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Original Article

Comparison of functional outcomes between teriparatide and vitamin D_3 in distal end radius fractures of osteoporotic patients

Prakash D. Samant[1], Rohit M. Sane[1], Rajendraprasad R. Butala[1], Aditya M. Sane[2]

[1]Department of Orthopaedics, D Y Patil University School of Medicine, Navi Mumbai, Maharashtra, India;
[2]Department of Radiology, D Y Patil University School of Medicine, Navi Mumbai, Maharashtra, India

Abstract

Objectives: The objective of this study was to evaluate and compare the efficacy of teriparatide (osteoanabolic agent) versus vitamin D3 supplementation to improve functional outcomes in osteoporotic patients with distal end radius fractures (DERF). **Methods**: We conducted a prospective, randomized clinical study to compare the functional outcomes. Sixty osteoporotic DERF patients, treated with either conservative or surgical management were randomized to receive either teriparatide (20 mcg/day) or vitamin D_3 (1000 IU/day) for a period of 3 months, along with calcium (500 mg/day) supplementation. The treatment outcomes were evaluated pre and post-management (1-month and 3-months) by Green and O'Brien scale, Patient-rated Wrist Evaluation (PRWE) scale, and Sarmiento scale. **Results**: There was a significant difference between the two groups at 3-months post-management. Teriparatide showed a significantly greater improvement of functional outcome (P=0.036) and patient-reported outcome (P<0.001) in comparison to vitamin D_3 in total Green and O'Brien score and PRWE score, respectively. **Conclusion**: Teriparatide supplementation was effective and resulted in greater improvement in functional and radiologic outcomes in comparison to vitamin D_3. Adjuvant teriparatide therapy may be a therapeutic option to improve the functional outcomes in DERF of osteoporotic patients.

Keywords: Distal end radius fracture, Functional Outcome, Osteoporosis, Teriparatide, Vitamin D_3

Introduction

Distal end radius fracture (DERF) is one of the most frequent upper extremity fractures occurring in all age groups and associated with osteoporosis and vitamin D deficiency, particularly in aging population. They account for 16-20% of all fractures treated by orthopaedic surgeons in clinical practice[1-3]. At times, fixing and managing these fractures, is most challenging in patients with advancing age due to related degenerative changes, delayed wound healing, with a high epidemic of osteoporosis and vitamin D deficiency in such population[4-8].

Supplementation of vitamin D_3 along with calcium is now a routine standard treatment for osteoporosis and for prevention of osteoporotic fractures[9,10]. Recently, there has been heightened interest in using osteoanabolic agents to accelerate up fracture healing in fracture management. Teriparatide is the first bone anabolic agent, which is a recombinant human amino acid, having a biologically active N-terminal 34-amino acid fragment of the 84-amino acid native parathyroid hormone[11]. Teriparatide's stimulatory osteoanabolic effect on bone formation is explained by the 'anabolic window' (stimulates bone formation without stimulating bone resorption), which causes a net gain of bone deposition[11,12]. Teriparatide's positive influence on bone density, microarchitecture, and bone geometry is seen predominantly in the cancellous bone[12], and the distal

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Corresponding author: *Dr. Aditya M. Sane, Junior Resident, Department of Radiology, D Y Patil University School of Medicine, Navi Mumbai, Maharashtra, India 400706*

E-mail: *saneaditya@hotmail.com*

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end of the radius has both cortical as well as trabecular components[13].

In human clinical trials, teriparatide administration has shown to accelerate callus formation and lessen the risk of nonunion, and improve fracture healing[14-16]. Theoretically, the positive impact of teriparatide in early callus formation and fracture healing is important for an early return of functional outcomes and for preventing late complications. However, there is paucity in literature and a limited number of adjunctive therapies that can be used to accelerate the fracture healing process to improve functional outcomes, especially in DERF. Therefore, the purpose of this study was to evaluate and compare the efficacy of teriparatide (osteoanabolic agent) with vitamin D_3 supplementation to improve functional outcomes in DERF of osteoporotic patients.

