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Research Paper

Placebo-controlled Trial of Oral Vitamin D and Alendronate Efficacy for Pain and Modic Changes in Lumbar Fusion Surgery

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ABSTRACT

Background and Aim: Modic changes are alterations in the spine endplates and subchondral bone shock absorption, seen by magnetic resonance imaging (MRI). No studies have investigated the effect of vitamin D and alendronate as oral drugs on reducing and modifying Modic changes after degenerative spine fusion surgery. This study aimed to evaluate the efficacy of oral vitamin D and alendronate administration in patients with low back pain, and Modic changes undergoing lumbar fusion surgery.

Methods and Materials/Patients: A total of 81 middle age women with a normal range of serum vitamin d were enrolled in three groups who underwent lumbar fusion surgery according to neurosurgical criteria. Group 1 (n=27) received additional oral alendronate, group 2 (n=27) received oral vitamin D for six months postoperatively, and group 3 (n=27) received no drug (except simple analgesics and antibiotics). The patients were followed up with a visual analog scale (VAS) and Oswestry disability index (ODI). MRI was done before and six months after surgery.

Results: There was no significant difference between the three groups in VAS and ODI scores (P=0.416, P=0.601, respectively), but the mean VAS and ODI in all three groups decreased over six months, which was statistically significant (P<0.001). Modic changes in all three groups changed significantly over 6 months (P<0.01). In the vitamin D and alendronate groups, Modic type 3 increased significantly, but Modic type 2 and Modic type 1 decreased significantly in the vitamin d and no medication groups, respectively.

Conclusion: Oral vitamin D administration has a desirable effect not only on clinical outcomes after lumbar spinal fusion surgery because of degenerative surgery but also on vertebral endplate Modic changes compared to oral bisphosphonate.

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Highlights

• Oral vitamin D administration has a beneficial effect on clinical outcomes after lumbar spinal fusion surgery due to degenerative surgery.

• It also has a good effect on vertebral endplate Modic change compared with oral bisphosphonate.

• Further studies with larger sample sizes should be conducted to definitively prove vitamin D effects on spine fusion and Modic changes conversion.

Plain Language Summary

Modic changes are alterations in the spine endplates and subchondral bone shock absorption, which can be seen by MRI. Due to our study results, oral vitamin D administration may have beneficial effects on clinical outcomes after lumbar spinal fusion procedures and vertebral endplate Modic change compared with oral bisphosphonate.

1. Introduction

Low back pain (LBP) is known as pain between the intercostal margin and inferior gluteal folds, which may have radiation to the lower limbs and is sometimes associated with severe motor disabilities [1]. LBP results from fractures, direct trauma, or systemic diseases such as spondylodiscitis, tumors, infections, etc. [2, 3].

The important cause of LBP is a degenerative disease caused by disk herniation or spinal stenosis [4, 5, 6]. Accordingly, only 20% of patients with lumbar pain have known anatomic and pathologic changes, and 80% have an unknown cause of low back pain. Recent studies have shown that Modic changes are strongly linked with LBP [7, 8].

The Modic classification was presented in 1988 [7]. According to this classification, type I is characterized by bone marrow edema and inflammation, type II is related to the conversion of normal red hematopoietic bone marrow into yellow fatty marrow as a consequence of ischemia, and type III is characterized by subchondral bone sclerosis. Modic changes are alterations in the spine endplates and subchondral bone signal absorption based on MRI imaging. These changes could regularly be found in the general population, asymptomatic individuals, and patients with LBP. Modic et al. reported that type I changes normally progress to type II, but they can also revert to normal [7]. Braithwaite et al. recommended that Modic changes can convert from one type to another, and they all present different stages of the same pathologic course [9]. When different types, usually type 1 and 2 or 2 and 3, are detected at the same adjacent vertebral body, they are labeled mixed types (1/2 or 2/3, respectively) [8, 9]. However, several previous studies considered that type I Modic change, including type 1/2, represents an active inflammatory process; therefore, these previous studies classified type 1 and type 1/2 as “type 1” groups in the analyses [7-9].

In asymptomatic individuals, the frequency of Modic changes is 12%-13%, and 18%-58% of patients with LBP have Modic changes, so there is a sturdy association between Modic changes and LBP [7-9] (Figure 1).

