Retrospective Assessment

The Impact of Vitamin D Deficiency to Treatment Success of Transforaminal Epidural Steroid Injection

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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 10-31-2020
Revised manuscript received: 12-09-2020
Accepted for publication: 01-08-2021

Free full manuscript: www.painphysicianjournal.com

Background: Transforaminal epidural steroid injection (TFESI) is an interventional technique used to relieve disc herniation related back and radicular pain. Although few studies have investigated the factors predicting positive outcomes after TFESI, there is no data concerning the possible relationship between pre-procedure serum 25-hydroxyvitamin D (25(OH)D) levels and the response to TFESI.

Objectives: To investigate the effect of vitamin D deficiency to treatment success of fluoroscopy-guided transforaminal epidural steroid injection.

Study Design: A retrospective assessment.

Setting: A university hospital interventional pain management center.

Methods: Nine hundred forty-eight patients received lumbosacral TFESI between January 2018 and December 2019 in a university hospital pain management center and were examined retrospectively for eligibility. Clinical and demographic data; magnetic resonance imaging (MRI); pre-procedure laboratory tests, including serum 25(OH)D; pain scores at baseline, third week, and third month follow-ups were collected.

Results: A total of 83 patients were recruited and divided into 2 groups with respect to vitamin D status. The number of patients with serum 25(OH)D level below 20 ng/mL was 57 and the number of patients with serum 25(OH)D level above 20 ng/mL was 26. Treatment success rates were significantly lower in vitamin D deficient group at third week and third month (P: 0.006, P: 0.01).

Limitations: Retrospective nature and the absence of functional outcomes.

Conclusion: Vitamin D deficiency is associated with a lower probability of meaningful pain relief following TFESI. It may worth assessing serum vitamin D level prior to this intervention, although prospective investigation is necessary.

Key words: Lumbar disc herniation, vitamin D deficiency, transforaminal epidural steroid injection, treatment success

Pain Physician 2021: 24:E619-E624

Transforaminal epidural steroid injection (TFESI) is a widely performed, interventional treatment for disc herniation related back and radicular pain. Therapeutic effects are thought to be due to anti-inflammatory features of steroids. Herniated disc can trigger pain via mechanical compression of the nerve root or inflammation induced by cytokines. TFESI is a target-specific technique delivering medication to the ventral epidural site, where pathological alterations occur. In addition to reduction of inflammation, TFESI

also improves ischemic neuritis by enhancing blood flow to nerve roots. It is also assumed to block nociceptive transmission through nerve fibers (1-3). While severity of nerve root compression and duration of symptoms are the suggested factors to predict outcomes after TFESI, there is limited and controversial data regarding parameters associated with treatment success (4-7).

Vitamin-D is a lipophilic molecule and hormone which has crucial functions in bone, muscle, and cartilage metabolism. The function of vitamin-D is meditated by vitamin-D receptors (VDR). Vitamin-D deficiency may lead to many skeletal pathologies and various chronic painful conditions, such as chronic low back pain (LBP). Furthermore, low concentration of serum 25-hydroxyvitamin D (25(OH)D) and polymorphisms in the VDR gene are shown to be related with lumbar disc disease, which is the main cause of chronic LBP (8-10). Although its predisposing effects in degenerative disc disease are investigated, the impact of deficient serum 25(OH)D to interventional treatment outcomes needs to be elucidated. Therefore, in the present study we aimed to identify the association between pre-procedure serum 25(OH)D levels and treatment success of fluoroscopy-guided TFESI for single level lumbar disc herniation (LDH). As far as we know, there has not been any study with regard to this possible relationship.

Methods

After approval by our ethics committee, we performed a retrospective review of patients who received lumbosacral TFESI between January 2018 and December 2019, in our university hospital pain management center. To acquire a homogeneous group, we included patients between 18 and 65 years of age, who had undergone fluoroscopy-guided single level unilateral TFESI due to paracentral/subarticular lumbar disc herniation, and who also completed 3 week and 3 month follow-up periods. Patients with metabolic diseases (hyperparathyroidism, hypoparathyroidism, hyperthyroidism, hypothyroidism, diabetes mellitus, etc.); post-laminectomy syndrome; foraminal disc herniation; spinal stenosis; multilevel disc herniation; multilevel spinal root compression; and/or whose magnetic resonance imaging (MRI), demographic, and clinical data and pre-procedure laboratory tests, including serum 25(OH)D, were lacking in the medical records system, were excluded.

