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Early initiation of zoledronic acid does not impact bone healing or clinical outcomes of hallux valgus orthomorphia

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Abstract

Objective: This prospective randomized controlled study was performed to determine whether early drug use for osteoporosis impacts bone healing after orthomorphic surgery for hallux valgus (HV) in menopausal patients with osteoporosis.

Methods: This study included 113 consecutive patients with osteoporosis who underwent a combination of Lapidus arthrodesis and Akin osteotomy for treatment of HV. The patients were randomly divided into a zoledronic acid (ZOL) group (5-mg intravenous injection of ZOL, n = 56) and a placebo group (n = 57); both ZOL and placebo were administered 1 week postoperatively. Radiographs were taken preoperatively and at 1, 6, 8, 10, and 12 weeks postoperatively to record the time of the first tarsometatarsal joint (FTJ) fusion and Akin osteotomy site healing. Clinical outcomes were evaluated using the American Orthopedic Foot and Ankle Society (AOFAS) scoring system 24 weeks after surgery.

Results: There were no statistically significant differences in the FTJ fusion time after Lapidus arthrodesis, healing time after Akin osteotomy, or postoperative AOFAS scores between the two groups.

Conclusion: Early initiation of ZOL does not impact the bone healing or clinical outcomes of orthomorphic surgery for HV in postmenopausal women diagnosed with osteoporosis after a combination of Lapidus arthrodesis and Akin osteotomy.

Keywords

Zoledronic acid, hallux valgus orthomorphia, osteoporosis, Lapidus arthrodesis, Akin osteotomy, postmenopause

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Introduction

Osteoporosis is a common public health concern, particularly among women. About 30% of postmenopausal women in developed countries are estimated to have osteoporosis.[1] Hallux valgus (HV) is a highly prevalent forefoot deformity that is more prevalent among older than younger individuals and among women than men.[2] HV is also associated with quality of life and general health.[3,4] Symptomatic HV, which is usually due to osteoarthritis in the first metatarsophalangeal joint (MTJ) or the first tarsometatarsal joint (FTJ), must be treated by surgery.

Since its introduction in 1934, Lapidus arthrodesis (arthrodesis of the FTJ) has been commonly applied in patients with HV with deformity of the metatarsal cuneiform angle.[5] The nonunion rate of Lapidus arthrodesis reportedly ranges from 3.3% to 12.0%, which is the highest rate of surgical failure among all surgeries for HV.[6] Although the correction power of Lapidus arthrodesis is very high, some patients with severe deformities still need additional angular or rotational correction in the proximal phalanx by undergoing combined surgical procedures. Akin osteotomy, the most widely used type of proximal phalanx osteotomy, is a well-known adjunct to other procedures in patients with an increased interphalangeal angle or distal articular set angle.[5,7]

Although no direct epidemiological investigation of HV and osteoporosis has been performed, postmenopausal women account for a significant proportion of patients with HV undergoing surgical orthomorphia. Therefore, attention should also be paid to osteoporosis treatment in these patients. However, whether early drug use for osteoporosis impacts the bone healing and clinical outcome after surgical orthomorphia remains unknown.

The effect of early initiation of bisphosphonates (BPs) after bone surgery is controversial.[8] BPs might inhibit bone metabolism, which may impact the remodeling of the bone mineral content and tensile strength of the healing bone.[9,10] Zoledronic acid (ZOL), one of the most commonly used BPs, has been found to be the most effective BP for prevention of fracture at any site. It is administered only once a year intravenously and can also improve hip structural and biomechanical properties.[11,12] Many randomized controlled trials have evaluated ZOL application after orthopedic surgery, and these studies have shown that ZOL has neither a clinically evident effect on fracture healing nor a negative effect on the transforaminal lumbar interbody fusion rate.[13,14] Because of the particularities of the procedure and location of surgical orthomorphia for HV, it is still necessary to demonstrate the effect of early BP initiation on women with osteoporosis undergoing surgical orthomorphia for HV. Therefore, we investigated such patients in this prospective randomized controlled study using ZOL under consideration of its safety and patient compliance. We hypothesized that early intravenous injection of ZOL has no adverse effect on bone healing or clinical outcomes of orthomorphic surgery for HV.

