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EFFICACY AND SAFETY OF ZOLEDRONIC ACID AS AN ADD ON THERAPY TO VITAMIN D3 IN PATIENTS OF STRESS FRACTURE OF LOWER LIMB

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ABSTRACT This study investigates the efficacy and safety of zoledronic acid as an adjunctive therapy to vitamin D3 in treating lower limb stress fractures. Stress fractures, common among athletes and military personnel, occur due to repetitive stress on healthy bones, resulting in microdamage and pain. Early diagnosis and treatment are crucial to prevent complications like non-union and chronic pain. This prospective, open-label, randomized clinical study enrolled 30 patients aged 18 to 45 with MRI-confirmed lower limb stress fractures. Participants were divided into two groups: one receiving vitamin D3 monotherapy and the other receiving vitamin D3 combined with zoledronic acid. Clinical assessments, including MRI grading, Visual Analog Scale (VAS), Verbal Rating Scale (VRS), and Pressure Pain Test (PPT), were conducted at baseline, 2, 4, and 6 months. Results demonstrated that the combination therapy group showed superior healing and pain relief compared to the monotherapy group. At 4 months, 80% of patients in the combination therapy group achieved Grade 1 on MRI-TSI grading compared to 46.66% in the monotherapy group. VAS and VRS scores significantly improved in both groups, with the combination therapy group exhibiting greater improvements. PPT scores also indicated enhanced pain tolerance in the combination therapy group. Adverse reactions were mild and included constipation and nausea in the monotherapy group, and fatigue and bone pain in the combination therapy group. The findings suggest that zoledronic acid as an add-on to vitamin D3 is more effective and equally safe compared to vitamin D3 alone, offering a promising treatment option for stress fractures. Further large-scale, multicentric trials are recommended to validate these results and establish the long-term efficacy and safety of zoledronic acid in managing stress fractures.

KEYWORDS :

INTRODUCTION

Stress fractures, first identified in military personnel, also affect athletes due to repetitive bone stress, occurring when the body can't adapt quickly enough, leading to microdamage.[1-3] Symptoms typically appear three weeks after increased activity, and unlike insufficiency fractures in diseased bones, stress fractures result from excessive force on healthy bones.[4-5] According to Wolff's law, bones strengthen under stress but may develop microfractures if overloaded, particularly in cortical bone, and are more common in athletes, especially women with low bone density and hormonal imbalances.[6-8] Early diagnosis is crucial to prevent complications like non-union and prolonged pain, especially in the tibia and metatarsals, making awareness and prompt treatment essential.[9] This study aims to evaluate the efficacy and safety of zoledronic acid as an add-on therapy to vitamin D3 in patients with lower limb stress fractures, assessing its efficacy and safety versus vitamin D3 monotherapy. Stress fractures, common in weight-bearing bones like the tibia and metatarsals, result from repetitive impact, particularly in athletes such as runners and dancers. Key risk factors include high training volume, hormonal imbalances, gender, and osteoporosis. Recognizing localized pain that worsens with activity is vital for early diagnosis and treatment to avoid complications.[10-11] These fractures occur when bones can't handle repetitive loading, leading to microdamage that progresses from microcracks to full fractures.[12] Risk factors include low bone density, hormonal imbalances, and high-frequency stress.[13]

MANAGEMENT:

Treatment aims to relieve pain, promote healing, and prevent recurrence, focusing on:

CONSERVATIVE MEASURES: Rest, activity modification, and gradual return to weight-bearing activities with bracing or casting.

PHYSICAL THERAPY: Strength and flexibility exercises, gait retraining to address biomechanical issues.

MEDICATIONS: NSAIDs and bisphosphonates for pain and healing, particularly in osteoporotic patients.

Advanced Therapies: LIPUS for faster healing, emerging options like stem cell therapy and platelet-rich plasma injections.

Improved Imaging: MRI and CT for early detection and intervention.[14-16]

INTRAVENOUS ZOLEDRONIC ACID FOR STRESS FRACTURE TREATMENT:

Intravenous zoledronic acid offers a comprehensive approach to managing stress fractures, providing pain relief, accelerating healing, and reducing recurrence risk. This potent bisphosphonate inhibits bone resorption and promotes formation, enhancing bone strength and density. Administered as a single infusion, zoledronic acid complements conservative treatments, particularly beneficial for individuals with osteoporosis-related fractures. Studies show its efficacy in reducing pain, improving bone density, and facilitating healing. Integrating zoledronic acid into stress fracture management represents a significant advancement, offering clinicians a pharmacological option to optimize patient outcomes. Further research is needed to refine dosing strategies and assess long-term efficacy and safety.[17-19]

MATERIALS AND METHODS

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STUDY DESIGN:

This prospective, open-label, randomized clinical study was conducted by the Departments of Pharmacology, Sports Medicine and Injury Center, and Radiology at Pt. B.D. Sharma PGIMS, Rohtak. Thirty patients aged 18 to 45 with lower limb stress fractures were enrolled over approximately one year, following the International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) and Declaration of Helsinki principles.