There is a stronger association between lumbar pain and type 1 Modic than type 2, which may be due to the occurrence of type 1 Modic in the acute phase of inflammation and the presence of type 2 in previous inflammation and degeneration [9, 10]. There is also a strong association between type 1 Modic changes and prior disk herniation. Also, Modic changes are more in patients undergoing lumbar disk surgery [11]. Genetics is a known risk factor in the degeneration and herniation of the vertebral endplates. Furthermore, the prevalence of Modic changes in different racial groups can be different [12]. Various studies have investigated the incidence, etiology, and clinical relevance of these spine degenerative changes, but without any definitive results [13, 14].

Different surgical methods and drugs have been studied in this era. There are different results in the literature about the effect of spine fusion techniques on the reduction and modification of post-surgical Modic changes and their related clinical symptoms [15, 16].

Recent studies have documented the efficacy of the administration of bisphosphonates, especially via injection, in reducing degenerative Modic changes and improving patients' lumbar pain symptoms. They have repeatedly recommended more comprehensive studies [17-20]. Also, some reports show an important relationship between vitamin D deficiency and Modic changes [21].

Since different studies and theories do not allow the efficient use of various therapies, this study was designed and optimized as a clinical trial in patients undergoing these surgeries.

Despite the importance of back pain and fusion surgery, no studies have investigated the consequence of vitamin D and alendronate as oral drugs on pre- and post-lumbar fusion surgery. Therefore, this study aimed to evaluate the efficacy of oral vitamin D and alendronate administration in patients with LBP and Modic changes who have undergone lumbar fusion surgical procedures.

2. Methods and Materials/Patients

Protocol review

This trial was a double-blind, randomized, placebo-controlled study focused principally on achieving efficacy and safety data on using alendronate and vitamin D in lumbar spine fusion surgery. The study was approved by the local Institutional Ethics Committee (Code: IR.MAZUMS.REC.94. 1769). This clinical trial was registered with the trial (Code: IRCT20140915019185N2). In addition, the patient signs up an informed consent form before the beginning of the study.

Study subjects

The study population consisted of 20-65 years old women registered over 1.5 years among those referred to our spine clinic and underwent lumbar fusion surgery according to neurosurgical criteria.

Group 1 (n=27) received additional oral alendronate; group 2 (n=27) received oral vitamin D for six months postoperatively, and group 3 (n=27) received no drug (except simple analgesics and antibiotics) (Figure 2: Flow diagram).

Inclusion criteria

The study population comprised all patients with lumbar spine fusion surgery based on neurosurgery clinical and imaging findings. They should also have the following criteria: having spondylolisthesis, lumbar disk herniation, or spinal stenosis; being female (to eliminate the hormonal factor as a confounding factor); and their 25OHD level >50 nmol/L indicating sufficiency (a 25OHD level <30 nmol/L showed the risk of insufficiency or deficiency).

Exclusion criteria

Patients with traumatic, neoplastic lesions, infectious and history of surgery, diabetes, debilitating underlying problems, and rheumatic diseases were excluded in addition to the ones who did not have interpreted MRI images. Patients with glomerular filtration rate below 40 were excluded from the study due to the contraindication use of alendronate.

Pharmacological agents

The first group received a 70 mg alendronate tablet weekly for six months postoperatively. The second group received vitamin D Pearl 50000 units weekly for six months. The third group received no drug except simple analgesics and antibiotics.

Outcome variables

Preoperative MRI was performed for all patients and interpreted by a radiologist. At the beginning of the study, all patients completed the visual analog scale (VAS) of the pain assessment questionnaire and the Oswestry disability index (ODI). The VAS pain score and ODI disability score were administered again after one and six months. MRI control was again taken in the sixth month and was seen and interpreted by the same radiologist.

Statistical analysis

Data were analyzed by SPSS software version 19. Descriptive statistics and appropriate tables were used to describe the data. The Chi-square, Fisher exact test, and ANOVA were used to compare the variables. In this study, $P<0.05$ was considered significant.

3. Results

Finally, 81 patients (27 in each group) were evaluated. The Mean±SD age of the patients was 51.31±8.6 years. The Mean±SD body mass index (BMI) of the patients was 29.69±3.47 kg/m^2. One patient was a smoker. Most patients (40%) had spinal stenosis, and 64.19% had involvement at the L4-L5. Seventy-seven patients had fusion at four levels. There was no significant difference

between the variables of the three groups (P>0.05). Patient information is presented in Table 1.

There was no significant difference among the three groups in VAS and ODI (P=0.416, P=0.601, respectively), but the mean VAS and ODI in all three groups decreased over six months, which was statistically significant (P<0.001) (Table 2) (Figures 3 and 4).

