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Original Article

Effectiveness of monotherapy and combined therapy with calcitonin and minodronic acid hydrate, a bisphosphonate, for early treatment in patients with new vertebral fractures: An open-label, randomized, parallel-group study

Shinya Tanaka [a, *], Akira Yoshida [b], Shinjiro Kono [a], Manabu Ito [c]

[a] Department of Orthopaedic Surgery, Saitama Medical University, 38 Morohongo, Moroyama-cho, Iruma-gun, Saitama, 350-0495, Japan
[b] Yoshida Orthopedics Clinic, 49-54 Tateishi, Matsumae-City, Hokkaido, 049-1501, Japan
[c] National Hospital Organization Hokkaido Medical Center, Yamanote 5-7, Nishi-ku, Sapporo, Hokkaido, 063-0005, Japan

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ABSTRACT

Background: Evidence related to the effectiveness of combination drug therapy for the treatment of osteoporosis is currently considered insufficient. Therefore, this study was performed to clarify the effects of monotherapy, and combination therapy, with a bisphosphonate (minodronic acid hydrate), a bone resorption inhibitor, and calcitonin (elcatonin), which is effective for the alleviation of pain due to vertebral fractures in osteoporotic patients.

Methods: Study participants comprised of 51 female subjects with post-menopausal osteoporosis, whose main complaint was acute lower back pain caused by vertebral fractures. Subjects were randomly allocated into three groups and then administered with either intramuscular injections of elcatonin at a dose of 20 units weekly, minodronic acid hydrate at a dose of 1 mg daily, or a combination of these two drugs. As primary endpoints, time-dependent changes in levels of pain were assessed using a visual analog scale from baseline to 6 months of duration. In addition, we examined the effects of monotherapies, and a combination therapy on bone resorption, with changes in bone mineral density at 4 sites and advanced hip assessment parameters from baseline to 6 months. A two-tailed significance level of 5% was used for hypothesis testing.

Results: Elcatonin monotherapy showed some alleviation of pain immediately after any vertebral fractures, which was more than in the minodronic acid hydrate monotherapy group. In addition, the minodronic acid hydrate monotherapy group experienced more effective inhibited bone resorption than the elcatonin monotherapy group. In the combination therapy, the efficacy for alleviating pain and inhibiting bone resorption was equivalent to the effect observed in the elcatonin and minodronic acid hydrate monotherapy groups respectively, with further improved values of bone mineral density observed in the femoral neck and lumbar vertebrae, and in parameters of advanced hip assessment compared with both monotherapy groups.

Conclusions: Combination therapy with elcatonin and minodronic acid hydrate appears to be an effective treatment for osteoporosis patients with lower back pain, caused by fresh vertebral fractures.

1. Introduction

A number of new osteoporosis drugs have been introduced to the market in recent years, thus patients with osteoporosis have an increasing number of available drug choices and administration methods. Recommendation grades for each of these drugs are included in guidelines for the prevention and treatment of osteoporosis [1]; however, these recommendations are based solely on evidence from clinical trials in which the effects were determined in a standardized and controlled patient population. In actual clinical practice, various patient characteristics are taken into consideration when selecting treatment options such as combination therapy. Although the effectiveness of combination therapy for the treatment of osteoporosis has recently been investigated in numerous multicenter studies, led by groups such

* Corresponding author. Fax: +81 49 276 1772.
E-mail addresses: tnk_sny@saitama-med.ac.jp (S. Tanaka), s-jiro@ba2.so-net.ne.jp (S. Kono).

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as the Adequate Treatment of Osteoporosis Research Group [2], sufficient evidence is still lacking. Therefore, in this present study, we investigated the effects of combination therapy with minodronic acid hydrate (MIN), a bisphosphonate developed in Japan for osteoporosis, and elcatonin (EL), an analog of eel calcitonin, a bone resorption inhibitor, for pain, bone resorption, bone mineral density (BMD), and bone structure in patients who visited our outpatient clinic with acute lower back pain caused by new vertebral fractures.

2. Materials and methods

2.1. Study design

This was an open-label, randomized, parallel-group study conducted between August 8, 2010 and March 31, 2011, that compared 3 treatment groups, EL group, MIN group, and EL + MIN group. Patients were allocated into 3 groups using a sealed envelope method, and received either intramuscular injections (IM) of EL (Elcitonin®, Asahi Kasei Pharma Co., Ltd., Tokyo, Japan) at a dose of 20 units weekly (EL group), an oral administration of MIN (Ono Pharmaceutical Co., Ltd., Osaka, Japan) at a dose of 1 mg daily (MIN group), or a combination of these two drugs (EL + MIN group). Each group received treatment for 6 months.