Methods

The Ethics Committee of our university approved this study (approval no. [2014] 2014-7-3). All procedures in this study were in compliance with ethical standards. All patents participating in the study provided written informed consent.

Study population

This study included postmenopausal women who presented to the foot and ankle center of our university-affiliated hospital from August 2014 to June 2015 and were diagnosed with moderate or severe

HV by one experienced foot and ankle surgeon using the Manchester scale.[15] These patients were carefully evaluated for indications for a combination of Lapidus arthrodesis and Akin osteotomy.

Indications for combined surgery (Lapidus arthrodesis and Akin osteotomy)

The indications for combined surgery in this study were subjective clinical FTJ hypermobility of >1 cm,[16] an increased metatarsal cuneiform angle, and an interphalangeal angle of $>10^\circ$ as evaluated by an experienced foot and ankle surgeon; pain while walking; lesser metatarsal overload; and visible osteoarthritis in the first MTJ or FTJ on radiographs.[5] A preoperative X-ray of one 61-year-old woman is shown in Figure 1.

The inclusion criteria for this study were as follows: age of 50 to 65 years, premenopausal women diagnosed with HV and deemed suitable for combined surgery,[17] diagnosis of osteoporosis by dual energy X-ray absorptiometry examination, T-score of less than -2.5,[18] no history of treatment for osteoporosis, and consent to participate in the study.

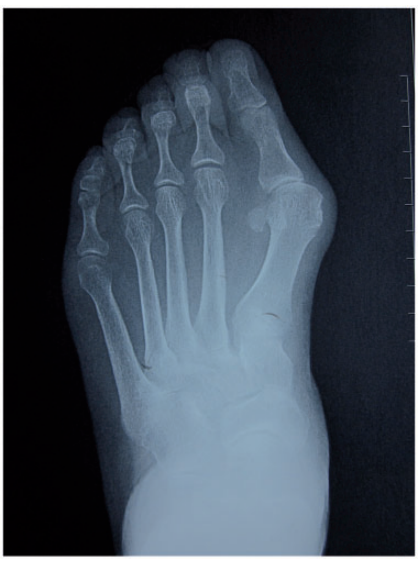

Figure 1. Radiograph of a 61-year-old woman who was diagnosed with hallux valgus. The preoperative anteroposterior radiograph showed a metatarsophalangeal angle of 45° and intermetatarsal angle of 21°.

The exclusion criteria were as follows: any contraindication to ZOL therapy; any condition capable of affecting the bone mineral density or bone metabolism, such as renal or adrenal insufficiency, rheumatoid arthritis, thyroid disease, Parkinson's disease, or chronic obstructive pulmonary disease or any history of taking any medication known to affect bone mineral density, such as corticosteroids; and a history of treatment with BPs or an allergy to BPs.

Group assignment and randomization

All eligible patients were randomly allocated to either the ZOL group or the placebo group (saline solution) using a computer-generated list. The CONSORT follow-up diagram is shown in Figure 2. The randomization and consecutive preparation of the study medications were labeled with the study number of the subject and supplied to the study personnel to ensure blinding of the patients, investigators, and site personnel by a pharmacist. All infusions were 100 mL in volume (containing 5 mg ZOL or just saline solution) and were infused over a period of 15 minutes. All patients were instructed to begin supplementary intake of calcium and vitamin D (1000 mg and 400 IU per day, respectively). All patients were followed up for 24 weeks after the surgery. No concomitant osteoporosis therapy such as raloxifene or hormone replacement therapy was allowed.