Materials and Methods

This open-label, prospective, randomized, comparative study was performed in single tertiary care teaching hospital in Navi-Mumbai (India). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. This study was approved by the Institutional Ethics Committee (IEC) (Approval reference no. DYP/IECBH/2020/06) of the hospital. Informed consent was obtained from all individual participants included in the study.

Between January 2020 and March 2020, sixty osteoporotic patients with DERF were enrolled in the study and followed up for the next 3 months. The study included osteoporotic patients with extra-articular DERF, with age equal or more than 50 years, and of either gender, and treated irrespective of the type of management (conservative or surgical). The participants were randomized to receive either teriparatide (20 mcg/day, subcutaneous injections) or vitamin D_3 (1000 IU/day, oral tablets) for a period of 3 months along with calcium (500 mg/day, oral tablets). A computer-generated list of random numbers was used. All participants were randomized with a 1:1 allocation using 4-block randomization.

Patients with age less than 50 years, having an existing wrist deformity or wrist disease (rheumatoid arthritis, etc.), previous fractures or bone surgery in the currently fractured distal forearm, elevated serum calcium, elevated serum PTH levels, elevated serum vitamin D levels, abnormal liver function, and renal function test, any contraindications/hypersensitivity to teriparatide or vitamin D_3, taking antiresorptive drugs, taking systemic glucocorticoids, increased risk of osteosarcoma (including Paget's disease of bone, etc.) and not willing for informed written consent were excluded.

Pre-management, the investigators looked into the clinical condition, investigations, and radiological scans to assess the fracture pattern and clinical profile of the patients. The study baseline treatment outcomes were assessed by Green and O'Brien score (Cooney modification)[17], Patient-rated Wrist Evaluation (PRWE) score[18] and Sarmiento score[19], respectively. After randomization, the clinical profile and treatment outcomes in both the groups were evaluated on post-management 1-month and 3-months. Participants in both the groups received the same standard of physiotherapy and rehabilitation care (depending on conservative or operative management), in the post-management period.

Post management - For conservative treatment, cast immobilization of the wrist was for 6 weeks followed by removal of cast and standard physiotherapy, while for operative treatment, it was immobilization of the wrist for 1-3 weeks followed by standard physiotherapy.

Treatment evaluation

Functional outcome assessment: The Green and O'Brien score (Cooney modification) is an examiner-rated assessment of pain, functional status, range of motion, and grip strength[17]. Each of the 4 parameters is given a weighting of 25 points, giving a total score of 100. With excellent being 90 to 100, good being 80 to 89, fair being 65 to 79, and poor being less than 65 scores[17].

Patient-reported outcome: Patient-rated pain and disability was measured using the Patient-rated Wrist Evaluation (PRWE). PRWE is a 15-item patient-reported outcome measure that measures a patient's rated pain and disability and has been shown to be reliable and highly responsive in the distal radius fracture population[18]. The PRWE allows participants to rate their levels of wrist pain and disability during a variety of activities of daily living for a total possible score of 100 (0 being the best possible score, 100 being the worst possible score)[18].

Radiography assessment: Radiological assessment was carried out by the Sarmiento scale. Sarmiento et al's modification of Lidstrom's scoring is a radiological assessment grading (excellent, good, fair, and poor) based on the deformity, dorsal angulation, radius length shortening, and loss of radial tilt/deviation. The assessment grades are excellent, good, fair, and poor[17,19].

Statistical analysis

Statistical Package for the Social Sciences (IBM SPSS, Windows) software version 20.0 was used for statistical analyses. Data were anonymized for all statistical analyses. Results were expressed as an actual number, mean with standard deviation, median with interquartile range, and frequency (percentage) as appropriate. Data normality was assessed using the Kolmogorov-Smirnov test. The Wilcoxon signed-rank test was used to compare the pre and post scores within the study groups. The Mann-Whitney U test was used to compare the difference in scores between the study groups. Categorical data were assessed by Chi-Square or Fishers Exact test, as appropriate. P values <0.05 were considered statistically significant.

