Elcatonin in Combination with Risedronate Is More Effective than Risedronate Alone for Relieving Back Pain in Postmenopausal Women with Osteoporosis

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Intramuscularly administered elcatonin (ECT) reduces pain *via* the central nervous system. A prospective study was performed to determine whether ECT has a beneficial effect on back pain and function in postmenopausal women with osteoporosis during bisphosphonate therapy. Sixty-one postmenopausal osteoporotic women with back pain (mean age: 73.7 years, range: 54–96 years) were divided into two groups: the control group (n=30) and the ECT (intramuscular, 20 units a week) group (n=31). All patients received treatment with risedronate (17.5 mg weekly). The duration of the study was 8 weeks. Urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX), visual analogue scale (VAS) for back pain at rest and movement, and Roland–Morris Disability Questionnaire (RDQ) score for function were assessed. Urinary NTX levels, VAS at rest and movement, and RDQ score markedly decreased during 8 weeks of treatment in both ECT and control groups. A significant reduction in VAS at movement, but not in VAS at rest and RDQ score, was noted in the ECT group than in the control group. This effect was observed from 2 weeks after the start of therapy. These results suggested that ECT in combination with risedronate was more effective than risedronate alone for reducing back pain in postmenopausal women with osteoporosis.

Key words elcatonin; risedronate; clinical vertebral fracture; postmenopausal woman; back pain

Osteoporosis is commonly observed particularly in postmenopausal women, placing them at a significant risk of a fracture. Risedronate has been widely used as the first-line treatment for postmenopausal osteoporosis, because current evidence, based strictly on the principles of evidence-based medicine (EBM), suggests the efficacy of risedronate to reduce fracture incidence as well as its safety in postmenopausal women with osteoporosis.[1–3] A recent systematic review analyzing 7 randomized controlled trials (RCTs) involving 14049 women confirms both clinically important and statistically significant reductions in vertebral, nonvertebral, and hip fractures after secondary prevention therapy.[4]

It has been reported that the effect of risedronate to prevent clinical vertebral and nonvertebral fractures is recognized as early as 6 months after the start of treatment in postmenopausal women with osteoporosis.[5,6] The anti-resorptive effects of nitrogen-containing bisphosphonates appear to result from their inhibition of an enzyme, farnesyl pyrophosphate synthase (FPPS), in osteoclasts.[7] FPPS is a key enzyme in the mevalonate pathway, which generates isoprenoid lipids utilized for *post*-translational modification of small guanosine 5′-triphosphate (GTP)-binding proteins that are essential for osteoclast function.[7] One possible explanation for the early anti-fracture effect of risedronate is such inhibitory effect on FPPS in osteoclasts.

Intramuscular treatment with elcatonin (ECT) is commonly used in Japan. ECT is a derivative of eel calcitonin synthesized by substituting an ethylene bond for its disulfide bond.[8] The ECT product for intramuscular use was developed in Japan and has been shown to have biological activity comparable to that of natural eel calcitonin.[8–10] Both *in vivo* and *in vitro* studies have also demonstrated that ECT suppresses bone resorption.[10,11] One RCT found a preventive effect of ECT on vertebral fractures in postmenopausal Japanese women with osteoporosis,[12] while another RCT indicated no evidence showing that ECT significantly reduces the incidence of vertebral fractures.[13] The anti-fracture efficacy of intramuscular ECT remains to be established. Several studies have shown that intramuscular ECT is useful for relieving pain and improving the quality of life (QOL) in postmenopausal Japanese women with or without osteoporosis.[14,15] The evidence-based clinical practice guidelines of the American Academy of Orthopaedic Surgeons (AAOS) suggest that calcitonin therapy is recommended to patients who present with an osteoporotic spinal compression fracture on imaging with correlating clinical signs and symptoms suggesting an acute injury (0–5 d after identifiable event or onset of symptoms) and who are neurologically intact be treated with nasal calcitonin for 4 weeks (strength of recommendation is moderate).[16] Therefore, ECT may primarily be used for pain relief in patients with osteoporosis.

