Efficacy of Zoledronic Acid in Conjunction with Calcium Carbonate and Vitamin D3 in Osteoporotic Hip Fracture and Its Effects on Bone Density and Bone Metabolism Markers

RONG LI, JUAN ZHOU AND YIJUN XIANG*

Department of Endocrinology, Chengdu Eighth People's Hospital (Chengdu Chronic Disease Hospital, Chengdu Elderly Service Demonstration and Training Center), Jinniu, Chengdu 610036, China

To investigate the efficacy of zoledronic acid in conjunction with calcium carbonate and vitamin D3 in elderly individuals with osteoporotic hip fracture and its effects on bone density and bone metabolism markers. Between June 2020 and June 2022, a total of 240 elderly individuals with osteoporotic hip fracture were enrolled in the study. They were then allocated into two equal-sized groups, namely the observation group and the control group, with 120 individuals in each group. For the control group, calcium carbonate and vitamin D3 were taken orally at a dosage of 600 mg/day, while the observation group received an annual intravenous infusion of zoledronic acid, totaling 5 mg, in addition to the standard control group treatment. Following treatment duration of 1 y, a comparison was made between the two groups in terms of bone density, bone metabolism markers (alkaline phosphatase), serum calcium and phosphorus levels, pain intensity, and 36-item short form survey life quality scores. At the end of a 1 y treatment period, substantial advancements in bone density, bone metabolism markers (alkaline phosphatase), hip joint function, and overall life quality were evident in both groups. A remarkable reduction in hip pain was observed, with the observation group exhibiting greater improvement compared to the control group ($p<0.05$). To sum up, the utilization of zoledronic acid in conjunction with calcium carbonate and vitamin D3 has demonstrated significant effectiveness in improving bone metabolism, reducing pain, enhancing joint function, and elevating the life quality among elderly individuals with osteoporotic hip fractures. As such, this treatment approach warrants wide-scale adoption and promotion.

Key words: Zoledronic acid, calcium carbonate, vitamin D3, osteoporotic hip fracture, bone density, bone metabolism markers

Scientific investigations have shown that osteoporosis is a systemic condition distinguished by the reduction of bone density and mass, along with the presence of structural impairments in bone microarchitecture. These factors contribute collectively to increased bone fragility and susceptibility to fractures[1,2]. Elderly hip fractures due to osteoporosis are common skeletal diseases, especially among the elderly population[3,4]. Currently, the main methods for treating elderly hip fractures caused by osteoporosis include surgical repair and medication. Traditional surgery only addresses the short-term fracture problem and cannot resolve long-term issues such as osteoporosis and poor stability of the implant surrounding bone, resulting in unsatisfactory treatment outcomes. Although surgery can restore fracture stability, rehabilitation after a fracture still poses challenges. Meanwhile, medication has achieved certain results in the prevention and treatment of osteoporosis, but there are still issues with insufficient efficacy and side effects. Researchers believe that enhancing postoperative bone mass and reducing fracture risk are the primary treatment objectives[5-7]. Zoledronic acid and calcium carbonate with vitamin D3 are