Patients were divided into 2 groups with respect to whether serum 25(OH)D is below or above 20 ng/mL. Serum 25(OH)D levels of at least 20 ng/mL (50 nmol/liter) are believed to cover the requirements of 97.5% of the population, so in the present survey we selected 20 ng/mL serum level as a cut-off (11). Pain scores derived from Numeric Rating Scale (NRS-11) at baseline, third week and third month were collected.

The classification system described by Pfirmann et al (12), which assesses the severity of nerve root compression using MRI, was implemented by a neuroradiologist. In this system grade 1 defines the disc as slightly in contact with the nerve root, grade 2 refers to a nerve root that is displaced but periradicular cerebrospinal fluid (CSF) is preserved, grade 3 indicates periradicular CSF, or adipose tissue, is erased, and in grade 4 the nerve root is morphologically affected. T2-weighted axial images were used for areas where the cerebrospinal fluid and nerve roots passed from the thecal sac to the inner region of the intervertebral foramen. T1-weighted axial images were used to evaluate adipose tissue around the root in the lateral recess and foramen. In this classification, grade 1 and 2 are classified as low, while grade 3 and 4 as high-grade compression (12).

We determined a reduction of 50% or more in NRS-11 scores at follow-ups, when compared to the baseline, as a successful outcome on the basis of previous reports (13). In addition, a reduction of 2.5 units or more was considered to be minimal clinically important change (MCIC) (14). The symptom duration of the patients was also noted.

Procedure

The patient was transported to the procedure suite and positioned prone on the fluoroscopic table with a pillow under the patient's abdomen to reduce the patient's lumbar lordosis. All pressure points were checked and padded appropriately. The patient's lower back was sterilely prepped with povidone iodine and sterile drapes were applied. Firstly, C-Arm was positioned to produce a true AP image, to determine the correct level, then placed at an optimal angle so that the relevant foramen could be clearly visualized. A 22-gauge 3.5-inch spinal needle was advanced to the subpedicula area to achieve epidural access and the lateral image was also obtained to avoid further advancement. One mL of contrast dye was given to check epidural dispersion prior to the injection of a mixture of dexamethasone (12 mg), 0.5% bupivacaine (1 mL), and saline (1 mL). All injections were performed by an interventional pain specialist with at least 10 years of experience. Patients were monitored for 1 hour after

the procedure and discharged to be evaluated at control visits.

Statistical Analysis

Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze normal distribution of quantitative data. For the comparison of non-normally distributed data, the Mann-Whitney U was used, while the independent t-test was used to compare normally distributed data. A *P* value of < 0.05 was considered statistically significant.

