

## Comparative Study To Evaluate The Effect Of Zolendronic Acid And Teriparatide On Bone Mineral Density In The Treatment Of Osteoporosis

\*Dr. Dilip Soring<sup>1</sup>, Prof. S. N. Chishti<sup>2</sup>, Prof. A. Mahendra Singh<sup>3</sup>,  
Dr. Shams Gulrez<sup>4</sup>, Dr. B. Punithavasanthan<sup>5</sup>, Dr. Rajkumar Debbarma<sup>6</sup>,  
Dr. Prabhu Shrinivas Prashanth<sup>7</sup>, Dr. Temjensunep<sup>8</sup>, Dr. Trinajit Debbarma<sup>9</sup>.  
<sup>1</sup>(Post graduate resident, Department of Orthopedics, Regional Institute of Medical Sciences, Imphal Manipur University, India)  
<sup>2,3</sup>(Professor Department of Orthopedics, Regional Institute of Medical Sciences, Imphal, Manipur University, India)  
<sup>4,5,6,7,8,9</sup>(Post graduate resident, Department of Orthopedics, Regional Institute of Medical Sciences, Imphal, Manipur University, India)  
Corresponding Author: \*Dr. Dilip Soring

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### Abstract:

**Background:** Osteoporosis is a systemic metabolic bone disease which is characterized by low bone mass and deterioration of bone micro-architecture, resulting in increased susceptibility to fractures. The pathological fracture due to osteoporosis is a serious medical problem and a notable burden on the health care system. Many patient will experience significant functional loss, poor health –related quality of life and higher mortality rate. Many breakthroughs have been made in order to prevent osteoporotic fracture and improve the quality of life. However, today, a completely safe, effective and generally accepted treatment for osteoporosis has not been defined yet. **Objectives:** This study is under taken to compare the effect of zolendronic acid and teriparatide on bone mineral density in the treatment of osteoporosis. **Methods:** 60 patient who attended Orthopedics department, RIMS, Imphal, during May 2015 to May 2017 and who fulfilled the inclusion criteria were included in the study, irrespective of sex and randomly divided into two group (30 patient each). Group-I was treated with zolendronic acid and Group-II was treated with teriparatide with equal amount of supplemental calcium and calcitriol. BMD by DEXA-scan was measured at the start of therapy, 6 months and 12 months after therapy. Statistical analysis was done using independent T-test value and results compared. **Result:** The mean T-score of the zolendronic acid group (group I) and teriparatide group (group II) at the start of therapy was  $-3.47 \pm 0.45$  and  $-3.40 \pm 0.49$ . The mean T-score of zolendronic acid group and teriparatide group after 6 month of therapy was  $-2.47 \pm 0.44$  and  $-2.46 \pm 0.43$ . The mean T-score of zolendronic acid group and teriparatide group after 12 months of therapy was  $-2.01 \pm 0.46$  and  $-1.39 \pm 0.40$ . **Conclusion:** Teriparatide results in better improvement of bone mineral density with better clinical improvement and less side effect compared to zolendronic acid.

**Keywords:** Osteoporosis, bone mineral density, DEXA- scan, teriparatide, zolendronic acid.

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### I. Introduction

Osteoporosis is a systemic metabolic bone disease which is characterized by low bone mass and deterioration of bone micro-architecture, resulting in increased susceptibility to fractures.<sup>1</sup> WHO has operationally define osteoporosis as bone density that falls 2.5 standard deviation below the mean for the young healthy adult of same sex and also referred to as T-score of  $-2.5$ .<sup>2,3</sup> The major concern with low BMD is the high risk of fractures to non-vertebral bones such as hip and to the wrist. A hip fracture may require extended hospital stay, surgical repair and rehabilitation therapy, and is associated with increased risk of death.<sup>4</sup> In addition, osteoporosis can lead to vertebral fractures which can be assessed both clinically and radiologically.<sup>5</sup> These pathological fracture due to osteoporosis is a serious medical problem and a notable burden on the health care system.<sup>6-8</sup> Many patient will experience significant functional loss, poor health–related quality of life and higher mortality rate.<sup>9-11</sup> The World Health Organization (WHO) reported that nearly 30% of woman over 50 years of age have osteoporosis and increased risk of fracture while one eighths of men carry risk of fracture.<sup>12</sup>

Many breakthroughs have been made in order to prevent osteoporotic fracture and improve the quality of life. However, today, a completely safe, effective and generally accepted treatment for osteoporosis has not been defined yet.<sup>13</sup>