In the vitamin D group, 12 patients had noticeable Modic changes (from type 2 to type 1), eight showed no Modic change, and in seven patients, Modic changes got worse (from a lower type to a higher type). In the alendronate group, six patients had favorable Modic changes (from type 2 to type 1), while ten patients showed worse changes and eleven patients were unchanged. In the control group, 6 patients had favorable Modic changes, eleven patients remained unchanged, and ten patients had worse changes (P=0.380). Thus, the Modic change in all three groups changed significantly over 6 months (P<0.01, Table 3). In the vitamin D and alendronate groups, Modic 3 increased significantly, but Modic type 2 and Modic type 1 decreased significantly in the vitamin D and no medication groups, respectively (Table 3, Figure 2).

4. Discussion

The rate of failure (non-union) in lumbar fusion surgery has been described as up to 56% [22], and research is focused on developing treatments that confirm bone union. Bisphosphonates are an anti-catabolic medica-

Table 1. Patients' demographic information of study groups

Variables		Mean±SD/No. (%)			P
		Alendronate	Vitamin D	No Medication	
Age (y)		48.73±7.98	53.58±7.93	51.04±9.47	0.122*
BMI (Kg/m^2)		28.41±3.54	30.05±3.53	31.03±2.89	0.056*
Diagnosis	Spondylolisthesis	13(48.15)	9(33.33)	9(33.33)	0.213**
	Disk herniation	6(22.23)	2(7.41)	5(18.52)	
	Spinal stenosis	8(29.62)	16(59.26)	13(48.15)	
Involvement level	L2-L3	1(3.70)	2(7.41)	1(3.70)	0.707***
	L3-L4	3(11.11)	10(37.04)	7(25.93)	
	L4-L5	15(55.56)	16(59.26)	19(70.37)	
	L5-S1	12(44.44)	14(51.85)	10(37.04)	
Number of levels involved	Three	8(29.63)	3(11.11)	7(25.93)	0.223**
	Four	19(70.37)	24(88.89)	20 (74.07)	
Modic changes in admission (type)	1	11(40.74)	7(25.93)	12(44.44)	0.313**
	2	16(59.26)	20(74.07)	14(51.85)	
	3	0(0)	0(0)	1(3.7)	
Modic changes after 6 months (type)	Non	2(7.41)	4(14.81)	5(18.52)	0.515**
	1	6(22.22)	9(33.33)	5(18.52)	
	2	16(59.26)	9(33.33)	14 (51.85)	
	3	3(11.11)	5(18.52)	3(11.11)	

P<0.05 is considered significant.

*One-way ANOVA, **The Fisher exact test, ***The Chi-square test

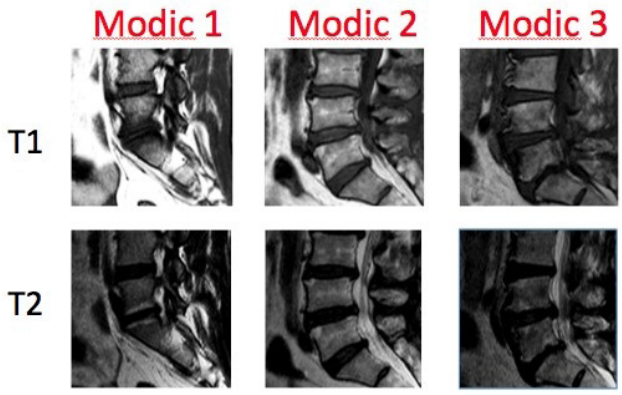

Figure 1. Modic changes classification based on MRI findings

tion and have been used to treat various bone illnesses considered by amplified bone turnover, such as osteoporosis [23]. Some studies showed that single-dose bisphosphonates usage briefly prevents bone catabolism and induces an increase in callus size to increase in open fracture models [24- 26].