Characteristics		Teriparatide (20 mcg/day)		Vitamin D_3 (1000 IU/day)	
		Value	%	Value	%
Total patients of distal end radius fracture (n)		30	100 %	30	100 %
Mean Age in years (± SD)		55.8 ± 4.9		57.4 ± 5.8	
Median Age in Years (IQR)		54 (52, 60)		57(52, 63)	
Gender	Male	10	33.3 %	08	26.7%
	Female	20	66.7 %	22	73.3 %
Smoker	Yes	2	6.67 %	4	13.3 %
	No	28	93.3 %	26	86.7 %
Alcohol consumer	Yes	5	16.6 %	8	26.7 %
	No	25	83.3 %	22	73.3 %
Fracture wrist	Left	07	23.3 %	07	23.3 %
	Right	23	76.7 %	23	76.7 %
Fracture type	Closed	30	100 %	30	100 %
	Compound	0	0 %	0	0 %
Management type	Conservative	10	33.3 %	15	50 %
	Operative	20	66.7 %	15	50 %

SD: standard deviation, IQR: inter quartile range.

Table 1. Baseline characteristics of the patients.

Parameters		Teriparatide (20 mcg/day)			Vitamin D_3 (1000 IU/day)		
		Baseline (Pre)	Post management 3-months	*P* value[a]	Baseline (Pre)	Post management 3-months	*P* value[a]
Green and O'Brien total score	Mean ± SD	8.5 ± 7.5	89.5 ± 8.2	<0.001	11.5 ± 6.4	85 ± 9.7	<0.001
	Median (IQR)	15 (0,15)	90 (80,100)		15 (11.25,15)	80 (78.75,96.25)	
Patient-rated Wrist Evaluation (PRWE) total score	Mean± SD	123.9 ± 9.8	8.5 ± 1.8	<0.001	120.1 ± 10.2	14.1 ± 6.9	<0.001
	Median (IQR)	127 (118,130)	9 (7.75,9)		118.5 (110,127.5)	12 (9,17.25)	

[a]*Wilcoxon signed-rank test.*

Table 2. Within group analysis of functional outcomes (pre and post management 3-months).

Results

Baseline characteristics

In this study, a total of 60 osteoporotic patients with DERF were enrolled (30 in each group). The baseline characteristics of the participants in both groups are included in Table 1. The mean age of the participants in the teriparatide group was 55.8±4.9 years, whereas in the vitamin D_3 group it was.57.4±5.8 years. The majority in both the groups had DERF involving the right wrist.

Treatment outcome

Functional outcome - Green and O'Brien score

Within the group

In the teriparatide group at post-management 3-months, there was a significant improvement in the functional outcome (total Green and O'Brien score) from the baseline (Z=-4.812, p<0.001). Similarly, in the vitamin D_3 group at post-management 3-months, there was a significant improvement in the functional outcome (total Green and

Parameter			Teriparatide (20 mcg/day)	Vitamin D_3 (1000 IU/day)	*P*-value [a]
Green and O'Brien score	Baseline (Pre-management)	Mean ± SD	8.5 ± 7.5	11.5 ± 6.4	0.103
		Median (IQR)	15 (0,15)	15 (11.25,15)	
	Post management 1- month	Mean ± SD	66.8 ± 10.3	64.8 ± 8.7	0.320
		Median (IQR)	65 (55,76.25)	65 (55,75)	
	Post management 3- months	Mean ± SD	89.5 ± 8.2	85 ± 9.7	0.036
		Median (IQR)	90 (80,100)	80 (78.75,96.25)	

SD: standard deviation, IQR: inter quartile range, [a]Mann-Whitney U test.

Table 3. Comparison of Green and O'Brien score in both the groups at various time points.

