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The impact of vitamin D deficiency on treatment success of cervical interlaminar epidural steroid injection

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ABSTRACT

Objective: Our aim is to investigate the effect of vitamin D deficiency on treatment success of cervical interlaminar epidural steroid injection (ILESI) in patients with cervical disc herniation-related chronic radiculopathy.

Patients and Methods: Fifty patients who had neck and unilateral extremity pain and received cervical ILESI were included. The patients were divided into two groups according to their serum 25 (OH) D levels as Group 1 (>20 ng/mL) and Group 2 (<20 ng/mL). Clinical and demographic data, magnetic resonance imaging (MRI) scans, pre-procedural laboratory tests, and pain scores were recorded. The patients were assessed before procedure and at three and six months after procedure.

Results: Mean serum 25(OH)D level was 29.49±10.9 in Group 1 and 12.06±3.49 in Group 2, indicating a statistically significant difference ($p<0.001$). A significant improvement in pain scores was observed in both groups at six months of follow-up ($p<0.001$). Treatment success rates were significantly lower in vitamin D-deficient group at three months ($p=0.024$), while there was no significant difference between the groups at six months.

Conclusions: Vitamin D level is a factor affecting short-term treatment success in patients undergoing cervical ILESI.

Keywords: Vitamin D deficiency, Cervical radiculopathy, Neck pain, Epidural injection

1. INTRODUCTION

Cervical radicular pain is defined as pain perceived in the upper limb and/or neck caused by irritation or injury of a cervical spine nerve [1] . Its annual incidence varies from 0.83 to 1.79/1,000 adults [2]. The most common causes of cervical radicular pain include cervical disc herniation and/or spinal stenosis. The first-line treatment is conservative with activity modification, medical treatment, physical therapy modalities, and exercises. In unresponsive cases, cervical interlaminar epidural steroid injections (ILESIs) are frequently used as an alternative treatment option before surgey [3].

There are several studies demonstrating that cervical ILESIs are effective and safe in the long-term management of cervical disc herniation-related chronic cervical radiculopathy [3-5]. Success of the treatment depends on various factors such as duration of symptoms, concomitant foraminal and central spinal stenosis, level of disc herniation, presence of possible neuropathic pain components, and coexisting central sensitization; however, there is still an ongoing debate regarding the exact role of aforementioned factors in the etiology of cervical radicular pain, which brings to mind the thought that there may be other clinical parameters that have not been the subject of research in identifying the patient group that would benefit from the treatment [5,6].

25-hydroxy vitamin D (25(OH)D) deficiency is associated with various skeletal disorders and chronic painful conditions [7]. Previous studies have shown that serum vitamin D levels are significantly lower in patients with chronic neck pain [8]. However, the exact physiological mechanism underlying

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vitamin D deficiency-related pain is still unclear. Vitamin D exerts anti-inflammatory effects by reducing the release of proinflammatory cytokines and inhibiting T-cell responses [7]. *In vitro* studies have demonstrated that vitamin D inhibits prostaglandin E2 (PGE2) synthesis [9]. Both observational and interventional studies have suggested that vitamin D plays a key role in the pain intensity and pain management in various clinical settings [10,11]. Therefore, concomitant low vitamin D levels may induce more inflammatory reaction around the spinal nerve root and dorsal root ganglion, implicating in the etiopathogenesis of disc herniation-related radicular pain.

In our knowledge, there is no study investigating the role of 25(OH)D levels on treatment success of ILESIs in patients with cervical disc herniation-related chronic radiculopathy in the literature. In the present study, we hypothesized that vitamin D deficiency could adversely affect the treatment success of ILESIs in this group of patients by increasing the proinflammatory response. We, therefore, aimed to investigate the role of vitamin D levels on treatment success of ILESIs in patients with cervical disc herniation-related chronic radiculopathy.