However, studies that evaluated bisphosphonate treatment in spinal fusion are scarce, and documents have mostly observed the consequence of continuous drug usage. Some authors evaluated the result of daily alendronate sodium (0.05 mg/kg) on rabbits' intertransverse spinal fusion model [27]. They reported that alen-

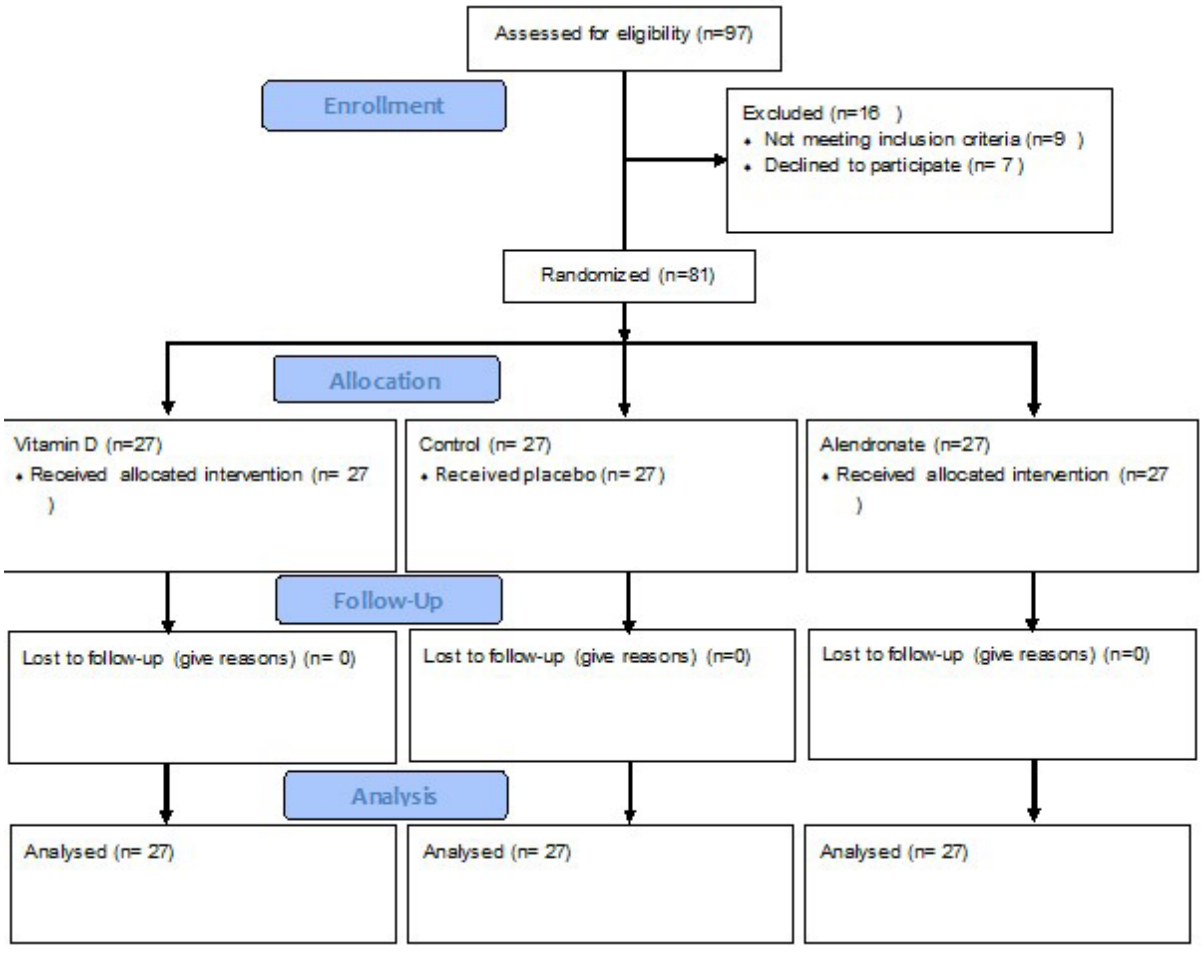

Figure 2. Flow diagram

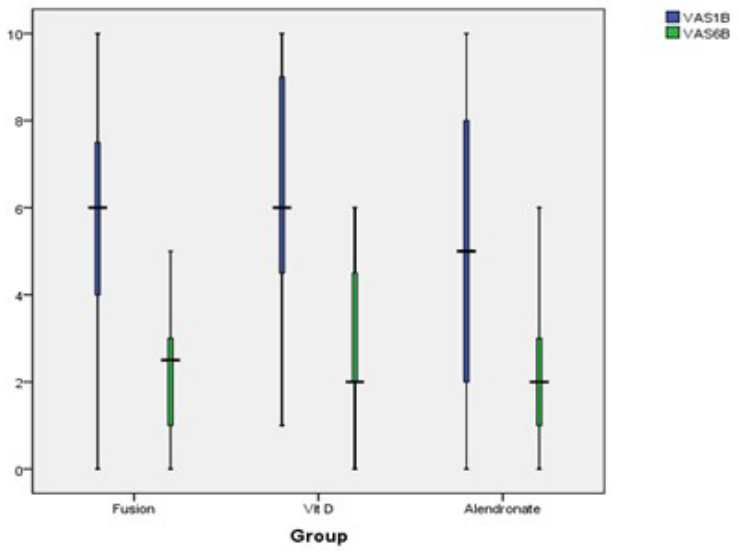

Figure 3. Visual analog scale changes before and after six months in the study groups