***Address for correspondence**
E-mail: 13208368333@163.com

commonly used medications in treating osteoporosis. Zoledronic acid, a third-generation bisphosphonate, exhibits the ability to selectively and swiftly bind to minerals in the bone, thereby directly and indirectly impeding osteoclast-induced bone resorption and mitigating the risk of fractures and bone loss[8-10]. Calcium carbonate with vitamin D3 tablets is a combination formulation of calcium carbonate and vitamin D3, which not only effectively supplements calcium in the body but also participates in calcium and phosphorus metabolism, promoting calcium absorption and playing an important role in bone formation[11]. However, there is still a lack of systematic and objective evaluation of the efficacy of zoledronic acid combined with calcium carbonate and its impact on bone density, bone metabolism markers, hip joint function, and quality of life in elderly hip fracture individuals. Accordingly, this research strives to explore the efficacy of combining zoledronic acid and calcium carbonate in managing osteoporosis-induced hip fractures in elderly individuals. Additionally, it seeks to appraise the influence of this treatment approach on bone density, bone metabolism markers, hip joint function, and life quality. Through a systematic research design and rigorous data analysis, we hope to provide more effective treatment strategies for clinical practice and improve the life quality and rehabilitation outcomes of elderly hip fracture individuals. The study population consisted of 240 elderly individuals who had experienced osteoporotic hip fractures and subsequently underwent Total Hip Arthroplasty (THA) at our hospital between June 2020 and June 2022. Inclusion criteria meeting the diagnostic criteria for osteoporosis in the elderly[12]; receiving THA treatment after hip fracture; aged 65 y to 85 y and approval from the medical ethics committee and signed informed consent forms by the patients and their family members. Patients with malignant tumors or severe cardiovascular, liver, or kidney dysfunction; secondary osteoporosis caused by endocrine or other diseases; patients with diseases affecting bone metabolism, such as parathyroid or adrenal disorders; patients with allergies to the medications used in this research and patients with mental or intellectual disabilities were excluded. Based on a random number table, the individuals were assigned to a control group and an observation group, with 120 cases in each group. Among them, the control group consisted of 52 males and 68 females, with an age range of 66 y to 78 y and a mean age of (70.68±4.52) y. There were 62 cases on the left side and 58 cases on the right side. The observation group consisted of 56 males and 64 females, with an age range of 65 y to 79 y and a mean age of (71.84±4.72) y. There were 59 cases on the left side and 61 cases on the right side. There were no notable disparities in demographic factors between groups ($p>0.05$), suggesting similarity. All patients received routine pain relief, anticoagulation, and infection prevention treatments after THA. In the control group, oral calcium carbonate with vitamin D3 (600 mg) was administered starting from the day after surgery, once daily. Rehabilitation training included ankle flexion-extension exercises using an ankle pump for patients to perform after awakening from anesthesia, routine lower limb pneumatic compression to prevent venous thrombosis, and assisted ambulation with walking aids on the 2nd d after surgery. From 1 w to 4 w post-surgery, family members engaged in leg massages, executed straightforward leg elevation exercises, facilitated muscle isometric contraction training, and administered passive joint range of motion exercises. Weight-bearing exercises with crutches were gradually started based on fracture healing progress between 6 w and 12 w after surgery. At 12 w post-surgery, weight-bearing exercises on the affected limb and training for activities of daily living continued. Alongside the treatment provided to the control group, the observation group underwent intravenous drip administration of zoledronic acid (5 mg) within the 1st w following the surgery, with a frequency of once per year. Adequate hydration was ensured through the administration of a 0.9 % sodium chloride solution before and after the treatment, aiming to prevent any adverse drug reactions. The evaluation of treatment effectiveness was conducted after the completion of one treatment course. After 1 y of treatment, the following indicators were compared between the two groups; bone density, bone metabolism markers (Alkaline Phosphatase (ALP)), serum calcium and phosphate levels, pain levels, and 36-Item Short Form Survey (SF-36) life quality scores. The real values of Lumbar spine (L1-L4) and the unaffected side femoral neck bone density were measured prior to treatment and 1 y following treatment using a WA-