Surgery and postoperative care

All procedures were performed by one expert foot and ankle surgeon. A longitudinal incision was used for the procedure on

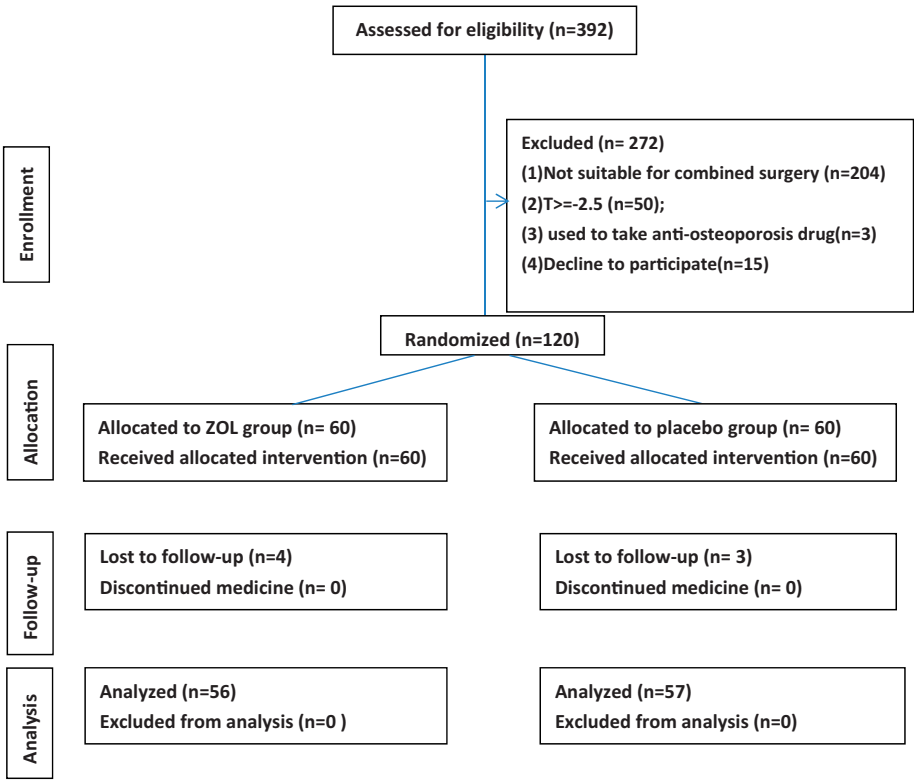

Figure 2. A CONSORT flow diagram for enrollment and analysis. ZOL group use zoledronic acid 5mg at one week postoperatively. Placebo group use saline solution at one week after surgery.

the first MTJ and FTJ. The first metatarsocuneiform joint was exposed through a transverse capsulotomy for Akin osteotomy, and a transarticular lateral release was then performed in all cases with release of the adductor halluces and lateral metatarsal sesamoid complex. The joint surfaces of the FTJ were completely debrided of all articular cartilage by means of a curette, burr, or sagittal saw. The first metatarsal was repositioned on the medial cuneiform to correct the metatarsus primus valgus deformity. An axial load was applied to the first metatarsal, compressing it against the first cuneiform. Fixation was accomplished with a minimum of two fully threaded, cannulated, stainless steel screws across the fusion site.[16,19] Akin medial closing wedge osteotomy of the proximal phalanx was added where both surfaces of the osteotomy were fully encountered, and stabilization was performed with a single screw.

The patients were placed in a non-weight bearing padded splint for 2 weeks after surgery. At 2 weeks, the sutures were removed and all patients were placed in DARCO OrthoWedge off-loading shoes (DARCO International, Inc., Huntington, WV, USA) to reduce the weight-bearing pressure on the forefoot. They remained non-weight bearing until 6 weeks postoperatively but were allowed to progress to full weight bearing as tolerated on the operative leg with the assistance of crutches and the protection of

the off-loading shoes. The time point at which they became full weight bearing was determined by our senior manager according to the radiographic outcomes.

Outcome measures

All patients were asked to return to our outpatient department at 6, 8, 10, and 12 weeks after surgery. Anteroposterior and oblique radiographs of the foot were taken. Fusion of the FTJ and bone healing of the Akin osteotomy site were assessed in terms of whether trabecular bone was seen going through the surface of the joint or osteotomy site (the surface of the FTJ or osteotomy site were vague) compared with the first radiograph taken 1 week after surgery (Figure 3(a) and (b)). Clinical outcomes including walking pain and foot function were assessed by the American Orthopedic Foot and Ankle Society (AOFAS) score before and 24 weeks after surgery.