Recent reports demonstrated the analgesic effect of oral bisphosphonates in postmenopausal women with osteoporosis.[17,18] ECT in combination with risedronate is speculated to be more useful for preventing osteoporotic fractures as early as possible and relieving pain than single treatment with either ECT or risedronate alone in postmenopausal women with osteoporosis. To the best of our knowledge, however, no controlled study has been conducted to determine the effect of ECT on back pain in postmenopausal women with osteoporosis during bisphosphonate therapy. The hypothesis is that ECT in combination with risedronate would be more effective than risedronate alone for relieving back pain and function in postmenopausal women with osteoporosis. A prospective study was performed to determine the effect of this combination therapy on back pain and function compared with risedronate alone in postmenopausal women with osteoporosis. The primary endpoint was the degree of back pain. The secondary

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endpoints included function score, a bone resorption marker, and lumbar bone mineral density (BMD).

SUBJECTS AND METHODS

Subjects Sixty-one postmenopausal women with osteoporosis (mean age: 73.7 years, range: 54–96 years) were recruited at our outpatient service during a 20-month period between April 2007 and November 2008. The inclusion criteria were postmenopausal women with osteoporosis, existing moderate to severe back pain, and no history of treatment for osteoporosis. The exclusion criteria included renal failure, allergy to calcitonin or bisphosphonates, difficulty in sitting or standing for 30 min, histories of reflux esophagitis, gastric or duodenal ulcers, gastrectomy, sciatica due to degenerative lumbar disc diseases, and bone diseases including bone metastasis of cancers, primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, multiple myeloma, rheumatoid arthritis, and osteogenesis imperfecta. Patients who had ever taken any medications known to affect bone metabolism were also excluded.

All the women had been diagnosed as having osteoporosis according to the Japanese diagnostic criteria.[19,20] Namely, women with a BMD less than 70% of the young adult mean (YAM) or of 70–80% of the YAM along with a history of an osteoporotic fracture were diagnosed as having osteoporosis. A preliminary screening included obtaining patient's medical history, physical examination, plain X-rays of the thoracic and lumbar spine and measurement of lumbar and/or femoral neck BMD using a dual-energy X-ray absorptiometry (Prodigy Advance, GE Healthcare, Madison, WI, U.S.A.) and urinary cross-linked N-terminal telopeptides of type I collagen (NTX) using an enzyme-linked immunosorbent assay. A diagnosis of osteoporosis was made based on prevalent vertebral fracture and lumbar or femoral neck BMD. Back pain and function were assessed using visual analogue scale (VAS) and Roland–Morris Disability Questionnaire (RDQ), respectively.

Each subject was numbered according to the sequence of the enrollment in the study. Then, the subjects were divided into two groups: the ECT (intramuscular, 20 units a week) group (odd numbers, n=31) and the control (CON) group (even numbers, n=30). All patients also received treatment with risedronate at 17.5 mg weekly. The doses of these agents indicated above are generally used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective.[21–23] All the subjects were instructed to avoid using hard braces or oral non-steroidal anti-inflammatory drugs (NSAIDs) for back pain. The duration of the trial was 8 weeks. Back pain (VAS) and function (RDQ score) were assessed at 1, 2, 4, 6, and 8 weeks after the start of therapy. The urinary levels of NTX and lumbar BMD were measured at 8 weeks after the start of therapy. Plain X-rays of the thoracic and lumbar spine were not taken in any of subjects at 8 weeks after the start of therapy because none of them experienced either occurrence of acute back pain or severe worsening of back pain during the 8-week study period. The discontinuation of participation in the study by the participants was permitted when adverse events of the treatment were observed or when they felt like withdrawing from the study. The participants who experienced any clinical fractures must have been excluded from the analyses. Informed consent was obtained from each participant prior to their participation in the study. This protocol was approved by the Ethics Committee of Takakuwa Orthopaedic Nagayama Clinic.

Assessment of Radiographic Vertebral Fractures A plain lateral X-ray of the thoracic and lumbar spine was performed to detect evidence of radiographic vertebral fractures. According to the Japanese criteria, a vertebral fracture was defined according to the vertebral height on lateral X-ray films.[19,20] Briefly, the vertebral height was measured at the anterior (A), central (C), and posterior (P) portions of the vertebral body, and the presence of a vertebral fracture was confirmed when (1) a reduction in the vertebral height at A, C, and P of more than 20% compared with the height of the adjacent vertebrae was observed, (2) the C/A or C/P was less than 0.8, or (3) the A/P was less than 0.75. The assessment for vertebral fractures was performed at the T4–L4 level.

