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Effects of Caudal Epidural Dexmedetomidine on Pain, Erythrocyte Sedimentation Rate and Quality of Life in Patients with Failed Back Surgery Syndrome; A Randomized Clinical Trial

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ABSTRACT

Objective: To evaluate the effects of dexmedetomidine in caudal epidural on controlling pain, erythrocyte sedimentation rate (ESR) and quality of life in patients with failed back surgery syndrome (FBSS).
Methods: The study was a single-blind clinical trial. From the total of 70 patients suffering from low back pain caused by a failed back surgery syndrome were referred to Akhtar and Imam Hossein Hospitals between the ages of 25 to 75 years with a history of back pain more than 12 weeks and a visual analogue scale (VAS) score of higher than 3, and 50 people were randomly selected and divided into two groups of dexmedetomidine and control. The control group received an epidural dose of 10 cc containing triamcinolone and bupivacaine, and the dexmedetomidine group received an epidural dose of 10 cc, containing dexmedetomidine, triamcinolones and bupivacaine with diluted normal saline. Epidural caudal injections were performed in the abdomen in a laid down position. Before starting the study and at the end of the fourth week, the two test groups were measured for visual analogue scale (VAS) and ESR and were asked to complete the quality of life questionnaire.
Results: Overall, 50 patients with FBSS were enrolled. The mean age was 53.88±8.9 years (range 25–75); 54% (27/50) were men. The results showed that the injection of dexmedetomidine in epidural caudal was associated with decreased pain (p=0.001) and improved quality of life (p=0.022), while showed no significant effect on ESR (p=0.110).
Conclusion: Administration of dexmedetomidine in the epidural caudal is effective in controlling pain and quality of life in patients with failed back surgery syndrome.
Clinical Trial Registry: IRCT20181012041316N1

Keywords: Quality of life; Disability; Failed back surgery syndrome; Spinal cord.

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Introduction

Lower back pain is one of the most common and costly musculoskeletal disorders in the world and is a major problem in the world [1]. Studies in this area show that 60 to 80 percent of people experience back pain at least once during their life [2]. In the United States, every year, 176 million hours of efficient work is wasted due to lower back pain, and in the UK, the back pain is estimated to cause 480 million pounds of direct loss per year and 5 billion pounds of indirect loss to the economy [3]. In Iran, according to epidemiological studies, the prevalence of low back pain in the general population is reported to be 14.8% [4]. Approximately 80 to 90 percent of back pain cases recover after six weeks, but in 86 percent of cases they recur in the first year [5]. The cause of 85 percent of low back pain is never detected; in these individuals, even radiological findings do not indicate a specific cause for pain. These kind of back pains are classified as non-specific chronic low back pain (CLBP) [6].

There is a controversy in explaining the exact mechanism of how pain causes disability. The findings indicate that there is a high correlation between the perception of pain and disability, and the fear of repeated pain restricts the activity at different times. People who suffer from back pain experience disability in returning to their activities. Consequently, they have problems, both physically and mentally [7]. Lower back pain in adults can be appeared sudden or gradual by one or more strikes, and can be continuous, or can be occurred in particular kind of activities. It can also be exacerbated by physiological stress [8].

Following surgical manipulation of the spine and surrounding tissue, significant changes, especially in the epidural, occur, which reduces the response to epidural steroid injection. Another drug used in cases there is a possibility of fibrosis and adhesion in the epidural space was the hypertonic saline in different concentrations that is effective in controlling pain by creating neural block and increasing edema in nervous tissue and myelin of nerve membrane. Also, co-administration of hyaluronidase has also helped to improve the treatment process by removing adhesions and spreading the drug. In the study of Gurt (2002), the effect of adding this drug during epiduroscopy and in the study of Davolder (1999), the effect of adding this drug during the transforaminal block was evaluated [9, 10]. The results of both studies indicated improvement in pain control process in both methods after adding hyaluronidase.

Epidural injection of corticosteroids has advantages compared to systemic therapies by them, including: delivery of higher concentrations of the drug into the required and involved areas, while significantly reducing the systemic side effects of drugs [11]. Immediate administration of the drug at the pathology site will reduce the dose of the injectable drug [12]. Regarding that there are not much studies about the efficacy of epidural injections in relation to the dose of steroids in patients with failed back surgery, the aim of this study was to investigate the effect of dexmedetomidine in epidural caudal on controlling pain, Esr factor and quality of life in patients with a failed back surgery syndrome.

