Trials

STUDY PROTOCOL

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Efficacy and safety of minodronate in the treatment of postmenopausal osteoporosis with low back pain: a single-centre, randomized and open-label controlled trial

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Abstract

Background Low back pain is one of the most common symptoms of osteoporosis. The pain can seriously affect patients' mood and quality of life; it can also further aggravate bone loss, causing a serious social burden. Minodronate is an oral bisphosphonate that needs to be administered daily. It significantly reduces levels of bone turnover markers (BTMs) and rapidly improves symptoms of low back pain in patients with osteoporosis. Osteoporosis requires long-term treatment, and daily dosing reduces patient compliance. Minodronate has a better safety profile than other bisphosphonates. The objective of the trial is to explore the efficacy and safety of minodronate in the treatment of low back pain in postmenopausal osteoporosis patients.

Methods This is a single-centre, randomized, open-label controlled trial with a 24-week duration. Seventy-two eligible patients will be randomly divided into 4 groups. Subjects will be randomized at a 1:1 ratio to receive either minodronate (1 mg/day) or alendronate (10 mg/day) every day; senior women (≥ 75 years old) and older women (< 75 years old) will be at a ratio of 1:2. The primary outcome is the time required for the visual analogue scale (VAS) score to decline by ≥ 10 from baseline. The secondary outcome is the changes in VAS scores from baseline, the frequency and dosage of rescue medication, BTMs, bone mineral density (BMD), and variations in upper gastrointestinal (GI) symptom scores from baseline (including heartburn, pain, and bloating).

Discussion This study will provide objective evidence for the efficiency and safety of minodronate. Furthermore, it will be helpful to evaluate the quantitative relationship between BTMs and BMD in patients with osteoporosis under different ages.

Trial registration This study protocol has been registered with ClinicalTrials.gov ID NCT05645289 (https://clinicaltrials.gov/search?term=NCT05645289) on December 8, 2022. The registry name is Peking University Third Hospital. This study protocol was reviewed and approved by the Peking University Third Hospital Medical Science Research Ethics Committee (M2022465, 2022.08.09, V2.0). The results will be published in scientific peer-reviewed journals.

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Trial status The protocol was registered at ClinicalTrials.gov (registration number: NCT05645289). Recruitment has started in January 2023 and is still ongoing.

Keywords Minodronate, Osteoporosis, Low back pain, Adverse reactions, Pharmacodynamic

Introduction

Background

Osteoporosis is a systemic metabolic bone disease that occurs in postmenopausal women. It is characterized by decreased bone mass and destruction of bone microstructure, resulting in decreased bone strength and increased fracture risk [1, 2]. The prevalence of osteoporosis increases with age, especially in those higher than 75 years old [3]. In a study conducted in Chinese adults in 2021, the prevalence of osteoporosis among women higher than 75 years old exceeded 50% [3]. As China enters an ageing society, the incidence of osteoporosis is expected to be two to three times higher than it is today by 2050 [4].

Low back pain is one of the most common symptoms in patients with osteoporosis. Pain not only severely affects patients' mood and quality of life but also further exacerbates bone loss [5]. The pain usually occurs when rolling over, sitting up, and walking for long periods. It may be accompanied by muscle spasms and even limited mobility. Studies showed that 67% of patients with osteoporosis have localized low back pain, 9% have low back pain with radiating pain in the extremities, and 10% have low back pain with limb numbness [6]. A survey revealed approximately 45% of patients with osteoporosis. The back pain described as "severe", "painful", or "tormenting", and 43% had pain lasting more than 5 years [7]. Another survey showed that postmenopausal osteoporosis patients had an average pain visual analogue scale (VAS) score of 4.33 before spinal compression fracture, which was equivalent to moderate pain affecting sleep [8]. And the aggravation of bone pain affected patients' balance and flexibility [9]. With the increase in pain score, the patients' balance and flexibility both showed a downward trend [9]. When patients' balance and flexibility are reduced, the patients often fall, which leads to hip fracture and head damage. In addition, adverse reactions such as anxiety and sleep disturbance caused by pain seriously affect the quality of life of patients; the main appeal of most patients seeking treatment is for pain relief [10]. Although the improvement of BMD and the reduction of fracture risk are important indicators to evaluate the efficacy of anti-osteoporosis drugs, pain as the main symptom of osteoporosis cannot be ignored. Pain relief greatly improves the subjective feeling and quality of life of patients, which is beneficial for increasing the compliance of osteoporosis patients.

Currently, the study showed that minodronate significantly reduced BTMs and rapidly improved symptoms of low back pain in patients with osteoporosis [11]. Compared with alendronate, minodronate is more effective in relieving pain. After 12 weeks of treatment, VAS scores changed by 21% in the minodronate group and 13% in the alendronate group [11]. Minodronate is a third-generation bisphosphonate that can effectively inhibit the bone resorption function of osteoclasts and exert a therapeutic effect on osteoporosis [12, 13].

Minodronate not only has the effect of relieving pain but also has a low incidence of adverse reactions. Oral bisphosphonate are associated with incidence of adverse events related to the upper gastrointestinal tract, including heartburn, epigastric pain, and epigastric distention [14]. Patients with osteoporosis may discontinue bisphosphonate therapy because of these adverse events [15, 16]. Therefore, it is of great clinical significance to evaluate the effect of minodronate on the upper digestive tract. Specific scores of heartburn, epigastric pain, and epigastric distention did not change significantly in the minodronate group, while the scores were significantly increased in the alendronate group in a Japanese study [11]. Additionally, a 10-year real-world study compared jaw fractures with seven intravenous or oral bisphosphonates from 2004 to 2014. The study results showed the lowest incidence of minodronate related osteonecrosis of the jaws (ONJ). As of 2018, no atypical femoral fractures (AFFs) during minodronate treatment were reported [17].