dronate could delay bone fusion in a rabbit model, as resolute by the histological assessment [28]. They also establish a decline in the fusion rate. Other authors confirmed dose-dependent results with alendronate in a similar rabbit spine fusion process [27]. They recognized substantial rises in fusion mass in both high-dose and low-dose treatment clusters, as revealed by computed tomography. Though, they originate that a high dose is directed to a lesser rate of fusion than the low dose or control groups. A recent study recommended that pamidronate can delay fusion, but the total effective dose was high and continuous [29].

This study aimed to evaluate the efficacy of oral vitamin D and alendronate administration in patients with LBP and Modic changes who had undergone lumbar fusion surgery in our department. In this study, 81 patients were enrolled, and there was no significant difference between the three groups based on diagnosis (diskopathy/listhesis/stenosis). Results displayed no significant difference in fusion levels and Modic changes in all three groups. Also, the results showed a significant

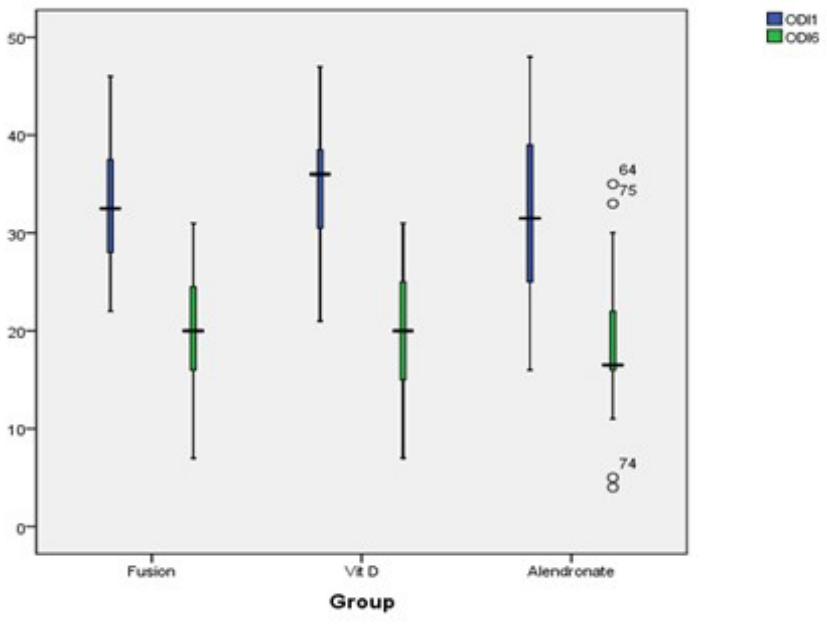

Figure 4. Oswestry disability index changes before and after six months in the study groups

Table 2. Visual analog scale (VAS), oswestry disability index (ODI), and modic changes before and six months after surgery

Variables		No. (%)			P
		Alendronate	Vitamin D	No Medication	
VAS	Before surgery	5.41(3.25)	6.15(2.59)	5.25(2.83)	0.416
	After six months	2.37(1.55)	2.85(1.83)	2.15(1.35)	
ODI	Before surgery	32.52(7.81)	34.33(6.47)	33.04(6.81)	0.601
	After six months	18.81(7.81)	20.11(6.69)	20.41(6.12)	

decrease in postoperative pain in all three groups based on VAS. Still, this reduction was not significantly different between the three groups.

In our study, although the postoperative disability improvement based on ODI criteria was significantly better in the vitamin D group than the other three groups, there was no difference between the three groups. It should be noted, however, that this decrease was present in all three groups but was lower in the vitamin D group.