2. PATIENTS and METHODS

Study Design and Study Population

This single-center, retrospective study was conducted at Pain Management Center of a tertiary care center between January 2020 and January 2021. The patients who had axial neck and unilateral radicular extremity pain for at least three months and were diagnosed with protruded disc herniation by magnetic resonance imaging (MRI) were screened using the hospital database. To acquire a homogeneous group, we searched a total of 312 patients between 18 and 65 years of age who underwent fluoroscopy-guided C7-T1 cervical ILESI. Patients with metabolic diseases (*e.g.*, hyperparathyroidism, hypoparathyroidism, hyperthyroidism, hypothyroidism, diabetes mellitus), having a history of cervical surgery, multilevel disc herniation, cervical spinal stenosis, and/or those with missing MRI, demographic, and clinical data and pre-procedural laboratory tests, including serum 25(OH)D levels were excluded from the study. Finally, a total of 50 patients who met the inclusion criteria were recruited. Clinical and demographic data, symptom duration, serum 25(OH)D levels, pre – and post-injection, three – and six-month Numerical Rating Scale (NRS) pain scores, painkiller use (paracetamol, non-steroidal anti-inflammatory drugs and opioids), chronic disease (disease other than metabolic diseases), and patients who underwent surgery after injection were noted. The patients were divided into two groups according to their serum 25(OH)D levels as Group 1 (>20 ng/mL) and Group 2 (<20 ng/mL). NRS was used for measuring pain intensity. It is expressed between 0 and 10. Zero means no pain, 10 means the most severe pain. A decrease of 50% or more in the NRS pain scores was defined as treatment success in the follow-up.

All patients were informed about the possible diagnostic and therapeutic procedures and a written informed consent was obtained. The study protocol was approved by the Marmara University School of Medicine Clinical Researches Ethics Committee (Date: 12/13/2021 Number: 09.2021.1390). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Injection Technique

The patient was placed in the prone position and cutaneous anesthesia was performed with 3 mL of 2% prilocaine using sterile technique. After imaging the C7-T1 space with fluoroscopy, we entered from the right/left paramedian part of the C7-T1 space with an 18-gauge Tuohy needle, and the C-arm was set in the contralateral oblique position to determine the depth of the needle. Under intermittent fluoroscopic imaging, the needle was advanced, and access to the epidural space was confirmed by the loss of resistance technique. The epidural spread was, then, verified with a contrast agent, and a mixture of 10 mg of dexamethasone, 1 mL of 2% lidocaine hydrochloride, and 1 mL of 0.9% saline was applied to the epidural space. The patient was discharged with recommendations after being kept under observation for 2 hours following the procedure. All injections were performed by a single pain medicine specialist who had at least 10 years of experience.

Statistical Analysis

According to a study by Ozturk et al., based on the relationship between pain and epidural treatment success at the third month the sample size should be 47 to achieve a 95% confidence interval and 90% power [11]. Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or number and frequency, where applicable. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the normal distribution of quantitative data. For the comparison of non-normally distributed data, the Mann-Whitney U test was used, while the independent t-test was used to compare normally distributed data. The chi-square test was used to measure the inter-group differences in data on treatment success, chronic disease history, use of painkillers, and post-treatment surgical procedures. The changes over time with treatment for non-normally distributed data was determined by Friedman test. A p value of <0.05 was considered statistically significant.

3. RESULTS

Of a total of 50 patients included in the study (Figure 1), 16 were males and 34 were females with a mean age of 48.40 (29-65) years. Group 1 included 24 patients and Group 2 included 26 patients. The mean serum 25(OH)D level was 29.49±10.9 in Group 1 and 12.06±3.49 in Group 2, indicating a statistically significant difference (p<0.001). The ILESI procedure was applied to all patients at the C7–T1 level, and no major complications were observed. There was no significant difference between the two groups in terms of sociodemographic and clinical characteristics such as age, sex, history of chronic diseases, body mass index,

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and symptom duration. In addition, there was no significant difference between the two groups in terms of undergoing surgery and painkiller use after treatment (Table I).

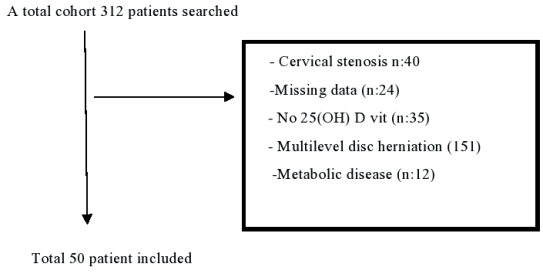

Figure 1. *Flow chart*

The pre-treatment NRS scores of Group 1 and Group 2 were 8.41±1.21 and 8.19±0.98, respectively, indicating no significant difference between the two groups (p>0.05) (Table I). However, at three months, 16 patients (67%) in Group 1 and nine patients (35%) in Group 2 achieved treatment success, indicating a significant difference between the two groups (p=0.024). On the other hand, there was no significant difference in the NRS scores of patients at six months (p>0.05) (Table II). In addition, there was a significant improvement in pain scores in all patients at three and six months compared to pre-treatment scores (Table III).