Currently, most of the targets of anti-osteoporosis drugs are elderly individuals, especially senior patients higher than 75 years old. With increasing age, the physiological functions of various organs in the body decrease to varying degrees [18]. One study showed that both creatinine clearance and glomerular filtration rate tended to decline with age, and the decline was more pronounced after age 75 [19]. Minodronate is mainly eliminated from the body renally rather than by liver metabolism [20]. The age-related changes in renal function may affect the pharmacokinetic (PK) and pharmacodynamic (PD) of the drug, which in turn affect the drug-response and dose–response relationships. In addition, BTMs, BMD, fracture incidence, and bone pain related to osteoporosis also change with age [21–23]. The International Conference on Harmonization (ICH) issued a guideline titled Studies in Support of Special Populations: Geriatrics E7, which

emphasized the importance of elderly patients in clinical trials, especially those higher than 75 years old [24]. Enrolling senior patients and obtaining data on the efficacy and safety of this population cannot only improve the effectiveness of the drug for this population but also reduce adverse drug reactions.

Objectives

Primary objectives

To explore the efficacy of minodronate in the treatment of low back pain in postmenopausal osteoporosis patients.

Secondary objectives

To evaluate BTMs, BMD, and safety characteristics of minodronate in Chinese postmenopausal osteoporosis patients of different ages.

Trial design

This is a single-centre, randomized, open-label controlled trial in Chinese postmenopausal osteoporosis patients receiving minodronate or alendronate. This study is divided into two stages: the first stage is 12 weeks, and at the end of the first stage. In the first phase, minodronate will be administered once daily for 12 weeks, and alendronate will be administered once daily for 12 weeks. In the second phase, all patients stopped minodronate for 12 weeks. The VAS score in this study ranges from 0 to 100 mm. During the screening, the patient's past pain relief methods, such as pain medication or the way of life intervention, will be recorded. The use of the above methods during the patients' treatment will be prohibited to prevent interference with the results. During the treatment, if patients experience sudden aggravation of low back pain, the VAS score is more than 70, and the patients could not bear the pain, a rescue drug (acetaminophen) will be used uniformly to relieve the pain. Throughout the trial, a total of 5 follow-up visits will be planned. VAS score and Izumo scale score will be performed at 1, 2, 4, 6, 8, and 12 weeks after administration. Vital signs, BTMs, serum calcium, and serum phosphorus will be measured during the screening period, day 1, week 8, 12, and 24. Blood routine, liver function, renal function, electrocardiogram, and BMD will be measured at 12 weeks and 24 weeks (Fig. 1 shows the flowchart of analysis, Fig 2 shows the flowchart of study and Fig 3 shows the detailed schedule).

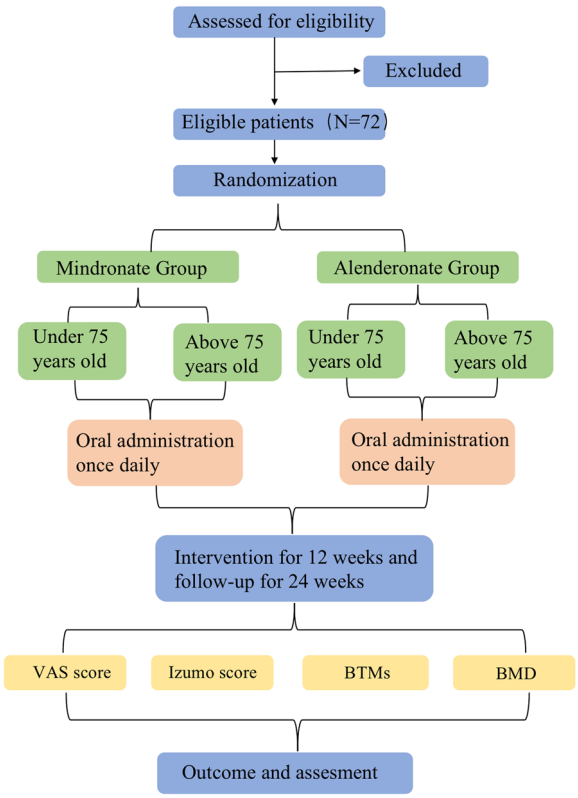

Fig. 1 The flowchart of enrolment, interventions and analysis

Methods

Study setting

Postmenopausal osteoporosis patients admitted to the outpatient department of Peking University Third Hospital will be enrolled in the trial. After signing the informed consent form, they will be randomly divided into four groups: the alendronate-old women (< 75 years old), alendronate-senior women (≥ 75 years old), minodronate-old women (< 75 years old), and minodronate senior women (≥ 75 years old) groups. The sealed envelopes methods will be used for randomization. The clinical research coordinator will generate the allocation sequence, enrol participants, and assign participants to interventions. The old groups consisted of 24 patients in each group, and the senior groups consisted of 12 patients in each group. The subjects in the four groups will be orally treated with alendronate and minodronate daily for 12 weeks, and drug administration will be stopped after 12 weeks. The entire trial is divided into two stages: the first stage is 12 weeks, and the second stage is 12 weeks. The efficacy of minodronate in the treatment of low back pain is mainly evaluated by the VAS score and the frequency and dose of rescue medication administered. The safety assessment is mainly based on the occurrence of fractures and gastrointestinal adverse reactions after oral administration.