Statistical analysis

SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Chi-square analysis was performed to estimate the relation between ZOL injection and the fusion time of the FTJ, healing of the Akin osteotomy, and clinical outcomes (AOFAS score). The level of significance was set at $P < 0.05$.

Results

Patients

In total, 392 postmenopausal women (50–65 years old) were assessed for eligibility in this study. We chose this age range because in our clinical experience, women of this age have the highest request for orthomorphia, have high mobility despite osteoporosis, and are mostly in good general health. These factors helped to exclude the effects of other systemic diseases. Of the 392 women, 272 were excluded for various reasons, and the remaining 120 were randomized (60 in the ZOL group and 60 in the placebo group). After loss to follow-up, 56 patients remained in the ZOL group and 57 remained in the placebo group. These data are presented in the CONSORT diagram (Figure 1). (Although 23 patients with HV were suitable for combined surgery in both feet, we performed surgery on one side first under consideration of their rehabilitation during the study). The baseline characteristics of the patients in the ZOL and placebo group, including nonsteroidal anti-inflammatory drug use, alcohol use, body mass index, age, diabetes, parathyroid hormone, and other factors are shown in Table 1.

Radiographic assessment

Anteroposterior and oblique radiographs of the foot were taken at 6, 8, 10, and 12 weeks to evaluate the fusion of the FTJ and bone healing of the Akin osteotomy. Bridging bony trabeculation across the surface of the FTJ or the osteotomy site was defined as either "none" when there was no change at the surface of the FTJ or the osteotomy site compared with the appearance on the radiograph obtained immediately after surgery (Figure 3(a) and (b)) or "present" when the surface of the FTJ or the osteotomy site was vague (Figure 3(c) and (d)).

At 8 weeks, 12 (21.4%) patients exhibited nonunion in the ZOL group and 14 (24.6%) patients exhibited nonunion in the placebo group. The difference was not statistically significant. At 12 weeks, one (1.8%) patient exhibited nonunion in the ZOL group and two (3.5%) patients exhibited nonunion in the placebo group. This difference was also not statistically significant. If the FTJ had failed to fuse after 12 weeks, revision surgery was performed. All three patients achieved FTJ fusion after the revision surgery.

The bone healing time of the Akin osteotomy was also determined. At 8 weeks, nine (16.0%) patients exhibited nonunion in the