On the other hand, regarding the Modic changes, the results of our study showed that 12 patients had better changes in the vitamin D group. These patients have dropped from a high-grade Modic grade to a low-grade one (type 2 to 1). In comparison, 6 cases in the alendronate group and 8 cases in the control group had better Modic changes. However, despite the superiority of vitamin D over the other groups, the Modic changes in the three treatment groups showed no statistically significant difference. Although, in our study, there was no difference in the outcome between the three groups, the effect of vitamin D administration was superior, which cannot be overlooked. Concerning this effect of vitamin D by Rodriguez et al. [18], in a review study, concluded that vitamin D deficiency might be a causal reason for persistent postoperative pain.

Vitamin D deficiency is asymptomatic, and the symptoms can be independent of musculoskeletal pathological changes. Moreover, physicians need to be aware of the effect of this vitamin deficiency and its effect on postoperative care. In a cross-sectional study by Johan-

Table 3. Modic changes before (1) and six months (6) after surgery in three study groups

Groups	Objects	Type	No. (%)		P
			Modic Type 1	Modic Type 6	
Vitamin D	Modic	1.00	7(8.64)	8(9.88)	<0.001
		2.00	38(46.91)	18(22.22)	
		3.00	0(0)	15(18.52)	
Alendronate		1.00	10(12.35)	7(8.64)	0.008
		2.00	34(41.98)	30(37.04)	
		3.00	0(0)	9(11.11)	
No Medication		1.00	13(16.05)	5(6.17)	0.039
		2.00	28(34.57)	30(37.04)	
		3.00	3(3.7)	9(11.11)	

sen et al. [21], the correlation between serum vitamin D levels and clinical signs and Modic changes on MRI was evaluated in 152 patients with low back pain. They reported a significant association between vitamin D deficiency and Modic changes. Studies show that vitamin D status is commonly ignored, and all healthcare physicians should know its significance in treating patients. In our study, vitamin D administration was also associated with a relatively better response than other groups, but due to the low sample size, further studies with larger sample sizes are recommended to evaluate this effect.

There have also been studies of the use of drugs similar to the alendronate family (bisphosphonates). Our study exhibited the same effect on alendronate groups as the control and vitamin D groups and showed no difference between the three groups. However, in terms of quantity and quality data, it was less effective than the vitamin D group.

For example, in a 2014 clinical trial, Cecchetti et al. [19] in France treated 24 patients with a degenerative disease and lumbar discopathy in two randomized groups with pamidronate, a bisphosphonates injectable 90 mg/d for two days and placebo in the other group. The VAS clinical criterion over three months recording showed the improvement effect of pamidronate on the clinical recovery of patients with LBP and Modic changes type 1. One of the limitations of this study was that it was performed only on patients with type 1 Modic changes, while in our study, all types of Modic changes were studied. In another study, Koivisto et al. [20] compared the efficacy of 5 mg zoledronic acid injection with placebo in two groups of patients with chronic LBP and Modic MRI changes in clinical parameters of VAS and ODI. They evaluated the short-term efficacy of this drug. The zoledronic acid effect was confirmed in decreasing the severity of LBP in the short term and decreasing the use of non-steroidal anti-inflammatory drugs for one year in patients with chronic LBP and chronic Modic changes on MRI. However, they recommended further studies with a larger number of patients. The difference between this study and our study could be due to differences in study design, sample size, and the type of patients with back pain who have been studied. It is recommended to conduct studies with a larger population and multicenter population and to evaluate the effect of vitamin D and alendronate on cervical fusion patients as well as laminectomy and discopathy to obtain the full effect of these drugs. It is suggested that cohort studies be conducted in a larger statistical population to achieve realistic goals in this area.

5. Conclusion:

The consequences of this study showed a significant effect of lumbar fusion surgery on pain relief and outcome in patients, but there was no difference between the control and vitamin D and alendronate groups. However, in the data obtained from the results, the vitamin D-treated group had better outcomes, but further studies with larger sample sizes should be conducted to prove this finding. Oral vitamin D administration has a beneficial effect not only on clinical outcomes after lumbar spinal fusion surgery because of degenerative surgery but also has a good effect on vertebral endplate Modic change compared with an oral bisphosphonate.

Ethical Considerations

The local Institutional Ethics Committee approved the study (Code: IR.MAZUMS.REC.94.1769).

Compliance with ethical guidelines

This study was conducted as a thesis in the Neurosurgery Specialty by Mahmoud Mehriyari. This project, as a clinical trial study, was registered with the trial (Code: IRCT20140915019185N2). All patients signed an informed conent form before the beginning of the study.