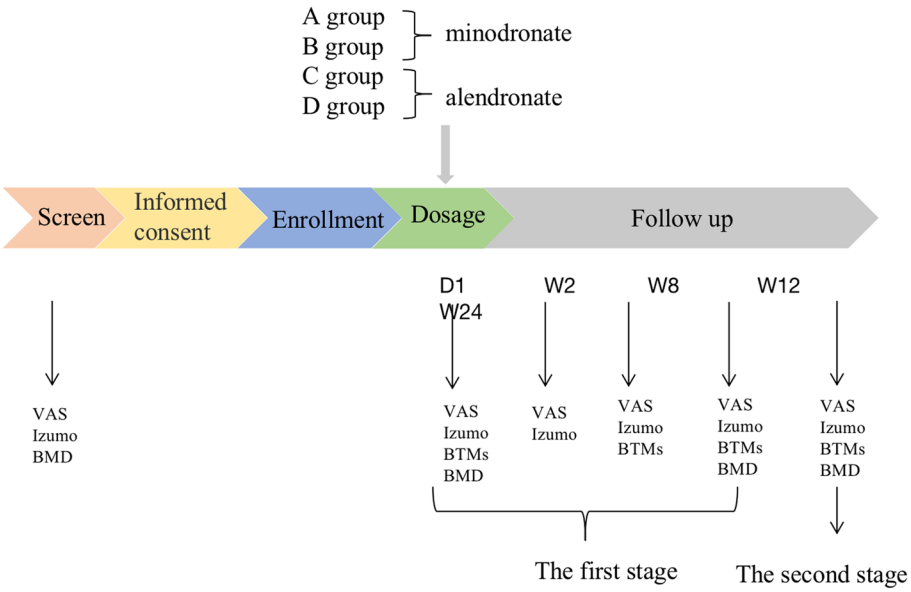

Fig. 2 Flowchart of the study

Periods	Screening	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
Visits	V1	V2	V3	V4	V5	V6
Days from randomization visit	Days-14 to 0	Day1	Week2	Week8	Week12	Week24
Informed consent	X					
Inclusion/exclusion criteria	X					
Demography	X					
Medical history	X					
Physical examination	X				X	X
Electrocardiogram	X				X	X
Vital signs	X	X	X	X	X	X
Lateral X-ray of the lumbar spine	X					
Hematology	X				X	X
Serum chemistry	X				X	X
Urine analysis	X				X	X
Randomization		X				
Blood calcium, blood phosphorus	X	X		X	X	X
Bone turnover markers		X		X	X	X
25OHD,PTH	X					
Bone mineral density examination (lumbar L1-L4, whole hip)	X				X	X
Administration of medication		X	X	X	X	
Recording combined medication	X	X	X	X	X	X
Recording adverse events	X	X	X	X	X	X
VAS—score for pain	X	X	X	X	X	
Izumo scale	X	X	X	X	X	
Distributing calcium and vitamins		X	X	X	X	X
Judgment of compliance		X	X	X	X	
Issuing subject diary card		X	X	X	X	
Retrieving subject diary card			X	X	X	X

Fig. 3 Information on the schedule of screening, enrolment, interventions and assessments

Eligibility criteria

Inclusion criteria

(1) Chinese postmenopausal patients with a diagnosis of osteoporosis.
(2) Patients with low back pain of at least 3 months and a VAS score ≥ 30.
(3) The value of lumbar L1–4 or total hip bone density measured by DXA is ≤ −2.5.
(4) Serum 25-hydroxyvitamin D (25-OHD) concentration ≥ 20 ng/mL.
(5) Patients with full capacity for civil conduct and understanding of the research process and methods voluntarily participated in this study and signed the informed consent form.

Exclusion criteria

(1) Patient who are allergic to minodronate, alendronate, or other bisphosphonates or any other component of the drug.
(2) Patients with a diagnosis of secondary osteoporosis.
(3) The following drugs affecting bone metabolism were used before the screening:

Received injections of bisphosphonates and denosumab within 3 years.
Received oral bisphosphonates, parathyroid hormones or analogues, strontium, or fluoride within 6 months.
Received glucocorticoids, steroids, immunosuppressants, calcitonin, calcitriol or its analogues, thiazide diuretics, and oestrogen/progesterone replacement therapy within 3 months.

(4) Patients with a diagnosis of diseases affecting bone metabolism (e.g. osteogenesis imperfecta, malignancy, progressive diaphyseal dysplasia, Paget's disease, rheumatoid arthritis, osteosclerosis, osteoporosis with a slipped disc and spinal stenosis, and liver and kidney failure).
(5) Patients are participating or have participated in an investigational drug study within 3 months before signing the informed consent form.
(6) Patients under 75 years old with a creatinine clearance rate < 60 mL/min and those higher than 75 years old with a creatinine clearance rate < 45 mL/min.
(7) Serum calcium levels < 2.0 mmol/L (8 mg/dL) or > 2.7 mmol/L (11.0 mg/dL).
(8) Patients with fever, severe infection, severe trauma, or major surgery within 30 days.
(9) Patients with a QTc interval of > 480 ms.
(10) Patients are undergoing or planning to undergo invasive dental treatment.
(11) Smoking history in the past 6 months.
(12) Patients with a history of alcohol abuse (> 15 g of alcohol per day, equivalent to 350 mL of beer or 150 mL of wine, more than twice per week) and drug abuse.
(13) Patients with a prior history of cerebral infarction, ischaemic or haemorrhagic stroke.
(14) Patients with implants and/or fractures in the lumbar spine or hip that interfere with BMD testing.
(15) Received pain relievers (e.g. nonsteroidal anti-inflammatory drugs, central analgesics) or life interventions to relieve pain within 1 week before screening.