Table I. *Comparison of demographic and treatment characteristics of the groups*

Variable		Group 1 (n=24)	Group 2 (n=26)	P value
Vitamin D level (ng/mL)*		29.49 ± 10.91	12.06 ±3.49	**< 0.001** *
Age (years)		51.71 ± 10.86	45.35 ± 12.23	0.058 **
BMI (kg/m^2)		25.21 ± 3.39	26.14 ± 3.54	0.257*
Pre-treatment NRS		8.41 ±1.21	8.19 ±0.98	0.321 *
Symptom duration (month)		11 (3 – 48)	10 (3 – 48)	0.452**
Sex	Male	10 (41%)	6 (23%)	
	Female	14 (59%)	20 (77%)	0.159 ***
Chronic diseases	Yes	16 (66%)	7 (27%)	
	No	8 (34%)	19 (73%)	0.050 ***
Painkiller use	Yes	8 (34%)	10 (38%)	
	No	16 (66%)	16 (62%)	0.706 ***
Post-treatment surgery	Yes	1 (4%)	1 (4%)	
	No	23 (96%)	25 (96%)	0.954 ***

*Data are given in mean ± standard deviation or number and %, unless otherwise stated. BMI: body mass index, NRS: Numerical Rating Scale, Group 1: serum 25(OH)D >20 ng/mL, Group 2: serum 25(OH)D <20 ng/mL. *Independent t test; **Mann-Whitney U test; ***Chi-square test.*

Table II. *Comparison of groups in terms of treatment success*

Variable	Group 1 (n=24)	Group 2 (n=26)	P value
Month3			
Yes (n = 25)	16 (67%)	9 (35%)	
			0.024
No (n = 25)	8 (33%)	17(65%)	
Month6			
Yes (n = 19)	9 (38%)	10 (38%)	
			0.944
No (n = 31)	15 (62%)	16 (62%)	

Chi-square test, Group 1: serum 25(OH)D >20 ng/mL, Group 2: serum 25(OH) D <20 ng/mL.

Table III. *Changes in NRS scores over time*

	Mean±SD	P value
Group 1-NRS Pre[1]	8.41 ± 1.21	
Group 1-NRS Month 3[2]	4.00 ± 2.62	<0.001[a]
Group 1-NRS Month 6[3]	5.00 ± 2.52	
Group 2-NRS.Pre[1]	8.19 ± 0.98	
Group 2-NRS Month 3[2]	4.92 ± 3.30	<0.001[b]
Group 2-NRS Month 6[3]	5.42 ± 3.27	
Total NRS Pre[1]	8.30 ± 1.09	
Total NRS Month 3[2]	4.48 ± 3.01	<0.001[c]
Total NRS Month 6[3]	5.22 ± 2.97	

aPost-hoc tests: 1-2, 1-3, 2-3, significant;bPost-hoc tests: 1-2, 1-3, significant ;cPost-hoc tests: 1-2, 1-3, significant;; Pre: before the procedure, Group 1: serum 25(OH)D >20 ng/mL, Group 2: serum 25(OH)D <20 ng/mL. NRS: Numerical Rating Scale.

4. DISCUSSION

In the present study, we investigated the role of vitamin D levels on treatment success of ILESIs in patients with cervical disc herniation-related chronic radiculopathy. Our study results showed that the mean serum 25(OH)D levels were significantly lower in Group 2 than Group 1. Considering a decrease of 50% or more in the NRS pain scores compared to baseline as treatment success, 16 patients (67%) in Group 1 and nine patients (35%) in Group 2 achieved treatment success at three months, indicating a significant difference between the two groups. These findings suggest that low 25(OH)D levels may adversely affect the treatment success of ILESIs in patients with chronic cervical radiculopathy. The lack of a significant difference in the six-month measurements between the groups indicates that these effects are short-term effects in this patient population.