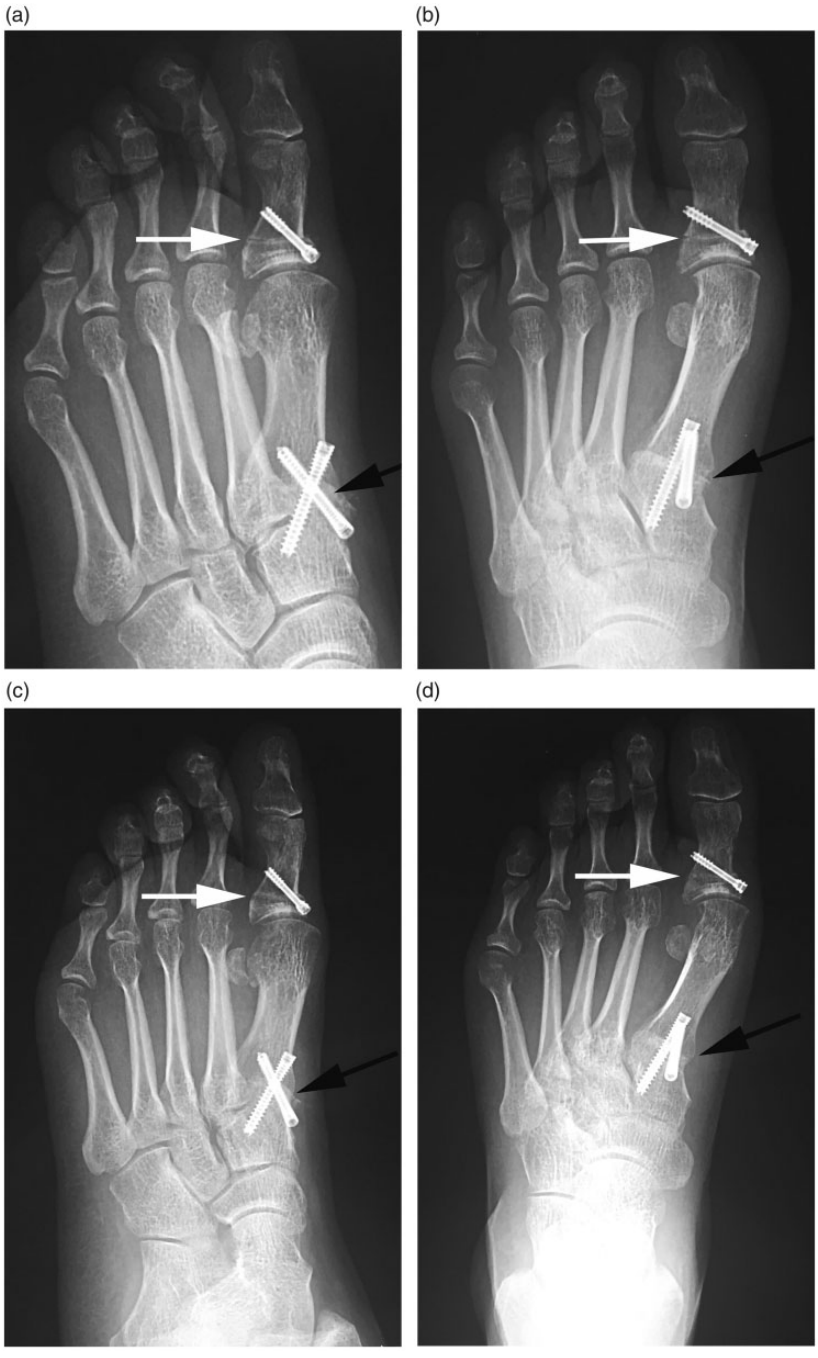

Figure 3. (a, b) Anteroposterior and lateral radiographs 1 week after surgery. The surface of the first tarsometatarsal joint was clear, and the radial cortex was determined to have no cortical bridging (black arrow). The surface of the Akin osteotomy site was also clear, and the radial cortex was determined to have no cortical bridging (white arrow). (c, d) Anteroposterior and lateral radiographs 8 weeks postoperatively. The surface of the first tarsometatarsal joint and Akin osteotomy site was determined to have cortical bridging (black and white arrows).

Table 1. Baseline characteristics of patients in the zoledronic acid and placebo groups

	Zoledronic acid n = 56	Placebo n = 57
Smoker	3 (5.4)	2 (3.5)
Alcohol user	2 (3.6)	4 (7.1)
NSAID user	24 (42.9)	20 (35.1)
Diabetes	8 (14.3)	6 (10.5)
Age (years)	56.9 ± 4.7	57.5 ± 4.2
BMI (kg/m^2)	22.01 ± 3.7	23.76 ± 3.6
Serum calcium (mmol/L)	2.22 ± 0.1	2.14 ± 0.1
Serum inorganic phosphorus (mmol/L)	1.22 ± 0.2	1.24 ± 0.2
Serum 25-hydroxyvitamin D (nmol/L)	53.4 ± 5.6	54.1 ± 6.3
PTH (pg/mL)	44.57 ± 14.6	42.86 ± 10.6

Data are presented as n (%) or mean ± standard error. NSAID, nonsteroidal anti-inflammatory drug; BMI, body mass index; PTH, parathyroid hormone.

ZOL group, whereas seven (12.2%) patients exhibited nonunion in the placebo group. The difference was not statistically significant. All patients exhibited bone healing after Akin osteotomy at 12 weeks.

Clinical outcomes assessment

Clinical outcomes were evaluated by the AOFAS scoring system before surgery and 24 weeks after surgery. This questionnaire is used to quantify general disabilities related to the lower extremity and is divided into three parts: pain, function, and ligaments. Scores range from 0 to 100, and higher scores indicate better clinical outcomes. All questionnaires were administered by an independent examiner who was not directly involved in the care of the patients and who was unaware of the group assignments. The average preoperative AOFAS score was 71.5 in the ZOL group and 69.2 in the placebo group. At 24 weeks, the average AOFAS score was 95.0 points (range, 91–99 points) in the ZOL group and 94.2 points (range, 90–99 points) in the placebo group. No significant difference was observed between the mean AOFAS scores in the two groups after surgery.