type dual-energy X-ray bone density scanner. In bone metabolism markers (ALP), and serum calcium and phosphate levels, venous blood samples were collected before treatment and 1 y after treatment from both groups. After centrifugation and serum separation, ALP levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA), and Calcium (Ca) and Phosphate (P) levels were measured using an automatic biochemical analyzer (model: ADVIA1800). Pain levels were assessed using the Visual Analog Scale (VAS) at 1 w and 1 y after surgery. The VAS is a self-reported pain measurement scale. Hip joint function was evaluated using the Harris hip score[13]. Within the range of 0 to 100, scores <70 are indicative of subpar function, scores falling between 70 and 79 signify moderate function, scores ranging from 80 to 89 signify commendable function, while scores exceeding 90 signify outstanding function. The SF-36 health survey was used to assess patients' life quality[14]. With a total of 8 dimensions and 36 items, the survey employs a scoring system that ranges from 0 to 100 for each dimension. Higher scores within each dimension correspond to a superior level of life quality. Statistical Package for the Social Sciences (SPSS) 25.0 will be utilized to perform the statistical analysis in this research. Continuous variables will be reported as means and standard deviations (x±s) and analyzed using t-tests. Categorical variables will be presented as frequencies and percentages (n %) and analyzed using Chi-square (χ^2) tests. To establish statistical significance, a significance level of $p<0.05$ will be employed. Prior to treatment commencement, no significant variation in bone density was observed at the L_{2-4} lumbar vertebrae and unaffected side femoral neck between the two groups ($p>0.05$). After a treatment duration of 1 y, there was a notable increase in bone density at the lumbar vertebrae and unaffected side femoral neck compared to baseline values, with a more notable improvement noted in the observation group ($p<0.05$) (Table 1). Before treatment initiation, no notable variation in the levels of the bone metabolism marker (ALP) was noted between the two groups ($p>0.05$). Subsequent to 1 y of treatment, both groups experienced a significant elevation in ALP levels when compared to pre-treatment levels, with a more distinct increase observed in the observation group ($p<0.05$). Additionally, no remarkable differences were found in the serum calcium and phosphate levels prior to and following treatment in either group ($p>0.05$) (Table 2). Before treatment was administered, no remarkable variation was observed in hip joint function and VAS scores between the two groups ($p>0.05$). Following 1 y of treatment, significant improvements in hip joint function were evident in both groups compared to pre-treatment levels, with a higher Harris score seen in the observation group ($p<0.05$). Notably, the VAS scores substantially decreased in both groups following treatment, with a lower score recorded in the observation group ($p<0.05$) (Table 3). At baseline, no notable disparities in the SF-36 scores between the two groups was observed ($p>0.05$). Following 1 y of treatment, significant improvements were observed in the SF-36 scores in both groups compared to pre-treatment levels, with a higher increase noted in the observation group ($p<0.05$) (Table 4). Osteoporotic hip fractures have garnered significant attention as a major health issue affecting the aging population. The postoperative rehabilitation process for osteoporotic hip fractures after THA is lengthy, and osteoporosis can accelerate the decline in postoperative bone mass, significantly impacting patient prognosis. Therefore, anti-osteoporosis treatment is highly significant in promoting patient recovery and minimizing the risk of recurrent fractures[15]. The objective of this research was to figure out the effectiveness of combining zoledronic acid and calcium carbonate in elderly individuals with osteoporotic hip fractures, with a particular emphasis on evaluating its impact on bone density and markers associated with bone metabolism. Initially, prior to treatment initiation, no notable variations between the observation and control groups in terms of bone density, markers of bone metabolism was observed, hip joint function, pain scores, and life quality scores. This indicates that the baseline data between groups were similar and comparable. Secondly, following 1 y of treatment, the observation group experienced substantial increases in bone density at the lumbar vertebrae and unaffected side femoral neck. Notably, these increases were remarkably higher in comparison to the control group. These findings indicated that the administration of zoledronic acid in combination with calcium carbonate has a favorable effect on improving bone density in

elderly patients suffering from osteoporotic hip fractures. In addition, the observation group displayed a greater increase in bone metabolism marker (ALP) levels, suggesting that the combination treatment might exert a favorable effect on the control of bone metabolism activity. Furthermore, we observed significant improvement in hip joint function, with higher Harris scores, in the observation group after treatment. The amelioration in hip joint function may be associated with the upsurge in bone density and the control of bone metabolism. Moreover, the VAS scores decreased more in the observation group compared to the control group following treatment, indicating that zoledronic acid combined with calcium carbonate not only improves bone quality but also alleviates pain symptoms. Additionally, the SF-36 scores, reflecting the life quality, significantly increased after treatment, with a higher increase in the observation group. This suggests that the combination treatment may contribute to overall health and an improved life quality for patients. However, it is important to acknowledge the limitations of this study. This research was conducted in a single center and was non-randomized, which may introduce biases due to the sample size and potential selection bias. Besides, it is worth noting that the study primarily observed short-term efficacy, and long-term follow-up and continuous observation might yield different outcomes. In summary, this research concludes that zoledronic acid in conjunction with calcium carbonate has the potential to improve bone density, bone metabolism activity, hip joint function, and life quality in elderly individuals with osteoporotic hip fractures. Nonetheless, additional randomized controlled trials are necessary to validate these findings and delve deeper into the mechanisms of treatment and long-term effectiveness of combining zoledronic acid with calcium carbonate.

TABLE 1: COMPARISON OF BONE DENSITY

Group (n=120)	L_{2-4}		Contralateral femoral neck	
	Before	After	Before	After
Observation	0.75±0.16	0.93±0.21	0.71±0.16	0.84±0.17
Control	0.77±0.16	0.85±0.18*	0.68±0.16	0.72±0.16
t	1.152	-3.162	-1.743	-5.668
p	0.250	0.002	0.083	0.000

Note: (*) indicates significant difference after treatment compared with before treatment

TABLE 2: COMPARISON OF ALP, CA AND P LEVELS

Group (n=120)	ALP (U/l)		Ca (nmol/l)		P (nmol/l)	
	Before	After	Before	After	Before	After
Observation	120.45±20.88	176.11±32.08*	2.21±0.20	2.26±0.24	1.56±0.31	1.58±0.30
Control	118.18±24.22	161.92±28.54*	2.20±0.21	2.32±0.24	1.60±0.32	1.54±0.34
t	-0.78	-3.62	-0.287	1.698	1.161	-0.939
p	0.436	0.000	0.774	0.091	0.247	0.349