Materials and Methods

Study Population

The study was a single-blind clinical trial that was carried out after approving by the ethics committee of Shahid Beheshti University of Medical Sciences. From the total of 70 patients suffering from low back pain caused by a failed back surgery syndrome were referred to Akhtar and Imam Hossein Hospitals between the ages of 25 to 75 years with a history of back pain more than 12 weeks and a visual analogue scale (VAS) score of higher than 3, and 50 people were randomly selected. The sampling method was simple non-random. The criteria for entering the study included: the age range of 25 to 75 years old, suffering from disseminated back pain, previous history of spine surgery without a response to treatment that has showed dick involvement or stenosis of the spinal cord in MRI, and the positive straight leg raise test, having idiopathic low back pain with months' history, negative neurological and rheumatologic findings and lack of the ability to walk. Excluding criteria included included the absence of involvement of sacroiliac joints, lack of sensory and motor disorders, arachnoiditis, lack of spinal cord tumors, lack of severe heart disease and diabetes, obesity, addiction, infection and coagulation disease, pregnancy, kidney and liver disease, parathyroid and thyroid disorders, various types of disorders associated with calcium metabolism, sarcoidosis, of diuretics, heparin and anticonvulsants, malignancies and various types of mental disorders and dementia. Ethical Criteria in this study was approved with the approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences with the ethics code of IR.SBMU.RETECH.REC.1397.581 and was registered in Iranian Registry of Clinical Trials (IRCT20181012041316N1; www.irct.ir).

Randomization and Intervention

All eligible individuals were selected accordingly, in order to complete the sample. They were randomly divided into two groups of 25 patients with control and dexmedetomidine. To perform random allocation, a block of four was applied. Each patient in a block assigned to letters A, B, C, and D. The possible groups that could assign to dexmedetomidine group were AB, AC, AD, BC, BD, and DC. Then one number from 1-6 was selected at random, for assigning to dexmedetomidine group; for instance, if

number 5 was selected, number 2 would be allocated to the control group. In this study, patients were not aware which belonged to either of the control or case groups (single-blind). In the stage of performing the research, the aims of the study were explained to the patients. They were also assured that they could be excluded from the study whenever they no willing full, and this lack of cooperation with the physician and the hospital will not affect their treatment and all patient's information as will be kept confidential. All patients filled and signed the informed consent form for participation in the study.

Patients were randomly divided into two control and experiment groups after providing explanations about the treatment protocol and pain measurements based on the VAS scale. Before the onset of the study, subjects were asked to complete the quality of life questionnaire (SF 36). If the patient's VAS was equal to or greater than 4, he would receive 500 mg of acetaminophen. At first, a dose of 10 cc normal saline and a hyaluronidase was injected into caudal space for both groups. Then, the control group received an epidural caudal injection of 10 cc containing triamcinolone (80 mg) and bupivacaine (0.5 mg) diluted with normal saline. Also, the experiment group (dexmedetomidine) received 10 cc dexmedetomidine with the doses of 1 µg / kg, triamcinolone (80 mg) and bupivacaine (0.5 mg) diluted with normal saline into epidural caudal space. Epidural caudal injections were performed in the abdomen in a laid down position. Skin and subcutaneous tissues were numb with 5 cc lidocaine 1% injection in sacrum gap and needle no.22 was inserted approximately 2 to 3 cm in sacral cleft. Then, as mentioned above, the solution was injected depending on the group that patient was placed. VAS levels were measured before the injection and the fourth week. Also, patients were tested for ESR and also they completed the quality of life questionnaires.

Outcome Measures

Visual Analog Scale for Pain (VAS): This scale indicates the general pain of patients. This scale is plotted as a 10-cm line, and the pain range is graded as between 0 and 10 cm. The zero number does not show any pain, 1 to 3 mild pain, 4 to 6 average pain, and 7 to 10 severe pain [13]. The internal stability of this tool has been reported as 0.85 to 0.95 [14].

Quality of Life Questionnaire: A SF36 questionnaire was used to collect data. Many questionnaires have been invented for measuring quality of life, which the most famous one is the SF-36 quality of life questionnaire with 36 questions. It is containing 36 questions and consists of 2 scales of physical and mental health. Each scale has 4 sub-scales, and the questionnaire is generally composed of 8 sub-scales, each subscale is consisted of 2 to 10 items. The physical health subscale of this questionnaire is including: physical function (10 questions), role impairment due to physical health (4 questions), physical pain (7 items) and general health (4 questions). The mental health subscale of this questionnaire is including: emotional restriction (3 questions), energy/fatigue (4 questions), emotional health (5 questions) and social function (2 questions). In this questionnaire, lower scores represent lower quality of life and higher scores represent higher quality of life [15]. Validity and reliability of this tool in Iran was investigated by Ibrahimzadeh *et al*. and was validated in Farsi. Cronbach's alpha of this tool was estimated as 0.9 [16]. For analysis of the data, means, standard deviations, frequency, tables and charts were used to categorize and summarize the collected data.