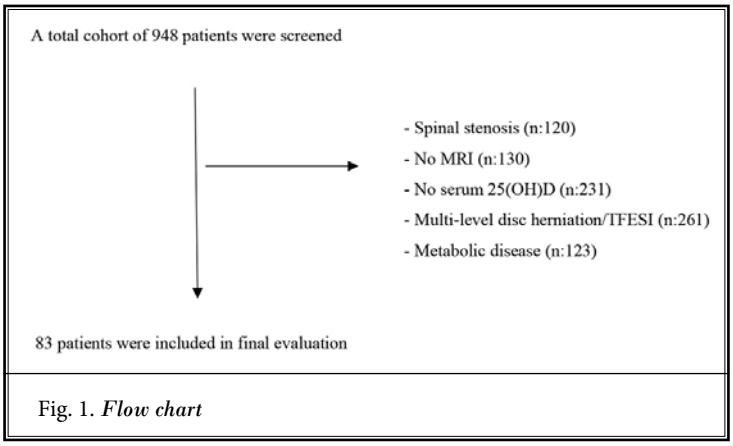

Fig. 1. *Flow chart*

Results

Finally, a total of 83 out of 948 patients met the inclusion and exclusion criteria (Fig. 1). The number of patients with deficient serum 25(OH)D level was 57 (denominated as first group), and the number of patients with serum 25(OH)D above 20 ng/mL was 26 (denominated as second group). The mean serum 25(OH)D levels of the groups were 13.8 ± 3.4 and 33.0 ± 2.9 respectively, where a significant difference was found (*P* < 0.001). There was no difference between the groups in terms of age, gender, BMI, symptom duration, or severity of nerve root compression, but pretreatment NRS-11 scores were significantly higher in the first group (*P*: 0.02) (Table 1). By the third week, the number of patients with treatment success defined as ≥ 50% improvement in NRS-11 scores were 33 (57%) in the first group and 23 (88%) in the second group, indicating a significant difference between the groups (*P*: 0.006). At the third month follow-up, the difference remained significant with treatment success rates of 46% (26 out of 57) and 81% (21 out of 26) respectively (*P*: 0.01) (Table 2). When the groups were analyzed with respect to MCIC the difference was also significant for both follow-up periods. At the third week follow-up, 39 (68%) patients in the first group and 23 (88%) patients in the second group had 2.5 or more units improvement in NRS-11scores (*P*: 0.049). At the third month follow-up, it was 33 (57%) and 23 (88%) respectively (*P*: 0.006) (Table 3).

Table 1. *Comparison of demographic, clinical and radiologic features*

	Group 1 (n = 57)	Group 2 (n = 26)	*P*
Serum 25(OH)D level	13.8 ± 3.4	33.0 ± 12.9	0.000*
Age (Years)	42.01 ± 13.2	46.8 ± 16.8	0.171*
BMI (kg/m^2)	26.8 ± 3.4	28.3 ± 4.3	0.091*
Pretreatment NRS-11	8.29 ± 1.2	7.4 ± 1.6	0.02**
Nerve root compression			
Low grade (1-2)	30 (53%)	14 (54%)	0.918***
High grade (3-4)	27 (47%)	12 (46%)	
Symptom duration (months)	9.3 ± 10.4 (5.0)	12.4 ± 13.7 (4.0)	0.321*

Values are presented as mean ± standard deviation (median), or n (%).
BMI: body mass index, NRS-11: Numeric 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 2. *Comparison of treatment success rates between groups*

	Group 1 (n = 57)	Group 2 (n = 26)	*P*
3rd week treatment success			
Yes (n = 56)	33 (57%)	23 (88%)	0.006*
No (n = 27)	24 (42%)	3 (12%)	
3rd month treatment success			
Yes (n = 47)	26 (46%)	23 (81%)	0.01*
No (n = 36)	31 (54%)	3 (19%)	

Values are presented as n (%).
Group 1: serum 25(OH)D < 20 ng/mL, Group 2: serum 25(OH)D > 20 ng/mL.
* Chi-square test

Discussion

In the current study, our main focus was to investigate the effect of pre-procedure serum 25(OH)D levels on pain scores after fluoroscopy-guided single level unilateral lumbosacral TFESI. Pretreatment NRS-11 scores of vitamin-D deficient patients were significantly higher. Similarly, third week and third month follow-

Table 3. *Comparison treatment response rates with respect to minimal clinically important change between groups*

	Group 1 (n = 57)	Group 2 (n = 26)	*P*
3rd week MCIC			
Yes (n = 62)	39 (68%)	23 (88%)	0.049*
No (n = 21)	18 (32%)	3 (12%)	
3rd month MCIC			
Yes (n = 56)	33 (57%)	23 (88%)	0.006*
No (n = 27)	24 (43%)	3 (12%)	

Values are presented as n (%).
MCIC: minimal clinically important change
Group 1: serum 25(OH)D < 20 ng/mL, Group 2: serum 25(OH)D > 20 ng/mL.
* Chi-square test

ups showed treatment success rates in the same group were lower, in contrast to those with acceptable serum 25(OH)D. The differences between the groups at the same follow-up periods were also significant with respect to MCID. To the best of our knowledge this is the first study to reveal an association between pre-procedure serum 25(OH)D levels and treatment response to TFESI.

Vitamin-D is crucial for a healthy skeleton and plays a key role in various processes in our body. It regulates the immune system, via inducing antimicrobial peptides, which generates the first barrier on mucosal surfaces. On the other hand, vitamin-D switches T helper cell response from Th1 to Th2 and decreases inflammatory Prostaglandin E2 levels. In consequence, vitamin-D deficiency leads to an excessive inflammatory response and is considered to be a risk factor for autoinflammatory diseases and chronic pain syndromes (15,16).