Different pharmacologic drugs are available but none are considered superior as all these drugs are associated with some side-effects. The pharmacologic drugs which are available for the treatment of osteoporosis are bisphosphonate (zoledronic acid), parathyroid hormone 1 to 34 (teriparatide), calcitonin-tibolone and new experimental therapies - strontium ranelate, parathyroid 1 to 84, bazedoxifene, lasofoxifene, denosumab. Among these, bisphosphonate is most commonly used anti-resorptive agent which directly reduces the number of active osteoclasts by inhibiting their recruitment and also by inhibiting the osteoclasts-stimulating activity of osteoblasts.<sup>15-18</sup> Thereby bisphosphonates normalizes bone turnover, reduces number of bone remodeling units, prevents bone loss and deterioration of bone structure, and reduces fracture risk in patient with osteoporosis. Parathyroid hormone is an anabolic agent which directly increases osteoblasts production rate and inhibits apoptosis of osteoblasts, thereby leading to a rapid increases in skeletal mass as well as improvement of bone micro-architecture and strength.<sup>18-20</sup>

This study is under taken to compare the effect of zoledronic acid and teriparatide on bone mineral density in the treatment of osteoporosis.

## II. Materials And Method

Comparative randomized control study was conducted in the department of Orthopedics, Regional Institute of Medical Sciences, Imphal, Manipur from May 2015 to May 2017 after taking the ethical approval from the RIMS – Institutional ethics committee. Atleast 60 patient who fulfilled the inclusion criteria was included in the study, irrespective of sex and randomly divided in to two groups (30 patient each). Both the group received equal amounts of supplemental calcium and calcitriol in-combination.

Group I: Zoledronic acid was given in a dose of 5 mg IV infusion over a period of 30 minutes (single dose) in 30 patients.

Group II: Teriparatide was given in a dose of 20µg/day by subcutaneous injection for 3 month in 30 patients.

Inclusion criteria

1. Patient with primary osteoporosis, irrespective of sex.
2. BMD score of < 2.5.
3. 12 month follow up possible.

Exclusion criteria

1. Patient with secondary osteoporosis.
2. 12 month follow up not possible.
3. Allergic to zoledronic acid or teriparatide.
4. Significant medical co-morbidity.

Informed consent was taken from all the participants and details were recorded. All routine investigation and BMD by DEXA-scan was done routinely. After the treatment was initiated, each patient were followed-up at 6 months and 12 months and enquire about the subjective improvement such as decrease in bone pain, feeling of well being etc. A bone mineral density by DEXA-scan was taken at 6 months and 12 months. The results of BMD by DEXA-scan at the start of treatment and after the start of treatment at 6 months and 12 months were compared and analyzed using SPSS IBM Inc.

## III. Results

A total of 60 patients were included in the study (30 patients for each group) from May 2015 to May 2017. Each patient was followed-up at 6 and 12 month after the start of therapy. Out of 60 patients, 50 were female and 10 were male patient. The male and female ratio was 1:5. In group I (zoledronic acid group), there were 24 (80%) female patients and 6 (20%) male patients. In group II (teriparatide group), there were 26 (86.7%) female patients and 4 (13.3%) male patients. The mean age of the patient in Group I was 71.7±8.7 (range, 55-86) and in group II, the mean age was 72.1±8.4 (range, 59-88).

**Table 1:** Demographic data of treatment group.

Parameter	Group I (Zoledronic acid group)	Group II (Teriparatide group)	P-value
Age in years (mean±SD)	71.73±8.7	72.07±8.4	0.94
Gender (women/men)	24/6	26/4	0.49

During the subsequent follow up period, the subjective improvement in the clinical profile (decrease in bone pain, feeling of well-being, increase in weight and increased physical activity) of each patient were recorded at the 6 months and 12 months of therapy and compared between two groups. Of 30 patients in zolendronic acid group, 22 patient reported decreases in bone pain, 23 patient reported feeling of well-being, 15 patient showed increases in weight and 20 patients reported increase level of physical activity. Whereas in teriparatide group, out of 30 patient, 27 patient reported decrease in bone pain, 25 patient reported feeling of well-being, 4 patient reported increase in weight and 26 patient reported increase in the level of activity.