Interventions

Description

Subjects will be orally given 1 mg minodronate or 10 mg alendronate tablets daily and 200 mL of water in the morning. They could not lie down and eat anything except water for at least 30 min after administration. The treatment lasted for 12 weeks, corresponding to a total of 84 doses.

Calcium and vitamin D are the basic treatment for osteoporosis. Adequate calcium intake and vitamin D are beneficial for improving bone mineralization and maintaining bone health. Therefore, all subjects will receive an oral calcium carbonate and vitamin D3 tablet (calcium 600 mg, vitamin D3 125 IU) after dinner throughout the study period.

If subjects take minodronate and alendronate, the low back pain suddenly will worsen, the pain VAS score is still more than 70, and the subjects cannot tolerate the pain, they will be uniformly treated with rescue medicine (acetaminophen), and the pain relief time should not exceed 5 days. During this period, patients will be required to fill in the VAS score form and the frequency and dose of rescue medication in the diary booklet.

Modifications

Subjects will be free to withdraw their informed consent and withdraw from the study. The investigator may withdraw the participant from the study under any of the following conditions:

1) Subjects withdraw consent.

2) Serious changes in clinical or laboratory examination results occur during the trial that would be detrimental to the subject's health care as observed by the investigator.
3) Subjects who exhibit poor compliance, refuse to undergo all required tests, and cannot adhere to the study plan.
4) Subjects who are unable to attend the follow-up or dropped out.

Adherence

Informed and reminded to ensure that patients fully understand the trial, intervention drugs, and treatment process before carrying out. Subjects should also be informed of the precautions and possible adverse drug reactions in detail to try to win the understanding and cooperation. In addition, compliance education for subjects and their families should be strengthened to make them realize the importance of following the doctor's advice.

Concomitant care

During the screening, the subjects' past pain relief methods, such as pain medication or the way of life intervention will be recorded. The use of the above methods will be prohibited to prevent interference with the results of the clinical trials.

Recruitment

All eligible participants will be invited to participate in the trial. The main recruitment approach will involve recruiting outpatients from our hospital. Our researcher will identify the participants of interest, and the investigator or clinician will approach the interested participants to provide information about this study and ask if they would like to participate. They will provide written informed consent in the presence of a qualified clinician (Sup Informed Consent). The clinician will then complete the screening process.

Outcomes

Primary outcome

The time required for a VAS score decrease ≥ 10 from baseline after administration.

Secondary and other outcomes

(1) Changes in VAS scores from baseline at 1, 2, 4, 6, 8, 12, and 24 weeks and the frequency and dosage of rescue medication.

(2) Comparison of BTMs and BMD of minodronate and alendronate in Chinese postmenopausal osteoporosis patients of different ages.

The outcomes of BTMs:

Bone formation markers: serum procollagen type I N-terminal propeptide (P1NP) and serum osteocalcin (OCN).

Markers of bone resorption: β-isomerized C-terminal telopeptide of type 1 collagen (β-CTX).

Markers of bone metabolism regulation: 25-OHD, parathyroid hormone (PTH).

Blood biochemical markers: blood calcium, blood phosphorus, and creatinine.

The outcomes of BMD:

Changes in BMD (lumbar L1–L4, whole hip).

(3) Safety evaluation: changes in upper gastrointestinal symptom scores from baseline at 1, 2, 4, 6, 8, 12, and 24 weeks after administration (e.g. heartburn, stomach ache, distension).

Participant timeline

The study will last 24 weeks and will be divided into two stages. The first stage is 12 weeks and will primarily focus on the relief of subjects' low back pain and the incidence of gastrointestinal adverse reactions after administration. The second stage is 12 weeks, during which the effect of age on the quantitative relationship of BTMs-BMD will be evaluated.

Sample size

The study is an exploratory study with a small sample. According to a randomized controlled trial published in the *Journal of Bone and Mineral Metabolism* in 2013 [11], the mean percentage change in VAS score was 49.8% for alendronate and 56.4% for minodronate at 24 weeks post-treatment. In this study, a 1:1 design method is adopted to estimate the sample size required by the T test of two independent samples, and $\alpha = 0.05$, $1-\beta = 0.90$, considering a 10% loss to follow-up rate. A total of 72 patients will be each required for the alendronate group and minodronate group, including 24 patients in the elderly group and 48 patients in the senior group.

Recruitment

All eligible subjects will be invited to participate in the trial. The main recruitment approach will involve recruiting outpatients from Peking University Third Hospital. Our researcher will identify the participants of interest, and investigator or clinician will approach the interested participants to provide information about this study and ask if they would like to participate. They will provide written informed consent in the presence of a qualified clinician (Sup Informed Consent). The clinician will then complete the screening process.

Allocation

The sealed envelopes methods will be used for randomized allocation. Before the study begins, a series of random numbers will be generated using SPSS software. The random sequence composed of generated random numbers and corresponding serial numbers will be designated as the experimental or control group. A random assignment table with grouping information will be then identified and recorded. And the statisticians involved in the study will place them in sealed, opaque envelopes labelled with patient numbers in order. After the researchers who generated the allocation sequence packaged the envelopes, they distributed them to the researchers responsible for screening and assigning subjects. The envelope will be kept in the drug clinical trial centre. Once a patient consented to participate, a researcher who is on call that time will open the envelope to reveal the name of the assigned group. Researchers will write the names and detailed information of qualified subjects on the appropriate envelope surface before opening the envelopes in order. And it will be grouped according to the random allocation scheme in the envelope.