Evaluation of Back Pain Back pain at rest and movement was rated at the time of getting up and each follow-up visit using a horizontal 100-mm VAS, ranging from 0 mm (no back pain) to 100 mm (possibly worst back pain). This type of VAS is reliable and reproducible for the measurement of pain.[24]

Evaluation of Function The RDQ, a widely used health status measurement tool for low back pain, was used to evaluate the progress of the patient's functional improvement with low back pain over time.[25,26] This questionnaire consisted of 24 items.[25,26] Patients completed the questionnaire by checking the box of any statements associated with their condition. The RDQ score corresponds to the total number of items checked—*i.e.* from a minimum of 0 to a maximum of 24. The total score was recorded and followed over time to evaluate the patient's functional progress. In particular, the Japanese version of the RDQ is a useful scale that is easy to use with reliability, validity, and responsiveness when assessing patients with low back pain.[27]

Statistical Analysis The intention to treat analysis was adopted. Data are expressed as the mean±standard deviation (S.D.) in tables and the mean and 95% confidence interval (CI) in figures. The use of 95% CI facilitates the distinction between statistical significance and clinical significance or practical importance in figures. Cross-sectional data comparisons between the two groups were performed using the unpaired t-test or Fisher's exact test. In particular, cross-sectional comparisons of RDQ scores between the two groups were additionally performed using the Mann–Whitney's U-test. The significance of longitudinal changes in the parameters in either group was determined using the one-way analysis of variance (ANOVA) with repeated measurements. Longitudinal changes in the parameters were compared between the two groups using the two-way ANOVA with repeated measurements. Longitudinal changes in pain and function parameters (VAS and RDQ scores) were compared between the two groups using the analysis of covariance (ANCOVA) with the number of prevalent vertebral fractures as covariates. All statistical analyses were performed using the Stat View-J5.0 program and the PC SAS v9.0 (SAS Institute, Cary, NC, U.S.A.) on Microsoft Windows operating system. A significance level of $p<0.01$ was used for all comparisons.

RESULTS

Patient Demographic Characteristics Table 1 shows baseline demographic characteristics of the study subjects.

There were no significant differences in age, height, body weight, body mass index, lumbar and femoral neck BMD, YAM of lumbar and femoral neck BMD, and urinary NTX between the two groups. However, the percentage of patients with any vertebral fracture was significantly higher in the ECT group than in the CON group (83.9% *vs.* 50.0%). The number of patients with one, two, and three vertebral fractures was 13, 2, and 0, respectively in the CON group and 19, 5, and 2, respectively in the ECT group. No patients had four or more vertebral fractures. Table 2 shows VAS and RDQ scores at baseline. There were no significant differences in VAS at rest and movement at the time of getting up and clinic visit, as well as RDQ score. VAS at rest was obviously lower than VAS at movement.

Dropout during the Study No patients in the two groups experienced any clinical fractures. No patients in the ECT group discontinued therapy during the study period. However, 5 patients withdrew from the study because they were treated in other clinics or were non-compliant during the 8-week period. Of these 5 patients, 4 withdrew within 2 weeks and 1 within 4 weeks. No serious adverse events requiring hospitalization were observed in either group. Study treatment was completed in 31 women (100%) in the ECT group and 25 patients (83.3%) in the CON group. Therapy with risedronate and ECT was safe and well tolerated in these participants.

Table 1. Patient Demographic Characteristics

	ECT (n=31)	CON (n=30)
Age (years)	75.4±7.9	72.0±9.6
Height (m)	1.45±0.07	1.45±0.06
Body weight (kg)	46.7±7.6	46.2±9.6
Body mass index (kg/m^2)	22.3±3.3	21.8±3.6
Lumbar BMD (g/cm^2)	0.769±0.149	0.730±0.099
YAM of lumbar BMD (%)	66.0±12.3	64.7±8.5
Femoral neck BMD (g/cm^2)	0.629±0.141	0.626±0.114
YAM of femoral neck BMD	69.7±15.9	68.8±12.5
Urinary NTX (nM BCE/mM Cr)	50.0±21.3	42.7±18.8
Number (%) of patients with prevalent vertebral fracture	26 (83.9%)*	15 (50.0%)

Data are expressed as means±S.D. Unpaired t-test was used to compare data between the two groups. Fisher's exact test was used to compare the number of patients with prevalent vertebral fracture. * Significant as compared with CON. ECT, elcatonin; CON, control; BMD, bone mineral density; YAM, young adult mean; NTX, cross-linked N-terminal telopeptides of type I collagen.