**Table 1:** Comparison of improvement in the clinical profile in both group at 12 months after therapy.

Clinical profile	Number of patient	
	Group I (Zolendronic acid group)	Group II (Teriparatide group)
Decrease in bone pain	22	27
Feeling of well-being	23	25
Increase in weight	15	4
Increased level of Physical activity	20	26

The T-score of the zolendronic acid group (group I) at the start of therapy range from -2.7 to -4.3 with a mean of  $-3.47 \pm 0.45$  whereas the T-score of the teriparatide group (group II) at the start of therapy range from -2.5 to -4.3 with a mean of  $-3.40 \pm 0.49$ . The T-score of zolendronic acid group after 6 month of therapy ranges from -2.0 to -3.5 with a mean of  $-2.47 \pm 0.44$  whereas in the teriparatide group, the T-score after 6 months of therapy ranges between -1.7 to -3.3 with a mean of  $-2.46 \pm 0.43$ . At the final follow-up, the T-score of zolendronic acid group after 12 months of therapy ranges between -1.2 to -2.8 with a mean of  $-2.01 \pm 0.46$  whereas the T-score of teriparatide group after 12 months of therapy ranges between -0.90 to -2.0 with a mean of  $-1.39 \pm 0.40$ .

The independent T-test value at the start of therapy is -0.55, after 6 months of therapy is -2.54 and after 12 months of therapy is -5.61. The degree of freedom at the start of therapy, after 6 months of therapy and after 12 months of therapy is 58. The P-value at the start of therapy was 0.58 which is statistically not significant. The P-value after 6 months of therapy and after 12 months of therapy is 0.01 and 0.00 which is statistically significant.

**Table 2:** The Comparison of T-score at the start of therapy, after 6 months and after 12 months of therapy.

Time point	T-score ( Mean $\pm$ SD )		Independent T-test value	Degree of freedom	P-value and inference
	Group I (Zolendronic acid group)	Group II (Teriparatide Group)			
At start of therapy	$-3.47 \pm 0.45$	$-3.40 \pm 0.49$	-0.55	58	0.58 (not significant)
After 6 months of therapy	$-2.74 \pm 0.44$	$-2.46 \pm 0.43$	-2.54	58	0.01 (significant)
After 12 months of therapy	$-2.01 \pm 0.46$	$-1.39 \pm 0.40$	-5.61	58	0.00 (significant)

In my present study, the T-score of the two groups are comparable before the start of therapy as the P-value is not significant. However, the T-score of teriparatide group shows higher value after 6 months and 12 months of therapy with better improvement of clinical profile as compared with the zolendronic acid group. Therefore, it can be concluded that teriparatide results in better improvement in the bone mineral density as compared to zolendronic acid.

In my present study, zolendronic acid group, 5 patient complain of fever, 8 patient complain malaise, and 6 patient complain of nausea whereas in the teriparatide group, 4 patient complain of skin problem (pain, redness, bruising) at the site of injection, 3 patient complain of leg cramps and 2 patient complain of dizziness after administration. No major adverse event or death was reported in both the group during study period.

#### IV. Discussion

Osteoporosis is a major global health problem associated with significant morbidity, mortality and socio-economic burden.<sup>21</sup> Most commonly it affects post-menopausal woman reflecting the hormonal cause in the development of osteoporosis. However, males are also affected. The major concern with osteoporosis are high risk of non-vertebral fractures of wrist or hip and also of vertebral fracture which can lead to compression of spinal vertebra.<sup>4,5</sup> However, osteoporosis is a preventable condition and different pharmacologic drugs have

been introduced for the treatment of osteoporosis which reduces the rate of bone loss and increases the strength of bone.

In our present study, we have compared the effect of zolendronic acid and teriparatide on bone mineral density in the treatment of osteoporosis and analyzed result by measuring the T-score at the start of therapy, at 6 months of therapy and at 12 months of therapy.

Zolendronic acid is a potent nitrogen containing bisphosphonate with a unique administration regime (once yearly, IV).<sup>14</sup> It is anti-resorptive agent which has a high affinity for mineralized bone and especially for sites of high bone turnover.<sup>14</sup> It inhibits osteoclast proliferation and induces osteoclast apoptotic cell death.<sup>17,18</sup> Once yearly zolendronic acid was initially approved for the treatment of multiple myeloma and for metastasis from solid tumour. However, it is now approved by the FDA for the treatment of post-menopausal osteoporosis.

In the HORIZON-PFT study conducted to determine the effects of the zolendronic acid in the case of post-menopausal osteoporosis, zolendronic acid was administered to 3881 patients at base line, 12<sup>th</sup> and 24<sup>th</sup> months. In zolendronic acid group, the morphometric vertebral fracture risk and hip fracture risk decreased by 70% and 41% respectively within 3 years as compared to placebo group.<sup>22</sup> Voskariddou et al<sup>23</sup> studied osteoporosis on thalassemia patient and administered 4mg IV zolendronate once every 6 months to one group, 4 mg IV zolendronate once every 3 months to another group and placebo treatment was applied to another group once every 3 months for 1 year. The patient who received 4 mg IV zolendronate once every 3 months were found to have higher lumbar spine BMD, whereas no such changes was detected in placebo group. Meenal Jain et al<sup>14</sup> reported mean T-score of -2.35 at the beginning of study and after 6 months of therapy with zolendronic acid, the T-score values were improved to -1.39. In our present study, the mean T-score at the beginning of study was -3.47±0.45, which improved to -2.74±0.44 after 6 months of therapy and -2.01±0.46 after the 12 months of therapy with zolendronic acid.

