is a scale that evaluates the patient's neuropathic symptoms with 4 questions. On a scale with a total score of 10, those with scores above 4 indicate the presence of neuropathic pain.

Processing Technique

Caudal Epidural Steroid Injection (CESI):

CESI procedure, which is a treatment method applied in routine clinical practice in patients diagnosed with FBSS who do not respond to conservative treatments, will be performed by an algologist (ŞŞ or OHG) with at least 10 years of experience in this field. During the procedure, the distance rule will be observed as much as possible (the person performing the procedure must be as close to the patient).

After patients are placed in the prone position, a pillow will be placed under the patient's abdomen to reduce lumbar lordosis. The injection site will be cleaned three times with povidone-iodine antiseptic and then covered with a sterile drape. In the operating room, patients will receive standard monitoring (ECG, MAP, SpO2) and vascular access will be established with a 20 G branule. Short-acting local anesthesia (3 mL 2% prilocaine) will be applied to the skin and subcutaneous tissue. A 3.5-inch, 22-gauge spinal needle will be inserted into the caudal epidural space, verifying that the needle does not exceed the level of the S3 foramen. 1- 2 mL contrast material (300 mg/50 ml iohexol) will be administered and the distribution of the injectate will be monitored simultaneously in Doppler mode, and the distribution pattern showing bilateral L5-S3 spread without vascular spread will be displayed. A mixture of 40 mg (1 mL) triamcinolone acetonide, 7 mL physiological saline and 2 mL (0.5%) bupivacaine will be injected, a total of 10 mL mixture will be used, all patients will be monitored and evaluated for one hour after the procedure. Patients without any procedural complications will be discharged.

Power analysis

According to the study conducted by Sacaklı R. et al., based on the improvement in pain scores in the 3rd month, the number of samples was found to be 21 for the CS group and 25 for the non-CS group, with a 95% confidence interval and 90% power. Considering that 10% of the patients could not continue the study, a total of 51 patients were planned to be included.

Sacakli, R., Sanal-Toprak, C., Yucel, FN, Gunduz, OH, & Sencan, S. (2022). The Effect of Central Sensitization on Interlaminar Epidural Steroid Injection Treatment Outcomes in Patients with Cervical Disc Herniation: An Observational Study. Pain Physician, 25(6), E823-E829.

D-OTHER INFORMATION ABOUT VOLUNTEERS

Minimum number of volunteers to be included in the study	Total	Age range
Group-1 CS ones	24	18-75
Group-2 non-CS	27	18-75

12- CRITERIA FOR INCLUSION, EXCLUSION AND REMOVAL FROM THE RESEARCH

INCLUDING:

- Being between the ages of 18-75
- Those who meet FBSS diagnostic criteria (according to CBLP)
- Radicular pain that begins at any time after surgery and persists for at least 6 months
- Those with clinically compatible epidural fibrosis and/or disc herniation at the L5 and/or S1 vertebra level on contrast-enhanced MRI
- Nrs is greater than or equal to 4
- Failure to achieve significant improvement with conservative methods

- Volunteering to participate in the study and signing a consent form

EXCLUSION:

- Those with acute or chronic uncontrolled medical illness,
- Lumbar structural pathologies (e.g., traumatic spinal injuries, infections, tumor and ankylosing spondylitis)
- Those with isolated axial low back pain
- Those with a history of lumbar surgery other than lumbar stabilization or microdiscectomy
- History of adverse reactions to local anesthesia or steroids
- Being pregnant or breastfeeding
- History of allergy to the injectables to be administered
- Those with bleeding diathesis
- Mental, psychiatric or neurological diagnosis that may complicate the implementation of the study
- Not wanting to participate in the study

VOLUNTARY CONSENT FORM (Separate Page)

I read the text above showing the information that should be given to the volunteer before the research. Written and verbal explanations were given to me about these. Under these conditions, I agree to participate in the clinical research in question with my own consent, without any pressure or coercion.

Due to the ongoing Covid-19 epidemic, the precautions to be taken during the process are listed below:

1. In the evaluations to be made before the procedure, the patient and the physician; will comply with basic rules such as mask, distance and hand hygiene.

2. Before the procedure, the area where patients wait will be wide enough and mask and distance rules will be observed.

3. Our patients who are diagnosed with or have been in contact with Covid-19 will not be treated until the quarantine period expires.

4. During the procedure, the mask and distance rules will be followed as much as possible (the physician performing the procedure must be at a close distance to you).

5. After the procedure, mask and distance rules will be observed in the waiting area.

Volunteer:

Name-Surname: Signature:

Address/Phone:

Parent/Guardian:

Name-Surname: Signature:

Address/Phone:

The researcher:

Name and surname:

Signature:

Name-surname, signature and position of the organization official who witnessed the consent process from beginning to end

ANNEX-II

PATIENT FOLLOW-UP FORM

Name surname:

History:

Phone:

TC Identification number :

Age:

Address:

Gender:

Kilo:

Size:

BMI:

Marital status: □ Married □Single

Occupation: □ Housewife □ Student □ Civil servant □ Worker □ Retired

Educational status: □ Illiterate □Literate □ Primary school □Middle school □High school

□ College □ University

Previous surgery;

The party to be transacted; Duration of symptoms: Comorbidity:

Radicular pain; **Previous treatments / duration** : Medications used

	Before Procedure	**1st hour**	**Three weeks**	**3 months**
NRS (Waist)				
NRS (Leg)				
CSI				
BDI				

ODI				
PPT				
DN4				