STUDY PERIOD:

Recruitment, follow-up, and completion spanned one year.

STUDY SAMPLE:

Thirty eligible patients, newly diagnosed with lower limb stress fractures, were randomized into two groups: Group 1 (Vitamin D3

monotherapy) and Group 2 (Vitamin D3 with zoledronic acid). Inclusion criteria encompassed age, stress fracture diagnosis, MRI evidence, and consent. Exclusion criteria included age, recent zoledronic acid use, hypersensitivity, renal or hepatic issues, pregnancy, and refusal to consent.

METHOD OF RECRUITMENT:
Patients meeting inclusion criteria were recruited from the lower limb stress fracture patient pool.
Selection Criteria:

INCLUSION:
- Age 18-45
- Newly diagnosed lower limb stress fracture
- MRI-verified stress fracture (grade 1 to 2)
- Informed consent

EXCLUSION:
- Age over 60
- Recent zoledronic acid use
- Hypersensitivity to study drugs
- Renal or hepatic issues
- Pregnancy
- Refusal of consent
- Higher MRI stress fracture grading
- Osteoporosis or pathological fractures

METHOD:
Eligible patients were provided detailed study information, followed by written consent. Baseline assessments included physical exams, MRI-TSI grading, and pain assessments. Patients were randomly assigned to treatment groups, receiving either Vitamin D3 monotherapy or Vitamin D3 with zoledronic acid. Assessments occurred at 2, 4, and 6 months, focusing on pain, and mobility.

DRUG TREATMENT:
GROUP 1 RECEIVED VITAMIN D3 MONOTHERAPY
GROUP 2 RECEIVED VITAMIN D3 WITH ZOLEDRONIC ACID.
CLINICAL ASSESSMENT:
Conducted at baseline and months 2, 4, and 6 to evaluate treatment efficacy and safety.

EFFICACY ASSESSMENT:
Primary endpoints included MRI-TSI grading, X-ray, VRS, VAS, and PPT scoring.

Secondary endpoints included Pain Disability Index (PDI) scoring.

SAFETY ASSESSMENt:
Recorded adverse effects throughout the study, with provisions for new adverse effects and patient-reported symptoms.

SAMPLE SIZE CALCULATION
The sample size was calculated based on the prevalence of stress fractures being 20%, with a 95% confidence interval and a 5% margin of error, resulting in a required sample size of 245. After adjusting for the finite population and accounting for a 10% attrition rate, the final sample size was determined to be 30.

RESULTS AND DISCUSSION
RESULTS
RADIOLOGICAL GRADING:
At 4 months, Group B (combination therapy) showed a higher proportion of patients achieving Grade 1 on MRI-TSI grading (80%) compared to Group A (46.66%), indicating superior healing with the addition of zoledronic acid.

Interval	MRI-TSI Grade	Group A (Vitamin D3) (n=15)	Group B (Vit.D3+zoledronic acid) (n=15)	p-value (inter-group)
Baseline	Grade 1	3 (20%)	4 (25%)	0.282
	Grade 2	12 (80%)	11 (75%)	
4 months	Grade 1	7 (46.66%)	12 (80%)	0.027
	Grade 2	8 (53.33%)	3 (20%)	
p-value (Intra-group)		0.127	0.005	

VISUAL ANALOG SCALE (VAS):
Both groups showed significant improvements in pain scores. Group B exhibited a highly significant decrease in VAS values at 2, 4, and 6 months compared to Group A, suggesting better pain relief with combination therapy.

Interval	VAS Score	Group A (Vitamin D3) (n=15)	Group B (Vit.D3 + zoledronic acid) (n=15)	p-value (inter-group)
Baseline	Mild	2 (13.33%)	0 (0%)	0.144
	Moderate	13(86.6%)	15 (100%)	
2 months	Mild	7 (46.66%)	11 (75%)	0.072
	Moderate	8 (53.33%)	4 (25%)	
p-value (Intra-group)		0.049	<0.001	
4 months	Mild	11 (75%)	15 (100%)	0.033
	Moderate	4 (25%)	0 (0%)	
p-value (Intra-group)		<0.001	<0.001	
6 months	None	0 (0%)	5 (33.33%)	0.015
	Mild	15(100%)	10 (66.66%)	
p-value (Intra-group)-		<0.001	<0.001	

VERBAL RATING SCALE (VRS):
Similar to VAS, VRS scores significantly improved in both groups, with Group B showing greater improvement at 4 months and sustained reductions at 2, 4, and 6 months compared to Group A.