There have been a reasonable number of surveys focusing on the relationship between LBP and vitamin-D deficiency. Pishgahi et al, demonstrated low serum 25(OH)D concentration among patients with LBP in a case-control observational study. A randomized prospective study of Lakkireddy et al, which included 84 patients suffering from mechanical LBP, noted hypovitaminosis D can be a potential reason for LBP and supplementation of vitamin D may provide significant pain relief and functional improvement (17). On the contrary, Zadro et al, postulated in their systematic review and meta-analysis that vitamin-D may not be more effective than placebo for LBP (18). Another meta-analysis also revealed high prevalence of hypovitaminosis D in LBP patients (19). A remarkable molecular study from Poland addresses a potential mechanism underlying how hypovitaminosis D deteriorates LBP. Dzik et al, established higher oxidative stress and increased antioxidant enzyme activity in multifidus muscle samples of LBP patients deficient in serum 25(OH)D. Although the causative relationship is still debated, with the current evidence, increased oxidative stress and inflammation, muscle atrophy and reduced mitochondrial activity are the most reasonable explanations to the link between hypovitaminosis D and LBP (20-22). Moreover, hypovitaminosis D was indicated to influence spinal surgery outcomes adversely. In their systematic review Kerezouidis et al, found significant relevance between deficient serum 25(OH) D and worsened quality of life and functionality after spinal fusion surgery, which were improved together with LBP intensity after postoperative supplementation (23). When it comes to the impact of hypovitaminosis D on success rates after interventional spine procedures there is paucity of data in the literature. As a result, we inquired about whether pre-procedure serum 25(OH) D levels had altered treatment success of lumbosacral TFESI performed between January 2018 and December 2019 in a university hospital pain clinic.

Factors associated with treatment outcomes after lumbar TFESI are investigated in a few surveys. While Ekedahl et al, claimed that younger age, short duration of leg pain, high grade nerve compression, central/subarticular disc herniation may predict a favorable response, Ghahreman et al, reported that low grade nerve root compression is the only radiologic feature that foresees higher success rates (5,7). None of these publications found any relationship between clinical features and response to TFESI. Furthermore, McCormick et al, concluded that greater baseline pain scores, a history of a lack of worsening pain with walking, and positive provocative maneuvers for nerve root testing predict a positive likelihood of pain reduction following lumbar TFESI (24). Conversely, in our study population, baseline pain scores were significantly higher in patients with low serum 25(OH)D levels. Symptom duration, severity of nerve root compression, and location of disc herniation (subarticular/paracentral for all subjects), which might otherwise have confounded our results, were similar between patients with deficient and acceptable serum 25(OH)D. Social insurance, depressive status, and lifting requirement at work may also impact outcomes, which could not be evaluated due to retrospective design of this investigation (25,26). For this reason, better pain relief after TFESI can be moderately attributed to the difference in serum 25(OH)D levels.

Even so, evaluation of serum 25(OH)D levels before the procedure and supplementation in case of deficiency might enhance treatment outcomes.

Given the negative effects of glucocorticoids on bone mineral density (BMD), administration of steroids into the epidural space may elicit osteoporosis and vertebral fractures. Research has yielded that a cumulative methylprednisolone dose of 200 mg via epidural route over a 1 year period reduces BMD (27). Consequently, determining hypovitaminosis D before epidural steroid injections, may also be beneficial for lowering the risk of osteoporosis.

Limitations

Retrospective design and the absence of functional outcomes are the important limitations of this study. Besides the previously mentioned factors like initial psychiatric status or social insurance problems which might affect pain and functional scores after TFESI, could not be evaluated. The main strength of the study is that it is the first one to depict a link between pre-treatment serum 25(OH)D levels and success rates of TFESI. Secondly, we endeavored to eliminate most of the confounding factors reported previously by choosing a homogeneous patient group.

Conclusion

Vitamin D deficiency may cause an unfavorable response to TFESI. A blood test to investigate serum 25(OH)D levels and medication in case of deficiency may be helpful prior to the intervention. Further prospective investigations are warranted to enlighten this presumable association.

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