The random allocation table must be kept in duplicate and must not be leaked. It should be sealed in opaque envelopes and kept by both the researcher and the statistician. When revealing the grouping, both random allocation tables must be unsealed in person at the same time. If one or more of the seals are damaged, it must be explained, otherwise it will be declared that the grouping information has been leaked, which may even render the experiment invalid. In order to avoid leaking grouping information, individuals assigned to random number groups cannot participate in the enrolment of subjects.

Blinding

This is an open-label controlled trial, the blinding method is not applicable.

Data management

The assessments will be conducted in the Outpatient Department of Peking University Third Hospital, and the intervention process will be carried out in the Peking University Third Hospital Drug Clinical Trial Center. All the assessments will be carried out by trained and experienced clinicians.

The data management department will design case report form (CRF) based on the scheme. The researcher will complete the CRF accurately, completely, and promptly according to the original data. Raw data must remain attributable, legible, timely, and accurate. The original medical record should be complete and clear. Correction of data should be accompanied by an indication of the reason for correction, modification person, and modification date, and the modification trace should be retained. Inspectors will review the CRF and check it against the raw data to ensure its integrity and consistency. The data manager will check the data input into EDC (Microsoft Ware Excel 2019) logically to ensure the accuracy of the data. The data manager will raise questions regarding the questionable data, all questions will be resolved, and each CRF will be electronically signed by the investigator. Sponsor leaders, researchers, data managers, and statistical analysts will review the data together. The database will be eventually locked to archive the file.

Assessment of outcomes

VAS score

Subjective pain perception will be quantified using a VAS score. The VAS uses a straight line without any segmentation. 0 indicates no pain; less than 30 mm is defined as mild to tolerable pain; 40–60 mm is pain that affects sleep, which is tolerable; and 70–100 mm indicates that subjects has a gradual increase in pain that is unbearable and affects appetite and sleep.

Izumo scale

The gastrointestinal adverse reactions caused by the oral administration of minodronate and alendronate will be recorded by the Izumo scale. The Izumo scale included 15 questions for five clinical symptoms, including heartburn, stomach pain, bloating, constipation, and diarrhoea.

Bone turnover markers

Eight millilitres of the elbow vein will be collected into a vacuum tubes without anticoagulant and sent to the laboratory for testing on the 1st day (before administration), 8th week, 12th week, and 24th week.

Bone mineral density

BMD will be measured using a dual-energy X-ray absorptiometry (DXA). The BMD will be measured for the lumbar spine (L1 to L4) and total hip. The difference and percentage change between BMD and baseline at each time point after administration will be calculated.

Statistical methods

Statistical analysis data sets

There will be three statistical analysis data sets, including the effective analysis population (EAP), preprotocol population (PP), and safety sets (SS). All subjects enrolled in this study will be included in the intent-to-treat (ITT) analysis set. The efficacy analyses will be based on the EAP. Subjects with no significant protocol deviation in the EAP will be included in the PP, which will be used in the primary outcome analyses. In addition, all subjects who received treatment will be included in the SS, which will be used in the analysis of vital signs, laboratory tests, and AEs.

Statistical methods for primary and secondary outcomes

SAS and other statistical software will be used to analyse the outcomes. Quantitative data will be expressed as the mean ± standard deviation, and a T test will be used to compare the data between the 4 groups. For the comparison between groups, all hypothesis tests will be performed by a two-sided test ($\alpha = 0.05$, unless otherwise specified). $P < 0.05$ will be considered statistically significant. The confidence intervals for all tests will be 95%. The comparison of general conditions between groups will be analysed by appropriate methods according to the type of indicators. The T test, ANOVA, Wilcoxon test, or Kruskal–Wallis test will be used for the comparison between groups of quantitative data; the chi-square test or exact probability method will be used for the comparison between groups of classified data; and Wilcoxon rank-sum tests will be used for the rank data.

Investigations will be conducted to assess changes in VAS score, Izumo scale, BTMs, and BMD within 6 months in the four groups, including a comparison of the number of subjects who showed significant changes from baseline using the χ^2 tests and an assessment of the difference in mean values with t-tests.

Trial governance or oversight and monitoring

Data monitoring

The clinical trials will be monitored periodically by the sponsor or by CRO authorized by the sponsor. Quality control (QC) and quality assurance systems will be established related to this study, with corresponding duties performed in strict agreement. Investigators should do the corresponding work carefully in accordance with the requirements of Standard Operating Procedure (SOP) and trial protocol, and record it in a timely, completely, and standardized manner. The role of monitoring committee is to identify clinical trial qualifications and resources and check the consistency of CRF, raw data, and other test-related materials. The names and addresses of subjects will not be recorded in the database, and any material information containing the participants' names will not be stored in any file. Subject identity will be kept strictly confidential by the research investigator. The clinical trial monitor will conduct regular inspections and reviews of the trial during the trial, aiming to ensure the quality, compliance, and credibility of the trial. The Data and Safety Monitoring Committee (DSMC) is composed of clinicians, statisticians, and moralists. The DSMC is a committee independent of both the Steering Committee (SC) and any sponsor. It plays an important role in monitoring, evaluating, and protecting patient rights in clinical trials. The main responsibilities include safety monitoring, effectiveness monitoring, and overseeing the conduct of trials.