Parameter			Teriparatide (20 mcg/day)	Vitamin D_3 (100 IU/day)	*P*-value[a]
Patient-rated Wrist Evaluation (PRWE) total score	Baseline (Pre management)	Mean ± SD	123.9 ± 9.8	120.1 ± 10.2	0.150
		Median (IQR)	127 (118,130)	118.5 (110,127.5)	
	Post management 1-month	Mean ± SD	38.8 ± 13.9	46.2 ± 10.8	0.053
		Median (IQR)	31 (27,56)	49 (38,52.25)	
	Post- management 3-months	Mean ± SD	8.5 ± 1.8	14.1 ± 6.9	0.001
		Median (IQR)	9 (7.75,9)	12 (9,17.25)	

SD: standard deviation, IQR: inter quartile range, [a]Mann-Whitney U test.

Table 4. Comparison of Patient-rated Wrist Evaluation (PRWE) total score in both the groups at various time points.

O'Brien score) from the baseline (Z=-4.793, p<0.001). (Table 2).

Comparison between the two groups

At baseline (pre-management), the total Green and O'Brien scores in both groups were equally comparable. The total Green and O'Brien score was comparatively higher in the teriparatide group than the vitamin D_3 group at various time points (post-management 1-month and 3-months). However, at post-management 3-months, the median total Green and O'Brien score in the teriparatide group showed a significantly greater improvement of functional outcome (P=0.036) in comparison to the vitamin D_3 group. (Table 3)

Patient-reported outcome- Patient-rated Wrist Evaluation (PRWE)

Within the group

In the teriparatide group at post-management 3-months, there was a significant improvement in the patient-reported outcome (median total PRWE score) from the baseline (Z= -4.848, p<0.001). Similarly, in the vitamin D_3 group at post-management 3-months, there was a significant improvement in the patient-reported outcome (median total PRWE score) from the baseline (Z=-4.820, p<0.001) (Table 2).

Comparison between the two groups

At baseline (pre-management), the total PRWE scores in both groups were equally comparable. The total PRWE score was comparatively lower in the teriparatide group than the vitamin D_3 group at various time points (post-management 1-month and 3-months). However, at post-management 3-months, the median total PRWE score in the teriparatide group showed a significantly greater improvement of patient-reported outcome (P<0.001) in comparison to the vitamin D_3 group (Table 4).

Radiography assessment by Sarmiento score

At baseline (pre-management), the Sarmiento scores in both the groups were equally comparable and the majority in both groups were in 'Poor – Good 'grade. At post-management 1-month and 3-months, the teriparatide group showed a significantly greater improvement in the Sarmiento score as reflected by a higher frequency of patients in 'Good-Excellent' grade (P<0.05) in comparison to the vitamin D_3 group (Table 5).

Discussion

The findings of this study documented encouraging beneficial functional and radiological outcomes with

Parameter			Teriparatide (20 mcg/day)	Vitamin D_3 (100 IU/day)	*P*-value[a]
Sarmiento score	Baseline (Pre management)	Poor	7	4	0.079
		Fair	20	14	
		Good	1	5	
		Excellent	2	7	
	Post management 1-month	Fair	0	7	0.001
		Good	8	1	
		Excellent	22	22	
	Post management 3-months	Fair	0	7	0.002
		Good	7	1	
		Excellent	23	22	

[a]*Chi Square or Fishers Exact test, as appropriate.*

Table 5. Comparison of Sarmiento score in both the groups at various time points.

teriparatide supplementation, suggesting that teriparatide supplementation is a promising osteoanabolic agent to improve functional outcomes in DERF of osteoporotic patients.

Age-related decline in bone regenerative capacity and reduced bone mass remains a challenging issue, due to its negative impact on the progress of fracture healing and outcomes. Supplementation of vitamin D_3 along with calcium exerts a positive influence on bone health and now a routine standard treatment in the aging population for secondary prevention of fractures, osteoporosis, and fracture healing[9,10,20].