Complications

No case of neuropathy, infection, stiffness of the foot, or complex regional pain syndrome was encountered. Two patients in the placebo group and one patient in the ZOL group experienced failure of FTJ fusion after Lapidus arthrodesis. We considered that the reason for the failed fusion was early total weight bearing (<6 weeks) after surgery. All three patients achieved FTJ fusion after revision surgery.

Discussion

In this prospective randomized controlled study, early initiation of ZOL did not impact fusion of the FTJ or bone healing after a combination of Lapidus arthrodesis and Akin osteotomy and did not affect clinical outcomes. To the best of our knowledge, this is the first human study on the effect of osteoporosis drug use in the field of foot and ankle surgery.

Foot and ankle surgery has become a promising and independent orthopedic specialty. Foot disorders affect 20% to 60% of community-dwelling older adults and are associated with disability and falls. Quality of life often decreases in the elderly population based in large part on their foot health. A progressive reduction in both general health and foot health occurs as the severity of HV deformity increases; this reduction in health appears to be associated with the presence of a greater degree of HV.[4] HV is the most common foot disorder in adults and is more prevalent among older than younger individuals and among women than men, and it profoundly affects

women's quality of life.[2,3] With the development of foot and ankle surgery, increasingly more patients with severe HV are presenting to hospitals for surgical treatment. Among patients who undergo surgical orthomorphia for HV, postmenopausal women account for a high proportion because of the long-term use of high-heeled shoes in many of these women; such shoes increase the pressure under the metatarsal heads, limit motion of the first MTJ, and increase the stiffness of the Achilles tendon.[20]

Attention should be given to osteoporosis in postmenopausal women undergoing surgical orthomorphia for HV. First, about 30% of postmenopausal women in developed countries reportedly have osteoporosis.[1] Patients with severe HV have limited activity because of foot pain. This means that postmenopausal women with HV are more susceptible to osteoporosis. Second, most patients misunderstand osteoporosis as an inevitable condition of old age rather than a disease and are unwilling to undergo treatment. However, when foot pain is relieved after surgery, patients' activity increases, resulting in an increased risk of secondary fracture, especially in postmenopausal women with untreated osteoporosis. Finally, whether anti-osteoporosis drugs disturb the bone healing process after surgical orthomorphia for HV remains unknown. This makes the clinical condition of patients with HV and untreated osteoporosis even worse. These are the factors that prompted us to perform the present study.

Whether BPs are helpful or harmful in fracture healing and other bone fusion surgeries has long been debated. BP therapy inhibits osteoclast-mediated bone resorption to prevent bone loss and improve bone strength. However, osteoclasts are important for remodeling the callus into cortical bone, and it is reasonable that BPs may have a negative effect on the bone healing process because they can prevent callus remodeling. Solomon et al.[21] found that the use of BPs in the post-fracture period was associated with an increased probability of nonunion such as that of the humerus and hip, but the study only considered the use of oral BPs. Cao et al.[22] demonstrated that alendronate strongly suppressed remodeling of the callus, resulting in the highest content of woven bone and persistent visibility of the original fracture line in ovariectomized rats. Rozental et al.[23] reported a delay in the union time of <1 week for patients taking BPs (alendronate) compared with the untreated group. Nagahama et al.[24] reported that alendronate disturbed the healing process of posterior lumbar interbody fusion in their prospective randomized trial.

Conflicting opinions also exist. Animal experiments have shown that zoledronic acid, a new generation of BP, does not prevent bone healing; in contrast, it results in an increased callus size, higher bone mineral content, and increase in the tensile strength of the bone after experimental fracture.[9,10] Several studies have demonstrated that alendronate can also improve screw fixation in osteoporotic bone.[25,26] Furthermore, in a randomized controlled trial, a single dose of ZOL enhanced pin fixation in high tibial osteotomy using the hemicallotasis technique and other internal fixation.[27] These diverse results appear to be due to different fracture models, different kinds of BPs, and different fracture fixation methods.