Adverse events

Oral bisphosphonate are associated with a relatively high incidence of adverse events related to the upper gastrointestinal tract, including heartburn, epigastric pain, and epigastric distention. The adverse events (AEs) will be determined using the Common Adverse Event Evaluation criteria (CTCAE V5.0). When an AE occurs, researchers should actively take appropriate measures to ensure the safety of subjects. All AEs should be followed up until the event is resolved. Event resolution is when the subject's health returns to its baseline state or when the investigator does not expect any further improvement or deterioration in the AE. If follow-up is not possible for any reason, an explanation must be provided in the subject's original medical records and case report forms. All AEs, regardless of severity or causal association with the trial drug, will be recorded on the appropriate AE page in the subject's original medical record and case report form from the time the subject will provide informed consent. When a sudden adverse event, such as cardiac arrest, cerebrovascular accident, or respiratory failure, will be detected, the study physicians and principal investigators will be immediately rescued according to the hospital procedures. The team should take the following measures: immediate treatment, careful observation, detailed recording, and follow-up.

If a severe AE occurs, whether it is the first report or a follow-up report, the investigator will immediately fill in the Severe Adverse Event Report Form of the National Medical Products Administration (China). In addition, AEs will be reported to the ethics committee, the Beijing

Municipal Medical Products Administration, and the Bureau of Medical Administration of National Health Commission of the People's Republic of China.

Protocol amendments

Protocol amendments will be made required the consent of the investigators. In order to eliminate the direct harm to the subjects participating in the trial and the situation is urgent, it can be performed before the approval of the ethics committee, and then reported to the ethics committee as soon as possible. All other amendments will be subject to the approval of the ethics committee and the regulatory authorities.

For biological samples such as serum samples produced in the trial, but the detection of indicators not mentioned in the established research protocol. The subject can adjust or modify the established research protocol after informed consent, without violating research ethics and human heritage resource management law. The above modified protocol will be submitted to the ethics committee for approval in time.

Dissemination plans

The results of this trial will be presented at relevant conferences and published in academic journals in the future. Public will access to protocols and informed consent of this trial.

Auditing

Clinical trials will be audited by the quality assurance unit. The department will evaluate whether the trial-related activities and records are in compliance with the trial protocol, SOP, and regulations related to drug clinical trials. The investigator will conduct monthly audits of the raw data collected, as well as the interventions in the clinical trial. The Trial Steering Group and the DSMC will meet to review conduct throughout the trial period monthly. The auditors will work independent of the study staff or researchers. The main responsibilities include reviewing the original data and reports of clinical trials, conducting internal and external audits, and preserving relevant documents.

Ethics and dissemination

Ethical approval has been obtained from Peking University Third Hospital Medical Science Research Ethics Committee. This clinical trial must comply with the Declaration of Helsinki (2013), Good Clinical Practice issued by ICH, and Norms for the Management of Drug Clinical Trials (GCP) issued by the National Medical Products Administration. There are no interim analyses or extra auditing planned for this study beyond the continuous monitoring by the investigators. All protocol amendments will be submitted to the ethical committee. Before the commencement of a clinical trial, approval from the ethics committee is needed. The study's results will be published in scientific peer-reviewed journals with open access.

Informed consent

A signed informed consent must be obtained from the subjects prior to any operational procedures. It includes the collection of biological samples; biological samples can only be collected after the subject signs informed consent. It is the responsibility of the investigator to explain the purpose, methods, benefits, and potential risks of the clinical trial to each subject. And inform the subjects that they can voluntarily withdraw from the trial at any time. The informed consent form must be dated and signed by the subject themselves (or their legal guardian or independent witness, if applicable). The informed content is available in Sup Informed Consent.

Dissemination plans

The results of this trial will be presented at relevant conferences and published in academic journals in the future. Public will access to protocols and informed consent of this trial.

Discussion

In general, osteoporosis is a bone disease associated with ageing. With the increased ageing of the population, osteoporosis has become an important public health problem. Osteoporosis is a systemic disease, and pain is a common clinical symptom that seriously affects the quality of life of patients [25]. The rate of chronic pain among osteoporosis patients is 58%, with low back pain accounting for 70 to 80% of these cases [26]. Therefore, effective relief of low back pain is very important for the prevention and treatment of osteoporosis.

The cause of the pain may be due to the rapid bone turnover and the increased bone resorption [27]. The pain nerves of bone are widely distributed throughout the periosteum, endosteum, trabecular bone, cortical bone, and Haversian system [28]. When osteoporosis occurs in the lumbar and hips, the trabecular bone and cortical bone are absorbed, and the internal structure of the bone is destroyed and subjected to physical compression and chemical stimulation, resulting in pain.

In addition, magnetic resonance imaging (MRI) examination showed that the signal changes of the spinal body endplates (Modic changes) were positively

correlated with the degree of low back pain [29, 30]. Modic change is a common MRI finding in patients with nonspecific low back pain, and it is considered to be an independent factor associated with an increased risk of low back pain [31, 32]. The greater the lesion is, the more severe the low back pain [33]. Histological analysis further showed that endplate lesions were associated with low back pain [34]. Osteoclasts increase and become porous with ageing [35, 36]. Histological and μCT analyses further showed that the hardened endplates were highly porous [36, 37]. The spinal endplates are progressively porous, and narrowing of the IVD space is characteristic of spinal degeneration [36, 37]. Since pain is conducted through pain receptors, low back pain may be caused by sensory innervation of the endplate. Zoledronic acid and denosumab inhibit osteoclast activity and show analgesic effects in patients with low back pain with spinal Modic alterations. This suggests the potential role of osteoclast activity in sensory innervation and further proves that anti-bone resorption drugs have a significant effect on the treatment of osteoporosis low back pain.