Statistical Analysis

The sample size was determined to be 23 people with 95% confidence level, statistical power of 80%, and standard deviation observed. To obtain sample size, Cohen's formula was used as follows:

$$n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{ES} \right)^2$$

The data were analyzed by SPSS 22 software. Regarding demographic information of participants, descriptive statistics (mean, standard deviation, frequency, percentage) were calculated. The covariance and Shapiro-Wilk tests were used for analyzed variables and to evaluate the difference between groups. A 2-sided p-value of less than 0.05 was considered as significant.

Results

Overall we have evaluated a total number of 70 patients for eligibility, out of whom 50 randomly assigned to two study groups. All the patients finished the study and were included in the final analysis (Figure 1). There was no significant difference between the two study groups regarding the baseline characteristics. The baseline characterizes of the patients are summarized in the Table 1.

The results of Shapiro-Wilk test indicated normal distribution of the data (p=0.107). Covariance analysis was used for data analysis. Table 2 shows the results of covariance analysis for the comparison of quality of life, VAS score, and ESR with control of primary levels. Based on the data of this table, after the control of pre-test effect (η^2=0.022, F (1, 43)=0.945, p=0.336), the effect of the group on the VAS scale was statistically significant (η^2=0.876, p=0.001, F (1, 43)=303.098), meaning that there is a significant difference between the VAS of the dexmedetomidine and the control groups in the post-test. It could be stated that the pain level of the experimental group decreased significantly by the use of dexmedetomidine injection. After controlling the pre-test effect (η^2=0.013, P=0.456, F (1, 43)=0.565,

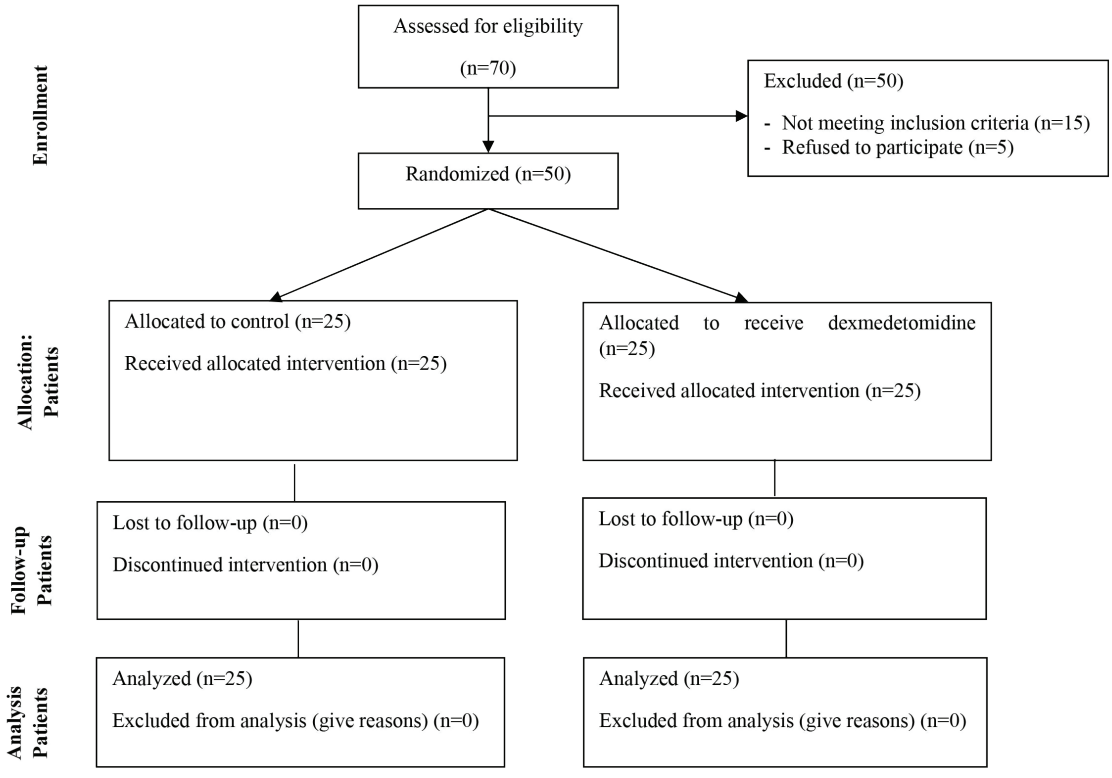

Fig. 1. Modified CONSORT flow diagram of the study.