ZOL is a new generation of BPs. Many recent studies have evaluated the effect of ZOL on bone healing. However, no clinical experiments to date have shown an association between ZOL treatment and delayed fracture healing. ZOL has no negative effect on the spinal union rate and it is remarkably free of serious adverse effects.[28] ZOL (5 mg) only needs to be intravenously administered once a year, and it is distributed to bones in all parts of the body. The concentration of ZOL in the local site of each bone or joint may be too low to

affect the healing or fusion rate.[27] Previous studies have also shown that ZOL can enhance the stability of various internal fixations.[27,29] Therefore, ZOL is the safest and least controversial BP to date. The present study demonstrated that ZOL had no effect on fusion of the FTJ or bone healing of the Akin osteotomy site. This result provides clinical evidence for the use of ZOL after Lapidus arthrodesis and Akin osteotomy in postmenopausal women diagnosed with osteoporosis.

In the present study, ZOL was used 1 week after surgery. Most patients who undergo Lapidus arthrodesis are discharged 10 days after surgery in our ward; therefore, ZOL was used 1 week after surgery because it was convenient for us to monitor the early condition of each patient after drug administration. Moreover, minor postoperative complications usually subside in 1 week, so the 3-day interval was long enough for us to distinguish side effects caused by the operation versus drug administration. The radiographic condition of the FTJ fusion, healing of the Akin osteotomy site, and clinical outcomes assessed by the AOFAS score were all evaluated in the ZOL and placebo groups. The results showed that the average fusion time after Lapidus arthrodesis and the healing time of the Akin osteotomy site were not significantly different between the ZOL and placebo groups. The AOFAS scores of the patients in both groups also showed no significant difference. This means that early initiation of ZOL did not affect the fusion rate of the FTJ or healing time of the Akin osteotomy site and suggests that ZOL can be initiated early after combined surgery.

More than 130 operations have been described to correct HV deformity, suggesting that no single procedure currently provides universally satisfactory results. Among these operative procedures, Lapidus arthrodesis has the highest risk of nonunion, ranging from 3.3% to 12.0%.[6,30] With the development of internal fixation devices and surgical techniques, the nonunion rate has recently fallen below 5%.[6] Patients who undergo Lapidus arthrodesis still need to avoid weight bearing for at least 8 weeks. Akin osteotomy is one of the most common options for HV treatment and is applied in patients who require additional angular or rotational correction. Akin osteotomy was recently shown to be an indispensable procedure in two osteotomies of double or bifocal osteotomies of the first metatarsal.[31] Because our study demonstrated that early initiation of ZOL had no adverse effects on fusion of the Lapidus arthrodesis or healing of the Akin osteotomy, it is reasonable to consider that early initiation of ZOL can also be applied to other surgeries for moderate HV such as Ludloff osteotomy and chevron osteotomy.

This study has some limitations. Our sample was small and the follow-up time was 24 weeks shorter than the adverse effects of ZOL, which can last for 1 year. However, the aim of our research was to detect the fusion condition of the FTJ after surgery, and according to previous research and our clinical experience, 12 weeks is long enough for such an examination. Moreover, at 3 months postoperatively, nonimpact sports and activities were gradually commenced, and at 6 months postoperatively, patients were allowed to participate in all activities. Therefore, the follow-up time was adequate to complete our study. In the present study, radiographs were used to measure the fusion condition of the FTJ and Akin osteotomy with the intent to decrease the economic burden on the patients. As shown in the present study, radiographs are able to show the fusion condition.

Conclusion

There was no significant difference between the ZOL group and placebo group in the

time of FTJ fusion, time of osteotomy healing, or clinical outcomes after a combination of Lapidus arthrodesis and Akin osteotomy. Thus, the fact that a patient is undergoing Lapidus arthrodesis and Akin osteotomy is not a valid reason to suspend or avoid treatment of osteoporosis with ZOL.

Declaration of conflicting interests

The authors declare no conflict of interest.

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