Minodronate is an anti-bone resorption inhibitor. It has a high affinity for bone hydroxyapatite, which can specifically bind to the bone surface active in bone reconstruction and inhibit osteoclast function, thus inhibiting bone resorption [38]. Increased bone resorption accelerates the destruction of trabecular bone in the lumbar, stimulating sensory nerves in the bone and causing low back pain [38]. Currently, studies have proven that minodronate can effectively relieve low back pain caused by osteoporosis [11]. Minodronate has the strongest inhibitory effect on bone resorption of all bisphosphonates, and the inhibitory intensity of minodronate is 10–100 times that of alendronate. Moreover, minodronate has similar efficacy but is administered at significantly lower doses (alendronate at 10 mg/day versus minodronate at 1 mg/day), improving patient compliance and reducing common adverse gastrointestinal reactions [11].

Therefore, a total of 72 postmenopausal Chinese patients with osteoporosis will be selected to receive minodronate and alendronate. The objective of trial is to explore the efficacy and safety of minodronate in the treatment of low back pain in postmenopausal osteoporosis patients. In addition, by enrolling senior patients, obtaining data on the efficacy and safety of this population cannot only improve the effectiveness of minodronate for this population but also reduce the rate of adverse drug reactions. In conclusion, this study is intended to guide the clinical application of minodronate in patients with osteoporosis in China.

Trial status

The protocol was registered at ClinicalTrials.gov (registration number: NCT05645289). Recruitment has started in January 2023 and is still ongoing.

Abbreviations

VAS	Visual analogue scale
PK	Pharmacokinetic
PD	Pharmacodynamic
GI	Upper gastrointestinal
BTMs	Bone turnover markers
BMD	Bone mineral density
ONJ	Osteonecrosis of the jaws
AFFs	Atypical femoral fractures
ICH	International Conference on Harmonization
25-OHD	Serum 25-hydroxyvitamin D

Supplementary Information

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Additional file 1. Informed consent form.

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Role of sponsor

The trial sponsor is Chunli Song. Chunli Song is the chief investigator, contributed to the study design, and led the development of the proposal and protocol.

Authors' contributions

Chunli Song is the chief investigator, contributed to the study design, and led the development of the proposal and protocol. Dongyang Liu is the coinvestigator and contributed to the study and protocol development. Huan Wang and Jie Huang made contributions to the study design and drafted the original manuscript. Outcome assessment and data analysis will be performed by Huang Wang. Liyuan Tao made contributions to the statistical analyses and sample size calculation. All authors read and commented on the manuscript.

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Availability of data materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study protocol has been registered with ClinicalTrials.gov ID NCT05645289. This study protocol was reviewed and approved by Peking University Third Hospital Medical Science Research Ethics Committee on 16 August 2022 (M2022465, 2022.08.09, V2.0). Written informed consent will be obtained from all participants prior to performing trial-related procedures. Participants will have the right to withdraw at any time and for any reason without prejudice related to their future medical care.

Consent for publication

The authors declare that they consent for publication.

Competing interests

The authors declare that they have no competing interests.