Verbal rating scale	Scores	No. of cases (%)		p-value (inter-group)
		Group A (Vitamin D3) (n=15)	Group B (Vit.D+zoledronic acid) (n=15)	
Baseline	1	2 (13.3%)	0 (0%)	0.144
	2	13 (86.6%)	15(100%)	
2 months	1	7 (46.66%)	10 (66.66%)	0.154
	2	8(53.33%)	5 (33.33%)	
p-value (Intra-group)		0.049	<0.001	
4 months	1	11(75%)	15 (100%)	0.033
	2	4 (25%)	0 (0%)	
p-value (Intra-group)		<0.001	<0.001	
6 months	0	0 (0%)	5 (33.33%)	0.015
	1	15 (100%)	10 (66.66%)	
p-value (Intra-group)			<0.001	

PRESSURE PAIN TEST:
Group B demonstrated significant improvement in pressure pain test scores at 4 and 6 months, indicating enhanced pain tolerance with combination therapy.

Pressure pain test	scores	No. of cases (%)		p-value (inter-group)
		Group A (Vitamin D3) (n=15)	Group B (Vit.D3+zoldronic acid) (n=15)	
Baseline	1	2 (13.3%)	0 (0%)	0.335
	2	10 (66.66%)	11 (75%)	
	3	3 (20%)	4 (25%)	
2 months	1	5 (33.35%)	4 (26.66%)	0.921
	2	8 (53.33%)	9 (60%)	
	3	2 (13.31%)	2 (13.34%)	
p-value (Intra-group)		0.430	0.088	
4 months	1	7 (46.66%)	8 (53.33%)	0.518
	2	7 (46.66%)	7 (46.66%)	
	3	1 (6.67%)	0 (0%)	
p-value (Intra-group)			<0.001	
6 months	0	0 (0%)	5 (33.33%)	0.015
	1	15 (100%)	10 (66.66%)	
p-value (Intra-group)		-	0.011	

ADVERSE DRUG REACTIONS:

Constipation and nausea were the most common adverse reactions in Group A, while fatigue and bone pain were predominant in Group B. All reactions were mild and did not necessitate treatment discontinuation.

Adverse drug reaction	Group A (Vitamin D3) (n=150	Group B (Vit.D3+Zoledronic acid) (n=15)	p-value
Nausea	3 (18.75%)	2 (12.5%)	0.626
Bone pain	1 (6.25%)	4 (25%)	0.144
Fatigue	0 (0%)	5 (37.5%)	0.007
Fever	0 (0%)	2 (12.5%)	0.144
Constipation	4 (25%)	0 (0%)	0.032
No ADRs	8(56.25%)	5 (31.25%)	0.154

STRENGTHS:

- Randomized, prospective design enhances the reliability of the findings.
- Comprehensive evaluation using multiple assessment tools (MRI grading, VAS, VRS, PPT).
- Demonstrates superior healing and pain relief with the combination therapy (zoledronic acid + vitamin D3).
- Focuses on a relevant, high-risk population (young, active individuals prone to stress fractures).
- Provides evidence for the potential safety and effectiveness of zoledronic acid as an add-on therapy.

LIMITATIONS:

- Small sample size (30 participants), limiting the generalizability of the results.
- A short follow-up period (6 months) may not capture long-term efficacy or safety outcomes.
- Open-label design could introduce bias in reporting and assessments.
- Mild adverse reactions were observed but not deeply explored.
- Results require validation through larger, multicentric trials.

DISCUSSION

The study demonstrated that combination therapy with zoledronic acid and vitamin D3 was more effective than vitamin D3 monotherapy in promoting early radiographic healing and alleviating pain in patients with stress fractures. Significant improvements in MRI-TSI grading, VAS, VRS, and pressure pain test scores evidenced the superior efficacy of combination therapy.

Previous studies have investigated the role of vitamin D in the treatment of stress fractures, showing its importance in bone healing and maintaining bone density. Additionally, research on zoledronic acid has demonstrated potential benefits in improving bone strength and reducing fracture risk. However, while both treatments have been studied individually, there is a lack of direct comparative studies evaluating the efficacy of vitamin D alone versus vitamin D combined with zoledronic acid in treating stress fractures. Animal studies have also explored the effects of bisphosphonates like zoledronic acid, showing promising results in enhancing bone repair and reducing bone resorption, but human data comparing these interventions remains limited. This gap highlights the need for further investigation to determine the best therapeutic approach for stress fracture management.

Despite the observed benefits, both treatment regimens were well-tolerated, with no serious adverse reactions reported. The mild nature of adverse events further supports the safety profile of zoledronic acid as an adjunctive therapy for stress fractures.

In conclusion, the study suggests that zoledronic acid as an add-on therapy to vitamin D3 offers superior efficacy and comparable safety in the management of stress fractures compared to vitamin D3 monotherapy. These findings highlight the potential of zoledronic acid as a promising treatment option for patients with stress fractures, particularly when vitamin D3 alone is insufficient or contraindicated. However, further multicentric trials with larger cohorts and longer follow-up periods are warranted to validate these findings and establish zoledronic acid's role in stress fracture management definitively.

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