Table 2. VAS and RDQ Scores

	ECT (n=31)	CON (n=30)
VAS at rest (when getting up)	19.7±28.5	17.5±20.5
VAS at rest (at the time of visit)	21.1±29.5	14.2±13.9
VAS at movement (when getting up)	76.3±27.0	68.0±13.9
VAS at movement (at the time of visit)	78.7±26.6	68.1±12.7
RDQ score	11.2±3.8	11.6±5.4

Data are expressed as means±S.D. Unpaired t-test was used to compare VAS between the two groups. Unpaired t-test and Mann–Whitney's U-test were used to compare RDQ score between the two groups. There were no significant differences in VAS or RDQ scores between the two groups. ECT, elcatonin; CON, control; VAS, visual analogue scale; RDQ, Roland–Morris Disability Questionnaire.

Changes in Lumbar BMD and Urinary NTX Figure 1 shows changes in lumbar BMD and urinary NTX during the 8-week treatment period. The one-way ANOVA with repeated measurements shows that urinary NTX levels significantly decreased in the two groups and that lumbar BMD significantly increased in the CON group but not in the ECT group (Table 3). The two-way ANOVA with repeated measurements shows no significant differences in changes in urinary NTX or lumbar BMD between the two groups (Table 3). The unpaired t-test shows no significant differences in urinary NTX or lumbar BMD at 8 weeks. Percentage changes in urinary NTX at 8 weeks were −28.9% in the CON group and −33.7% in the ECT group. Percentage changes in lumbar BMD at 8 weeks were +4.21% in the CON group and +1.74% in the ECT group.

Changes in VAS and RDQ Scores Figures 2 and 3 show changes in VAS and RDQ scores, respectively. The one-way ANOVA with repeated measurements shows that VAS at rest (when getting up), VAS at rest (at clinic visit), VAS at movement (when getting up), VAS at movement (at clinic visit), and RDQ scores significantly decreased in the two groups (Table 3). The two-way ANOVA with repeated measurements shows significant differences in changes in VAS at movement (when getting up and at clinic visit), but not VAS at rest (when getting up and at clinic visit) and RDQ scores, between the two groups (Table 3). The unpaired t-test shows that VAS at movement (when getting up) at 2, 4, and 6 weeks was significantly lower in the ECT group than in the CON group, and that VAS at movement (at clinic visit) at 4, 6, and 8 weeks was significantly lower in the ECT group than in the CON group. However, the unpaired t-test shows that there were no significant differences in VAS at rest (when getting up and at clinic visit) at any time points between the two groups. Neither the unpaired t-test nor the Mann–Whitney's U-test showed any significant differences in RDQ scores at any time points between the two groups.

The ANCOVA shows no significant effect of the number of prevalent vertebral fractures on differences in longitudinal changes in VAS at movement (when getting up and at clinic visit), VAS at rest (when getting up and at clinic visit) and RDQ scores between the two groups.

DISCUSSION

The objective of the present prospective study was to determine the effect of therapy with ECT in combination with risedronate on back pain and function compared with risedronate alone in postmenopausal women with osteoporosis. ECT combined with risedronate was more effective than risedronate alone for reducing back pain at movement, but not back pain at rest and function. Thus, the beneficial effect of ECT on back pain was confirmed in postmenopausal women with osteoporosis during bisphosphonate therapy.

Calcitonin reduces pain by acting on the central nervous system.[28] The serotonergic system in the spinal cord (dorsal horn) might be involved in anti-nociception. There are