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References

1. Srivastava M, Deal C. Osteoporosis in elderly: prevention and treatment. Clin Geriatr Med. 2002;18:529–55.
2. Ensrud KE, Crandall CJ. Osteoporosis. Ann Intern Med. 2017;167:ITC17-17ITC32.
3. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, et al. Prevalence of osteoporosis and fracture in China: the China osteoporosis prevalence study. JAMA Netw Open. 2021;4:e2121106.
4. Wang Y, Li H, Yang X, Zhang C, Xie H. Systematic review and meta-analysis: the value of MRI chemical-shift imaging in the evaluation of bone quality in patients with osteoporosis. Ann Palliat Med. 2021;10:12706–15.
5. Ringe JD. Too many osteoporosis patients are undertreated with analgesics. Chronic pain promotes bone loss. MMW Fortschr Med. 2003;145:43–5.
6. Melton LJ 3rd. How many women have osteoporosis now. J Bone Miner Res. 1995;10:175–7.
7. Ryan PJ, Blake G, Herd R, Fogelman I. A clinical profile of back pain and disability in patients with spinal osteoporosis. Bone. 1994;15:27–30.
8. Sawicki P, Tałałaj M, Życińska K, Zgliczyński WS, Wierzba W. Comparison of the characteristics of back pain in women with postmenopausal osteoporosis with and without vertebral compression fracture: a retrospective study at a single osteoporosis center in Poland. Med Sci Monit. 2021;27:e929853.
9. Liu-Ambrose T, Eng JJ, Khan KM, Mallinson A, Carter ND, McKay HA. The influence of back pain on balance and functional mobility in 65- to 75-year-old women with osteoporosis. Osteoporos Int. 2002;13:868–73.
10. Marshall P, Schabrun S, Knox MF. Physical activity and the mediating effect of fear, depression, anxiety, and catastrophizing on pain related disability in people with chronic low back pain. PLoS ONE. 2017;12:e0180788.
11. Yoshioka T, Okimoto N, Okamoto K, Sakai A. A comparative study of the effects of daily minodronate and weekly alendronate on upper gastrointestinal symptoms, bone resorption, and back pain in postmenopausal osteoporosis patients. J Bone Miner Metab. 2013;31:153–60.
12. Ito M, Sone T, Fukunaga M. Effect of minodronic acid hydrate on hip geometry in Japanese women with postmenopausal osteoporosis. J Bone Miner Metab. 2010;28:334–41.
13. Hagino H, Shiraki M, Fukunaga M, Nakano T, Takaoka K, Ohashi Y, et al. Three years of treatment with minodronate in patients with postmenopausal osteoporosis. J Bone Miner Metab. 2012;30:439–46.
14. Anastasilakis AD, Goulis DG, Kita M, Avramidis A. Oral bisphosphonate adverse effects in 849 patients with metabolic bone diseases. Hormones (Athens). 2007;6:233–41.
15. Woo C, Gao G, Wade S, Hochberg MC. Gastrointestinal side effects in postmenopausal women using osteoporosis therapy: 1-year findings in the POSSIBLE US study. Curr Med Res Opin. 2010;26:1003–9.
16. Hamilton B, McCoy K, Taggart H. Tolerability and compliance with risedronate in clinical practice. Osteoporos Int. 2003;14:259–62.
17. Nakamura M, Umetsu R, Abe J, Matsui T, Ueda N, Kato Y, et al. Analysis of the time-to-onset of osteonecrosis of jaw with bisphosphonate treatment using the data from a spontaneous reporting system of adverse drug events. J Pharm Health Care Sci. 2015;1:34.
18. Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. Aging Cell. 2017;16:624–33.
19. Sobamowo H, Prabhakar SS. The kidney in aging: physiological changes and pathological implications. Prog Mol Biol Transl Sci. 2017;146:303–40.
20. Zhou Y, He X, Li H, Ni Y, Xu M, Sattar H, et al. Pharmacokinetics and tolerability of minodronic acid tablets in healthy Chinese subjects and food and age effects on the pharmacokinetics. Clin Ther. 2015;37:869–76.
21. Miyagi M, Inoue G, Murata K, Koyama T, Kuroda A, Kawakubo A, et al. Factors associated with pain-related disorders and gait disturbance scores from the Japanese orthopedic association back pain evaluation questionnaire and Oswestry Disability Index in patients with osteoporosis. Arch Osteoporos. 2021;17:1.
22. von Friesendorff M, McGuigan FE, Wizert A, Rogmark C, Holmberg AH, Woolf AD, et al. Hip fracture, mortality risk, and cause of death over two decades. Osteoporos Int. 2016;27:2945–53.
23. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41:67–76.
24. Food and Drug Administration HHS. International Conference on Harmonisation; Guidance on E7 Studies in Support of Special Populations; Geriatrics; Questions and Answers; availability. Notice Fed Regist. 2012;77(34):9948–9.
25. Paolucci T, Saraceni VM, Piccinini G. Management of chronic pain in osteoporosis: challenges and solutions. J Pain Res. 2016;9:177–86.
26. Urushihara H, Yoh K, Hamaya E, Taketsuna M, Tanaka K. Responsiveness of the Japanese osteoporosis quality of life questionnaire in women with postmenopausal osteoporosis. Health Qual Life Outcomes. 2014;12:178.
27. Ringe JD, Body JJ. A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover. Clin Exp Rheumatol. 2007;25:766–74.
28. Brazill JM, Beeve AT, Craft CS, Ivanusic JJ, Scheller EL. Nerves in bone: evolving concepts in pain and anabolism. J Bone Miner Res. 2019;34:1393–406.
29. Rahme R, Moussa R. The modic vertebral endplate and marrow changes: pathologic significance and relation to low back pain and segmental instability of the lumbar spine. AJNR Am J Neuroradiol. 2008;29:838–42.
30. Luoma K, Vehmas T, Kerttula L, Grönblad M, Rinne E. Chronic low back pain in relation to Modic changes, bony endplate lesions, and disc degeneration in a prospective MRI study. Eur Spine J. 2016;25:2873–81.
31. Määttä JH, Wadge S, MacGregor A, Karppinen J, Williams FM. ISSLS prize winner: vertebral endplate (Modic) change is an independent risk factor for episodes of severe and disabling low back pain. Spine (Phila Pa 1976). 2015;40:1187–93.
32. Jensen OK, Nielsen CV, Sørensen JS, Stengaard-Pedersen K. Type 1 Modic changes was a significant risk factor for 1-year outcome in sick-listed low back pain patients: a nested cohort study using magnetic resonance imaging of the lumbar spine. Spine J. 2014;14:2568–81.
33. Järvinen J, Karppinen J, Niinimäki J, Haapea M, Grönblad M, Luoma K, et al. Association between changes in lumbar Modic changes and low back symptoms over a two-year period. BMC Musculoskelet Disord. 2015;16:98.
34. Wang Y, Videman T, Battié MC. ISSLS prize winner: lumbar vertebral endplate lesions: associations with disc degeneration and back pain history. Spine (Phila Pa. 1976;2012(37):1490–6.
35. Bian Q, Ma L, Jain A, Crane JL, Kebaish K, Wan M, et al. Mechanosignaling activation of TGFβ maintains intervertebral disc homeostasis. Bone Res. 2017;5:17008.
36. Rodriguez AG, Rodriguez-Soto AE, Burghardt AJ, Berven S, Majumdar S, Lotz JC. Morphology of the human vertebral endplate. J Orthop Res. 2012;30:280–7.
37. Taher F, Essig D, Lebl DR, Hughes AP, Sama AA, Cammisa FP, et al. Lumbar degenerative disc disease: current and future concepts of diagnosis and management. Adv Orthop. 2012;2012: 970752.
38. Matsumoto T, Hagino H, Shiraki M, Fukunaga M, Nakano T, Takaoka K, et al. Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis: a randomized placebo-controlled double-blind study. Osteoporos Int. 2009;20:1429–37.

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