Fracture healing is a very complicated process that involves a delicate balance between resorptive and formative mechanisms. Recently, there has been an appealing interest in teriparatide, an osteoanabolic agent in fracture healing and management. It increases bone remodeling, formation, and density in osteoporosis and it reduces the risk of vertebral and non-vertebral fractures[21]. Additionally, it also accelerates fracture healing by improving the fracture callus, increasing bone remodeling[22,23]. The stimulatory effects of teriparatide on bone formation mainly have been explained by the 'anabolic window' (stimulate bone formation without stimulating bone resorption) phenomena[11,12].

Published clinical studies have documented and suggested that teriparatide accelerates bone healing and improves the functional recovery after fracture at various skeletal sites including cancellous bon[21-27], and the distal end of the radius has both cortical as well as trabecular bone components[12,13].

There is limited data in the literature on the efficacy of teriparatide supplementation in accelerating fracture healing and functional outcomes in osteoporotic patients of wrist fractures. This study was important since it analyzed and compared the effectiveness of teriparatide as an adjuvant osteoanabolic agent to improve the functional recovery in DERF of osteoporotic patients.

In this study, within the group analysis revealed that teriparatide and vitamin D_3 supplementation both significantly (P<0.001) improved the functional and radiological outcomes (total Green and O'Brien score and PRWE score, respectively) at post-management 3-months in comparison to baseline.

However, on comparing the two groups, we observed that teriparatide supplementation showed a significantly greater improvement of functional outcome (P=0.036) and patient-reported outcome (P<0.001) at post-management 3-months in comparison to vitamin D_3 supplementation in total Green and O'Brien score and PRWE score, respectively. In the radiological assessment, teriparatide showed a significantly greater improvement in Sarmiento score at 1-month and 3-months post-management as reflected by higher frequency in "Good-Excellent" grade (P<0.05) in comparison to the vitamin D_3 supplementation.

Thus, teriparatide and vitamin D_3 supplementation both significantly improved the treatment outcomes in elderly patients with DERF, but the improvement was significantly greater in the teriparatide group at post-management 3-months in comparison to the vitamin D_3.

To date, there is no head to head comparison of teriparatide with vitamin D_3 in DERF. Hence, we are not able to compare the results of our study directly.

Aspenberg et al.[16] in a prospective, randomized, double-blinded study in 102 postmenopausal osteoporotic women with DERF documented that teriparatide (20 ug /day) had a highly significant effect on reducing the median time to healing in cortices compared with placebo (post hoc analysis), suggesting that a fracture repair can be accelerated by teriparatide[16]. The study documented comparatively higher improvement of functional and PRWE outcomes in teriparatide (20 ug /day) than placebo[16].

Another post-hoc analysis has also documented a significant difference in the early appearance of the callus at 5 weeks and the time to cortical continuity/healing with teriparatide (20 ug /day) in DERF[23].

The beneficial findings of teriparatide supplementation in our study are somewhat similar and consistent with the findings documented in post-hoc analysis of a randomized clinical trial by Aspenberg et al.[16,23]. in postmenopausal osteoporotic women with DERF.

To the best of our knowledge, this is a first of a kind clinical study documenting beneficial functional outcomes with adjuvant teriparatide supplementation over Vitamin D_3 in osteoporotic patients with DERF. Teriparatide supplementation may be an effective therapeutic option, however; further robust clinical trials and studies are warranted to validate these beneficial results for the recommendation.

The present study has certain limitations. The research was conducted in a single-center hospital, with a small sample size (pilot study) and limited short-term follow-ups. Also, the study included heterogenic treatment groups. Thereby the beneficial outcomes of teriparatide may be difficult to extrapolate to a broader population. A longer follow-up period with a larger sample size and robust design is warranted to further validate the beneficial effects of teriparatide in future studies.

Conclusion

Teriparatide supplementation was effective and resulted in greater improvement in functional and radiologic outcomes in comparison to vitamin D_3 in DERF of osteoporotic patients. Adjuvant teriparatide therapy may be a therapeutic option to improve functional outcomes, however, further robust clinical studies are warranted for the recommendation.

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