Zolendronic acid is mainly associated with some post-dose symptoms, including fever (18%), myalgia (9.4%), (flu like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%).<sup>24</sup> In the HORIZON study, patients treated with zolendronic acid were reported to suffer from the gastrointestinal side effects such as nausea (8.5% and 5.2%), vomiting (4.6% and 3.2%), diarrhea (6% and 5.6%), upper abdominal pain (4.6% and 3.1 %) and dyspepsia (4.3% and 4%) as compared to placebo group.<sup>25</sup> Osteonecrosis of the jaw bone can be seen in cancer patient using high dose of IV zolendronic acid.<sup>26</sup> The length of exposure seems to be the most important risk factor for this adverse event and caution is required for use of bisphosphonate beyond 2 years. The incidence is reported to be 71.5%.<sup>27</sup> In the our present study, 5 patient complain of fever, 8 patient complain myalgia, and 6 patient complain of nausea after IV zolendronic acid administration. Teriparatide is a recombinant human parathyroid hormone and clinically used as anabolic agent in the treatment of osteoporosis. It directly increases the osteoblast production rate and inhibits apoptosis of osteoblast, thereby leading to rapid increase in skeletal mass as well as improvement in the bone micro-architecture and strength.<sup>18-20</sup> Parathyroid hormone when administered intermittently activate osteoblast more than the osteoclast which is seen most markedly in cancellous bone. However, one of the potential limitations of parathyroid hormone is that its stimulatory effect on intra-cortical bone remodeling can increase cortical porosity. This may not translate into decreased mechanical strength, however because the porosity is concentrated at the endocortical surface and may be offset by increased periosteal apposition and increased cortical thickness.<sup>28-30</sup>

Teriparatide is should not be prescribed in patients with hypercalcemia, pregnancy & lactation, metabolic bone disease other than osteoporosis, severe renal impairment, open epiphysis or prior radiation therapy involving the bone and malignant bone disease such as osteosarcoma.<sup>31</sup> This risk was considered by FDA as extremely rare (1-100,000 people) and is only slightly more than the incidence in the population over 60 years old.

Neer et al<sup>32</sup> reported decrease in the vertebral and non-vertebral fractures in postmenopausal woman treated with teriparatide for the treatment of osteoporosis. Meenal Jain et al<sup>14</sup> reported mean T-score of -2.35 at the start of therapy which improved to -1.35 after 6 months of therapy with teriparatide. They concluded with result showing better improvement in teriparatide group compared to zolendronic acid group. In our present study, the mean T-score at start of therapy was -3.40±0.49 which improved to mean T-score of -2.46±0.43 at 6 months of therapy and -1.39±0.43 at 12 months of therapy. In teriparatide group, 4 patient complain of skin problem (pain, redness, bruising) at the site of injection, 3 patient complain of leg cramps and 2 patient complain of dizziness after administration. Both the group has shown reasonable improvement in the clinical profile and BMD (T-score) with reasonable safety profile. However, large scale comparative clinical trials are required to support our study.

## V. Conclusion

From our present study, we conclude that both zolendronic acid and teriparatide are good pharmacologic agents which results in significant improvement in bone mineral density in the treatment of osteoporosis. The teriparatide is expensive and require daily administration for 3 months as compared to

zolendronic acid which is available at reasonable price and require once yearly administration only. However, the teriparatide shows better clinical efficacy, better improvement in the bone mineral density and less side effect as compared to the zolendronic acid. We recommend a large clinical trial to ascertain the effects of zolendronic acid and teriparatide in the treatment of osteoporosis and to substantiate our findings.

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**Authours profile:**



**Dr. Dilip Soring** has passed MBBS in 2014 from Regional Institute Of Medical Science. He is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal , Manipur, India.

**Dr. S. N. Chishti** is a Professor, Department Of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. A. Mahendra Singh** is a Professor, Department Of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. Shams Gulrez** is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. Punithvasanthan** is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. Rajkumar Debbarma** is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. Shrinivas Prabhu** is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. Temjensunep** is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

**Dr. Trinajit Debbarma** is a postgraduate trainee, Department of Orthopaedic, Regional Institute Of Medical Science, Imphal, Manipur, India.

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