This study was conducted at the Yoshida orthopaedic clinic in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Hokkaido university's ethics committee.

2.2. Subjects

The selection criteria for this study was as follows: postmenopausal women; ≥50 years of age at the start of treatment; developed acute lower back pain (defined as the area between the inferior pole of the scapula and the gluteal sulcus), which was identified within the previous 2 weeks and caused by new osteoporotic thoracolumbar vertebral fractures [3]. Patients with either lower back or percussion pain were considered eligible for inclusion if they had new vertebral fractures confirmed by both X-ray and magnetic resonance imaging (MRI). Regarding MRI examinations, areas with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images were considered incident fracture sites.

Before the study began, the study's aims and content were explained by the attending physician, and written informed consent was obtained from all patients. Patients with any of the following were excluded from the study: secondary osteoporosis; a history of thoracolumbar vertebral surgery; signs of neurological deficit associated with spinal disorders; severe scoliosis; contraindications for either of the treatment drugs (EL, MIN); infectious spinal diseases; severe kidney, liver, or heart disease; or currently undergoing treatment for malignant tumors.

The use of any other osteoporosis drugs during the study was prohibited. In addition, from the time the study began until the administration of the treatment drugs ended, the use of oral or injected nonsteroidal anti-inflammatory drugs (NSAIDs) and non-NSAID analgesics was prohibited. However, if suppository NSAIDs were required, duration of use, method and dose were all recorded. The use of treatments such as thermal or silver spike point therapy, removable braces, or topical NSAIDs were all permitted.

2.3. Assessments

Pain was assessed using a visual analog scale (VAS) before the start of the study (baseline), and prior to EL administration during medical visits at 1, 2, 3 and 4 weeks, and 2, 3, and 6 months. In order to examine the effects on bone metabolism, tartrate-resistant acid phosphatase 5b (TRACP-5b), a marker of bone resorption was taken at baseline and at 2 and 4 weeks, also at 3 and 6 months after the start of the study. Blood samples were collected before medical visits at each observation time point.

In addition, at baseline and 6 months, the BMD of the lumbar vertebrae (mean of L2–L4) and left proximal femur (total hip and femoral neck) was measured using dual-energy X-ray absorptiometry (DEXA) (Prodigy Advance, GE Healthcare, Madison, WI). However, if there was a vertebral fracture in L2–L4, they were excluded from the calculation of the lumbar vertebral BMD value.

2.4. Efficacy endpoints

Primary endpoints of the study were time-dependent changes in VAS pain scores. The trends in changes from baseline were compared between each of the three treatment groups.

The secondary endpoints were inhibition of bone resorption based on changes in TRACP-5b levels; percent changes in BMD of the L2–L4 vertebrae, total hip and femoral neck; and percent change in advanced hip assessment (AHA) parameters. The AHA based on three variables, cortical bone instability (buckling ratio [BR]), torsional resistance (section modulus [SM]), and cross-sectional moment of inertia [CSMI] at the femoral neck were calculated by the software incorporated into DXA system. CSMI is derived from the integral of the bone mass profile across the bone weighted by the square of distance from the center of mass. BR is calculated as the ratio of maximum distance from the center of mass to the outer cortical margin divided by the mean cortical thickness. SM is calculated as CSMI divided by the greater of the measured distances from the center of mass to the medial or lateral surface [4].

2.5. Discontinuation criteria and adverse events (AEs)

The discontinuation of the study was deemed necessary due to the following: if a subject withdrew their consent or no longer wished to participate in the study; if it was discovered after the start of the study that the subject did not meet the inclusion criteria; if the subject could not continue the study due to complications or disease progression; or if there were any other non-specific reasons that warranted discontinuation.

Any AEs reported through medical inquiries, or volunteered by the subjects, were to be confirmed.

2.6. Statistical analysis

In order to ensure reliability, all data was sent to SOC Co., Ltd. (Tokyo, Japan) from the clinic for statistical analysis. The results were sent to the corresponding author.

To investigate the effects of the drugs, we analyzed VAS scores and TRACP-5b levels using repeated measured analysis of variance (ANOVA), including an analysis of the interaction among the three groups (EL group, MIN group, EL + MIN group) with observation time points set as explanatory variables. When a marked interaction was observed, the time-dependent changes were assumed to be different between the groups, and thus compared at each observation time point. ANOVA was used to assess the effects on BMD (percent change) and AHA (percent change) between the groups. For multiple comparisons, p values were adjusted in accordance with the Bonferroni method. A two-tailed significance level of 5% was used for hypothesis testing. SAS ver. 9.3 (SAS institute Japan Ltd., Tokyo, Japan) was used for all statistical analyses.

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