Note: (*) indicates significant difference after treatment compared with before treatment

TABLE 3: COMPARISON OF HIP JOINT FUNCTION AND VAS SCORE

Group (n=120)	Harris score		VAS score	
	Before	After	Before	After
Observation	39.55±4.14	80.73±6.67*	6.78±1.03	4.66±0.93*
Control	39.63±3.78	92.37±7.65*	6.74±0.92	5.20±0.85*
t	0.163	12.549	-0.330	4.718
p	0.871	0.000	0.742	0.000

Note: (*) indicates significant difference after treatment compared with before treatment

TABLE 4: COMPARISON OF SF-36 SCORES

Group (n=120)	SF-36		t	P
	Before	After		
Observation	29.86±5.13	83.18±7.32	65.342	0.000
Control	31.04±4.90	72.49±6.61	-55.156	0.000
t	1.828	11.868	-	-
p	0.069	0.000	-	-

Author's contributions:

Rong Li and Juan Zhou have contributed equally to this work.

Conflict of interests:

Rong Li and Juan Zhou have contributed equally to this work.

REFERENCES

1. Zhang J. Effect of calcitriol on osteoporotic hip fracture in postmenopausal women and its effect on bone metabolism and bone mineral density. J Math Med Pharmacol 2020;33(5):3.
2. Zhang S, Liu Z, Zhang P. Short-term efficacy of anti-osteoporosis capsule in the treatment of senile osteoporotic hip fracture. J Hubei Univ Tradit Chin Med 2020;5:3.
3. Wang X. Clinical effect of traditional Chinese medicine-assisted hip arthroplasty in the treatment of femoral neck fracture in the elderly. Med Health Care 2021;29:109110.
4. Guo Y. Analysis of types, treatment, mortality and related risk factors of hip fracture in the elderly. Proceedings of the 11th National Trauma Academic Conference of Chinese Medical Association; 2017. p. 278.
5. Li L, Jing S, Sun X. Effect of Danhong injection combined with osteopeptide injection on coagulation function and bone metabolism in elderly patients with osteoporotic hip fracture after operation. Chin J Gerontol 2019;39(18):3.
6. Ge M, Duan Z, Guo Y. Effect of alfacalcidol combined with tonifying kidney and activating blood circulation on bone metabolism and bone mineral density of osteoporotic hip fracture in elderly women. J Integr Tradit Chin West Med 2018;27 (17):4.
7. Morin SN, Yan L, Lix LM. Long-term risk of subsequent major osteoporotic fracture and hip fracture in men and women: A population-based observational study with a 25-year follow-up. Osteoporos Int 2021;32(12):2525-32.
8. Cui M. Effect of zoledronic acid on peripheral blood lymphocyte subsets in patients with osteoporosis and its significance. Shandong Univ 2017;6:2-8.
9. Wang D. Qu Y, Kang M. Comparative analysis of acute adverse reactions of zoledronic acid in conservative treatment and surgical treatment of postmenopausal osteoporotic fracture. Proceedings of the 17th Orthopaedic Conference of the Chinese Medical Association and the 10th COA International Congress; 2015. p. 1.
10. Chen Y, Sheng Yi, Liu D. Zoledronic acid improves low back pain after posterior lumbar interbody fusion in patients with osteoporosis. J Spinal Surg 2019;17(5):5.
11. Westby EP, Lynde C, Sussman GN. Chronic urticaria: Following practice guidelines. Skin Ther Lett 2018;23(3):1-4.
12. Zhang Z, Zhujun L, Li S, Yang H, Yu H, Tang G, *et al.* Chinese expert consensus on diagnostic criteria of osteoporosis. 3rd ed. Chin J Osteopor 2014;20(9):1007-10.
13. Xing L, Chi R, Wang Xi. Effect of acupoint massage combined with TCM emotional nursing on postoperative rehabilitation of osteoporotic hip fracture. Chin Rural Med 2023;30(4):20-1.
14. Li C, Shi X. Evaluation of bone mineral density and SF-36 effect of Yiwenjing prescription on prevention and treatment of postmenopausal osteoporotic hip fracture. Chin Mod Appl Pharm 2015;32(5):4.
15. Ye X, Tang Y, Wu M. Effect of zoledronic acid on serum levels of BGP, IGF-1, CTX, DPD and SHBG in elderly patients with osteoporotic hip fracture. Int J Lab Med 2019;40(8):4.

This article was originally published in a special issue, "Exploring the Role of Biomedicine in Pharmaceutical Sciences" Indian J Pharm Sci 2024:86(1) Spl Issue "205-209"