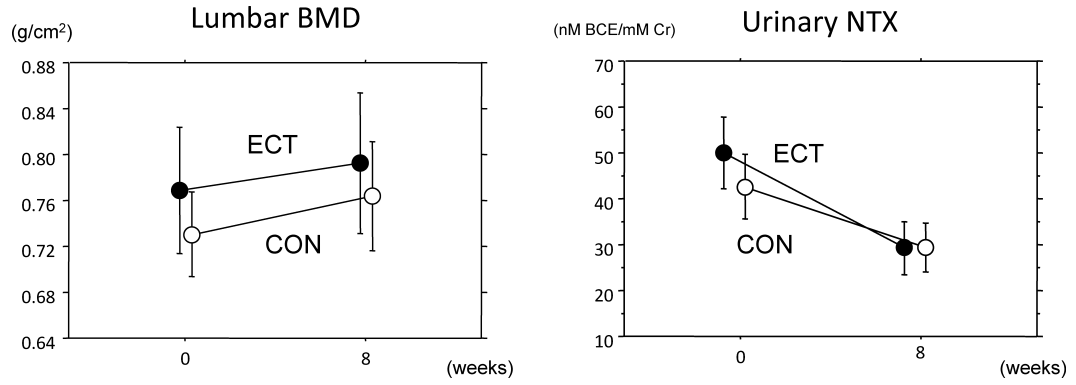

Fig. 1. Changes In Lumbar BMD and Urinary NTX

Data are expressed as mean±95% confidence interval. In total, 5 patients withdrew from the study. Of these 5 patients, 4 withdrew within 2 weeks and 1 within 4 weeks. The intention to treat analysis was adopted. The one-way ANOVA with repeated measurements was used to examine the significance of longitudinal changes in parameters in either group (Table 3). The two-way ANOVA with repeated measurements was used to compare longitudinal changes in parameters between the two groups (Table 3). The unpaired *t*-test was used to compare data at each time point between the two groups. There were no significant differences in lumbar BMD and urinary NTX at 8 weeks of treatment between the two groups.

ECT, elcatonin; CON, control; BMD, bone mineral density; NTX, cross-linked N-terminal telopeptide of type I collagen; ANOVA, analysis of variance.

Table 3. Results of One-Way and Two-Way ANOVA with Repeated Measurements

	One-way ANOVA		Two-way ANOVA
	ECT	CON	ECT *vs.* CON
Lumbar BMD	NS	0.0046	NS
Urinary NTX	<0.0001	<0.0001	NS
VAS at rest (when getting up)	<0.0001	<0.0001	NS
VAS at rest (at the time of visit)	0.0021	<0.0001	NS
VAS at movement (when getting up)	<0.0001	<0.0001	<0.0001
VAS at movement (at the time of visit)	<0.0001	<0.0001	<0.0001
RDQ score	<0.0001	<0.0001	NS

In total, 5 patients withdrew from the study. Of these 5 patients, 4 withdrew within 2 weeks and 1 within 4 weeks. The intention to treat analysis was adopted. The one-way ANOVA with repeated measurements was used to examine the significance of longitudinal changes in parameters in either group. The two-way ANOVA with repeated measurements was used to compare longitudinal changes in parameters between the two groups. ECT, elcatonin; CON, control; BMD, bone mineral density; NTX, cross-linked N-terminal telopeptides of type I collagen; VAS, visual analogue scale; RDQ, Roland–Morris Disability Questionnaire; ANOVA, analysis of variance; NS, not significant.

no significant differences in the analgesic effect of eel and salmon calcitonins and their influence on morphine analgesia.[29] Estrogen deficiency not only causes bone loss but also affects the spinal serotonergic system (serotonergic receptor expression), resulting in hyperalgesia.[30] Calcitonin corrects this change in the serotonergic system[30] and has an analgesic action in postmenopausal women. In the present study, treatment with ECT resulted in a significant decrease in back pain at movement in postmenopausal women with osteoporosis during risedronate therapy. However, ECT did not reduce back pain at rest probably because back pain related to osteoporosis may represent back pain at movement taking into account the baseline results showing that back pain at rest was apparently lower than back pain at movement. Further observation may be needed to determine whether ECT would improve function in postmenopausal women with osteoporosis during bisphosphonate therapy.

A previous study showed that weekly intramuscular injection of ECT at a dose of 20 units did not significantly decrease bone turnover markers such as urinary hydroxyproline and serum osteocalcin in patients with involutional osteoporosis.[21] In the present study, ECT did not significantly affect urinary NTX in patients treated with risedronate, being consistent with the results from our previous study of alendronate.[31] As no consensus has been reached with regard to the effect of ECT against vertebral fractures,[12,13] ECT therapy might be desirable for the relief of back pain at movement in postmenopausal women with osteoporosis.