The exact physiological mechanism underlying vitamin D deficiency-related pain has not been elucidated yet. Both animal and clinical studies have demonstrated that vitamin D deficiency affects peripheral and parasympathetic nervous system [12,13]. Besides vitamin D receptors and vitamin D-activating enzymes in the central nervous system, the effects of vitamin D on neurotransmitters have been studied to examine the possible relationship between pain and vitamin D deficiency in patients with fibromyalgia [14]. However, the most

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likely mechanism which explains the role of vitamin D in pain management is associated with its anti-inflammatory effects [7]. In case of vitamin D deficiency, the immune system favors a more inflammatory immune response involving Th1 and Th17 cells rather than Th2 and regulatory T cells (Tregs) [15]. On the contrary, adequate vitamin D levels results in less inflammation and lower levels of inflammatory cytokines and prostaglandins [16]. *In vitro* studies have demonstrated that vitamin D inhibits the PGE2 synthesis in fibroblasts [9]. In a study, vitamin D supplementation decreased musculoskeletal pain and was found to be associated with reduced inflammatory cytokine levels including PGE2 [17]. In the current study, the lower treatment success in the patients with low vitamin D levels in the short term can be attributed to the proinflammatory contribution of low vitamin D level to radiculitis due to cervical disc herniation in these patients.

Although, there are several studies investigating the effects of vitamin D level on postoperative outcomes in patients undergoing spinal surgery, only one study is available in the literature evaluating the role of vitamin D level in the success of interventional pain management [11,18]. In their study, Ozturk et al., investigated the effect of vitamin D deficiency on treatment success of fluoroscopy-guided transforaminal epidural steroid injection in patients with lumbar disc herniation-related chronic radiculopathy [11]. The treatment success was significantly lower in the patients with low vitamin D levels at three weeks and three months of follow-up. Our study included patients with cervical disc herniation-related chronic radicular pain and cervical ILESI was applied. At three months of follow-up, the treatment success was significantly lower in the patients with low vitamin D levels, consistent with the aforementioned study [11]. However, we observed no significant difference in the treatment success at six months between the groups. This can be attributed to the decrease in the long-term anti-inflammatory effect of cervical ILESI in both groups which had comparable pain scores at baseline.

Despite a high number of studies showing that cervical ILESI is effective and safe in the long-term treatment of chronic radiculopathy, consistent with our study findings, debates regarding which parameters are predictive for treatment success still continue [19,20]. In their study, Celenlioglu et al., investigated the predictors of treatment success at six months after cervical ILESI administration and concluded that severe foraminal and central spinal stenosis was the main predictor of poor treatment outcomes [5]. In another study, Oh et al., evaluated predictors of treatment success in the short term (2 to 3 weeks) after cervical ILESI administration [3]. The authors reported that spinal stenosis, prolonged symptom duration, and neuropathic pain were predictors of poor treatment outcomes. Unlike these studies, we excluded patients with foraminal and central spinal stenosis. In addition, we observed no significant difference in the symptom duration between the groups in our study. Also, we were unable to assess neuropathic pain components and central sensitiziation in our study, which may explain the lack of a significant difference in treatment success in the long term in both groups. In the literature, the effect of vitamin D on nociceptive and inflammatory pain are well documented; however, there is a limited number of data regarding its effect on neuropathic pain [17,21].

Nonetheless, there are some limitations to this study. First, the study has a single-center, retrospective design. Second, we were unable to evaluate quality of life and functional status of patients. Third, serum 25(OH)D levels were not high enough to be categorized. On the other hand, a serum 25(OH)D level of 20 ng/mL was defined as vitamin D deficiency, which was significantly lower compared to the other group. This allowed us to evaluate the effect of vitamin D on the treatment success of cervical ILESI. Despite all these limitations, to the best of our knowledge, this is the first study to investigate the effect of vitamin D on treatment success with cervical ILESI. With a specific population and long-term results, we believe that it provides a valuable contribution to the body of knowledge in the literature on this subject.

In conclusion, low serum 25(OH)D level before cervical ILESI administration should be considered a factor which may reduce the treatment success in the short term in patients with cervical disc herniation-related chronic radiculopathy. Therefore, evaluation of serum 25(OH)D levels before the procedure and its replacement, if necessary, may be associated with the increased treatment success after cervical ILESI. However, further large-scale, multi-center, prospective studies are warranted to gain a better understanding of the effect of 25(OH)D on treatment success in this patient population.

Compliance with Ethical Standards

Ethical approval: The study protocol was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Date: 12/13/2021 Number: 09.2021.1390). All patients were informed about the possible diagnostic and therapeutic procedures and a written informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Authors contributions: SS: Conceived and designed the analysis, made the research and prepared the original draft, AZD, OA, BD and MA : Collected the study data, RS: Performed data analysis with contributed analysis tool, OHG: Supervisor – reviewed the draft, OHG: Supervisor – reviewed and edited the draft. All authors approved the final version of the article to be published.

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