Table 1. Baseline characteristics of the 50 patients with failed back surgery syndrome in two study groups

	Dexmedetomidine (n=25)	Control (n=25)	*p*-value
Age (years)	54.3±9.2	53.47±8.7	0.731
Gender			
Men (%)	13 (26%)	14 (28%)	0.172
Women (%)	12 (24%)	11 (22%)	
Mean Baseline VAS	7.2±4.6	7.1±2.3	0.582

Table 2. The outcome measures of the 50 patients with failed back surgery syndrome randomized to two study groups

	Dexmedetomidine (n=25)	Control (n=25)	*p* value
VAS[a]			
Pretest	5.47±0.12	5.56±0.13	0.336
Posttest	2.56±0.1	5.21±0.1	0.001
ESR[b]			
Pretest	44.13±1.1	43.78±1.13	0.456
Posttest	45.3±0.81	42.75±1.1	0.110
Quality of life[c]			
Pretest	71.43±0.21	71.56±0.22	0.248
Posttest	74.43±0.72	72.08±0.34	0.022

[a]VAS: Visual Analogue Scale; [b]ESR: Erythrocyte Sedimentation Rate

the effect of the group on the ESR was not statistically significant (η^2=0.058, p=0.11, F (1, 43)=2.668). After controlling the pre-test effect (η^2=0.031, p=0.248, F (43.1)=1.371), the effect of the group on the quality of life scale was statistically significant (η^2=0.116, p=0.022, F (43,1)=5.626), meaning that there is a significant difference between the quality of life of the dexmedetomidine and control groups in the post-test. It can be stated that the quality of life of the experimental group has significantly improved with the use dexmedetomidine injections.

Discussion

The aim of this study was to evaluate the effect of dexmedetomidine injection in caudal epidural on controlling pain, Esr factor and quality of life in patients with failed back surgery syndrome. The

results of this study showed that the administration of dexmedetomidine in the epidural caudal reduced pain and improved the quality of life of patients, while there had no significant effect on ESR. Due to the fact that dexmedetomidine tend to bind to adrenergic alpha 2 receptors, it is widely used as a pain reliever [17]. In addition, dexmedetomidine have been studied as an auxiliary anesthetic drug [18, 19]. Since the analgesic effect of AR-2α agonist is common in the spinal cord, its neuroxalial application is also used. Additionally, the high lipophilic property allows rapid absorption into the cerebrospinal fluid and binding to AR-2 α [20]. In many studies, doses of 1-2 µg/kg have been injected epidural [21-23] and caudal to manage postoperative pain [19, 24-26]. In the present study dexmedetomidine doses of one µg / kg were prescribed epidural.

The findings indicated a significant reduction in pain and improvement of quality of life in patients with failed back surgery syndrome. These findings were in consistent with the results of studies that used dexmedetomidine for the treatment of chronic pain syndrome [27-30]. Jane *et al*., [28] for example, found that pre-operative dexmedetomidine injection had an important role in reducing the severity of chronic pain and improving the quality of life in breast cancer surgery cases. Nama Sherania (2010) confirmed the use of dexmedetomidine injected with intravenous ketamine in managing pain syndrome. The findings also were in consistent with the results of Lee *et al*. who studied the analgesic effects of dexmedetomidine on neuropathic pain, [30] and the results of Forgali *et al*. who studied the effects of intraperitoneal doses of dexmedetomidine alone and in combination with tramadol or amitriptyline in a model of neuropathic pain [31]. Aghamohammadi *et al*. showed that epidural injection of combination of bupivacaine and dexmedetomidine can provide better control of pain in the rib fracture in patients and is an appropriate alternative to bupivacaine [32].

The results of this study were similar to other studies that used other clonidine AR - 2 α agonist as epidural in controlling chronic pain. For example, Lundhom and De Cook (2006) found that epidural or intrathecal clonidine that has been added to topical anesthetics may prevent chronic postoperative pain and hyperalgesia after major abdominal surgery [33]. Loretti *et al*. reported the similar efficacy of epidural clonidine and ketamine in cancer chronic pain [34]. Ayad and El Masry (2012) found in a preliminary study that a combination of epidural steroids and clonidine may reduce pain after chronic thoracotomy [35].

There are several limitations in our study. We did not use a placebo group for ethical concerns and our study duration was limited to 24 hours postoperatively. It seems better to design future studies to compare 1) comparing doxedetomidine to placebo, 2) to test different doses of this drug. In conclusion, the present study showed that the administration of dexmedetomidine in epidural caudal was effective in controlling pain and quality of life of patients with failed back surgery syndrome.

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Conflicts of Interest: None declared.

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