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Authors' contributions

Conception, design, data collection, data analysis, and interpretation: Kaveh Haddadi, Saeed Ehteshami, Mohsen Aarabi. Drafting and Critically revising the manuscript: All authors. Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Rubin DI. Epidemiology and risk factors for spine pain. Neurologic Clinics. 2007; 25(2):353-71. [DOI:10.1016/j.ncl.2007.01.004] [PMID]

[2] Luoma K, Riihimaki H, Luukkonen R, Raininko R, Viikari-Juntura E, Lamminen A. Low back pain in relation to lumbar disc degeneration. Spine. 2000; 25(4):487-92. [DOI:10.1097/00007632-200002150-00016] [PMID]

[3] Haddadi K, Ehteshami S. Low lumbar fractures: Unique biomechanics and treatment options. Iranian Journal of Neurosurgery. 2020; 6(1):3-12. [DOI:10.32598/irjns.6.1.2]

[4] Mashinchi Sh, Yousefzadeh-Chabok Sh, Dibavand M. Demographic characteristics and family history of lumbar problems in patients with lumbar disc degenerative diseases candidate for surgery. Iranian Journal of Neurosurgery. 2020; 6(3):121-32. [DOI:10.32598/irjns.6.3.3]

[5] Farrokhi MR, Yadollahikhales G, Gholami M. Treatment of 44 cases with lumbar spine stenosis and degenerative instability: Outcomes of surgical intervention. Iranian Journal of Neurosurgery. 2017; 3(3):79-88. [DOI:10.29252/IRJNS.3.3.79]

[6] Albert HB, Lambert P, Rollason J, Sorensen JS, Worthington T, Pedersen MB, et al. Does nuclear tissue infected with bacteria following disc herniations lead to modic changes in the adjacent vertebrae? European Spine Journal. 2013; 22(4):690-6. [DOI:10.1007/s00586-013-2674-z] [PMID] [PMCID]

[7] Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: Assessment of changes in vertebral body marrow with MR imaging. Radiology. 1988; 166(1 Pt 1):193-9. [DOI:10.1148/radiology.166.1.3336678] [PMID]

[8] Teraguchi M, Hashizume H, Oka H, Cheung JPY, Samartzis D, Tamai H, et al. Detailed subphenotyping of lumbar modic changes and their association with low back pain in a large population-based study: The Wakayama spine study. Pain and Therapy. 2022; 11(1):57-71. [DOI:10.1007/s40122-021-00337-x] [PMID] [PMCID]

[9] Braithwaite I, White J, Saifuddin A, Renton P, Taylor BA. Vertebral endplate (Modic) changes on lumbar spine MRI: Correlation with pain reproduction at lumbar discography. European Spine Journal. 1998; 7(5):363-8. [DOI:10.1007/s005860050091] [PMID] [PMCID]

[10] Wang Y, Videman T, Battie MC. Modic changes: Prevalence, distribution patterns, and association with age in white men. The Spine Journal. 2012; 12(5):411-6. [DOI:10.1016/j.spinee.2012.03.026] [PMID] [PMCID]

[11] Colombini A, Cauci S, Lombardi G, Lanteri P, Croiset S, Brayda-Bruno M, et al. Relationship between vitamin D receptor gene (VDR) polymorphisms, vitamin D status, osteoarthritis and intervertebral disc degeneration. The Journal of Steroid Biochemistry and Molecular Biology. 2013; 138:24-40. [DOI:10.1016/j.jsbmb.2013.03.001] [PMID]

[12] Wilkens P, Scheel IB, Grundnes O, Hellum C, Storheim K. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: A randomized controlled trial. JAMA. 2010; 304(1):45-52. [DOI:10.1001/jama.2010.893] [PMID]

[13] Largo R, Alvarez-Soria MA, Díez-Ortego I, Calvo E, Sánchez-Pernaute O, Egido J, et al. Glucosamine inhibits IL-1β-induced NFκB activation in human osteoarthritic chondrocytes. Osteoarthritis and Cartilage. 2003; 11(4):290-8. [DOI:10.1016/S1063-4584(03)00028-1] [PMID]

[14] Nevitt MC, Cummings SR, Stone KL, Palermo L, Black DM, Bauer DC, et al. Risk factors for a first-incident radiographic vertebral fracture in women > or=65 years of age: The study of osteoporotic fractures. Journal of Bone and Mineral Research. 2005; 20(1):131-40. [DOI:10.1359/jbmr.2005.20.1.131] [PMID]

[15] Chin KR, Tomlinson DT, Auerbach JD, Shatsky JB, Deirmengian CA. Success of lumbar microdiscectomy in patients with modic changes and low-back pain: A prospective pilot study. Journal of Spinal Disorders & Techniques. 2008; 21(2):139-44. [DOI:10.1097/BSD.0b013e318093e5dc] [PMID]

[16] Arana E, Kovacs FM, Royuela A, Estremera A, Asenjo B, Sarasibar H, et al. Modic changes and associated features in southern European chronic low back pain patients. The Spine Journal. 2011; 11(5):402-11. [DOI:10.1016/j.spinee.2011.03.019] [PMID]

[17] Toyone T, Tanaka T, Kato D, Kaneyama R. Low-back pain following surgery for lumbar disc herniation: A prospective study. The Journal of Bone and Joint Surgery American. 2004; 86(5):893-6. [DOI:10.2106/00004623-200405000-00001] [PMID]

[18] Rodriguez WJ, Gromelski J. Vitamin D status and spine surgery outcomes. International Scholarly Research Notices. 2013; 471695. [DOI:10.1155/2013/471695]

[19] Cecchetti S, Pereira B, Roche A, Deschaumes C, Abdi D, Coudeyre E, et al. Efficacy and safety of pamidronate in Modic type 1 changes: Study protocol for a prospective randomized controlled clinical trial. Trials. 2014; 15(1):117. [DOI:10.1186/1745-6215-15-117] [PMID] [PMCID]

[20] Koivisto K, Kyllönen E, Haapea M, Niinimäki J, Sundqvist K, Pehkonen T, et al. Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging. BMC Musculoskeletal Disorders. 2014; 15:64. [DOI:10.1186/1471-2474-15-64] [PMID] [PMCID]

[21] Johansen JV, Manniche C, Kjaer P. Vitamin D levels appear to be normal in Danish patients attending secondary care for low back pain and a weak positive correlation between serum level Vitamin D and Modic changes was demonstrated: A cross-sectional cohort study of consecutive patients with non-specific low back pain. BMC Musculoskeletal Disorders 2013, 14:78. [DOI:10.1186/1471-2474-14-78] [PMID] [PMCID]

[22] Lee C, Dorcil J, Radomisli TE. Nonunion of the spine: A review. Clinical Orthopaedics and Related Research. 2004; (419):71-5. [DOI:10.1097/00003086-200402000-00012] [PMID]

[23] Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: The critical need for a uniform nomenclature based on their action on bone remodeling. Journal of Bone and Mineral Research. 2005; 20(2):177-84. [DOI:10.1359/JBMR.041114] [PMID]

[24] Amanat N, Brown R, Bilston LE, Little DG. A single systemic dose of pamidronate improves bone mineral content and accelerates restoration of strength in a rat model of fracture repair. Journal of Orthopaedic Research. 2005; 23(5):1029-34. [DOI:10.1016/j.orthres.2005.03.004] [PMID]

[25] Little DG, Cornell MS, Hile MS, Briody J, Cowell CT, Bilston L. Effect of pamidronate on distraction osteogenesis and fixator-related osteoporosis. Injury. 2001; 32 Suppl 4:SD14-20. [DOI:10.1016/S0020-1383(01)00161-9] [PMID]

[26] Little DG, Smith NC, Williams PR, Briody JN, Bilston LE, Smith EJ, et al. Zoledronic acid prevents osteopenia and increases bone strength in a rabbit model of distraction osteogenesis. Journal of Bone and Mineral Research. 2003; 18:1300-7. [DOI:10.1359/jbmr.2003.18.7.1300] [PMID]

[27] Lehman RA Jr, Kuklo TR, Freedman BA, Cowart JR, Mense MG, Riew KD. The effect of alendronate sodium on spinal fusion: A rabbit model. The Spine Journal. 2004; 4(1):36-43. [DOI:10.1016/S1529-9430(03)00427-3] [PMID]

[28] Emery SE, Brazinski MS, Koka A, Bensusan JS, Stevenson S. The biological and biomechanical effects of irradiation on anterior spinal bone grafts in a canine model. Journal of Bone and Joint Surgery. 1994; 76(4):540-8. [DOI:10.2106/00004623-199404000-00008] [PMID]

[29] Babat LB, McLain R, Milks R, Ferrara L, Sohn MJ. The effects of the antiresorptive agents calcitonin and pamidronate on spine fusion in a rabbit model. The Spine Journal. 2005; 5(5):542-7.[DOI:10.1016/j.spinee.2005.01.008] [PMID]