The degree of back pain decreased in the CON group. However, it remains uncertain whether this finding was seen in the natural course or attributable to the effect of risedronate therapy. Recently, the pain relief effect of bisphosphonates has been reported. An observational study has shown the acute effect of risedronate on back pain, disability, and QOL (as assessed by SF-36) in postmenopausal osteoporotic women without any vertebral fracture.[17] RCTs also confirmed the acute effect of alendronate on back pain and QOL in postmenopausal women with osteoporosis.[18,32] One possible mechanism for these pain relief effects is related to anti-resorptive effect of bisphosphonates, because the efficacy of this class of drugs for bone pain in patients with avascular necrosis of the hip, osteoporotic vertebral fractures, skeletal metastases, or Paget's disease of the bone has been demonstrated.[33–37] Another possible explanation is that bisphosphonates may relieve back pain by suppressing production of neuropeptides that are active during pain transmission, such as substance P and calcitonin gene-related peptide (CGRP), and inflammatory cytokines, such as tumor necrosis factor-α (TNF-α).[38–43]

Phase III Studies conducted in Japan have shown that risedronate decreases urinary NTX by about 33–40% from 4 to 12 weeks of treatment and increases lumbar BMD by about 2.7–3.0% at 12 weeks of treatment in postmenopausal women with osteoporosis.[22,23] In the present study, 8-week therapy with risedronate with or without ECT reduced urinary NTX

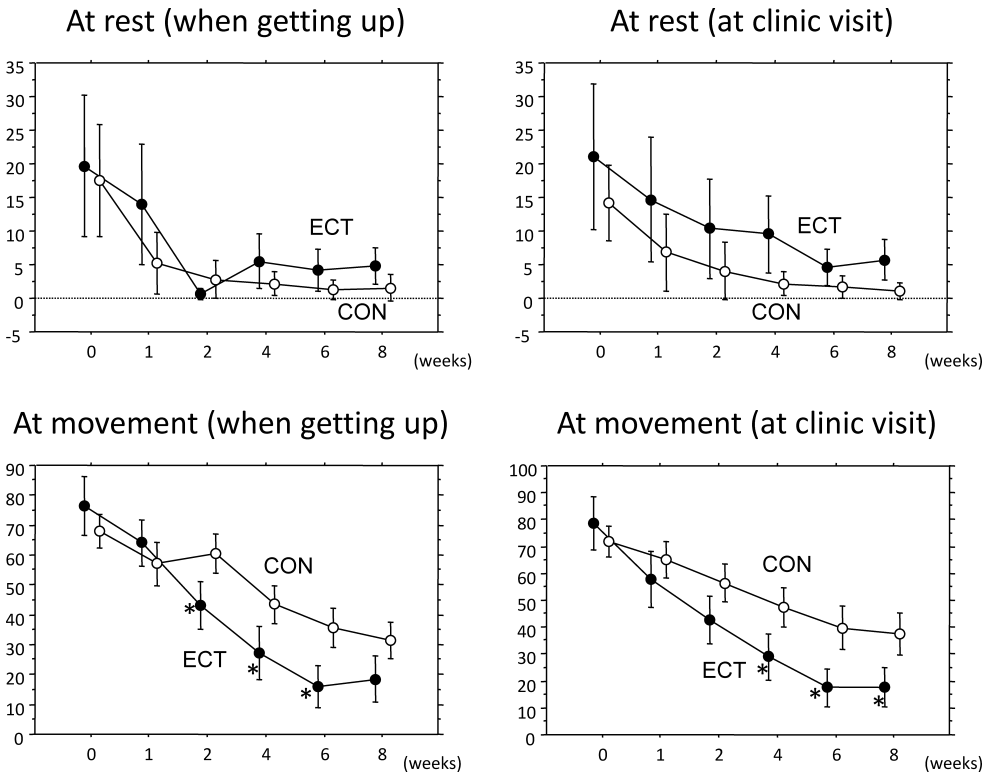

Fig. 2. Changes in VAS

Data are expressed as mean±95% confidence interval. In total, 5 patients withdrew from the study. Of these 5 patients, 4 withdrew within 2 weeks and 1 within 4 weeks. The intention to treat analysis was adopted. The one-way ANOVA with repeated measurements was used to examine the significance of longitudinal changes in parameters in either group (Table 3). The two-way ANOVA with repeated measurements was used to compare longitudinal changes in parameters between the two groups (Table 3). The unpaired *t*-test was used to compare data at each time point between the two groups. *Significant as compared with CON. ECT, elcatonin; CON, control; VAS, visual analogue scale; ANOVA, analysis of variance.

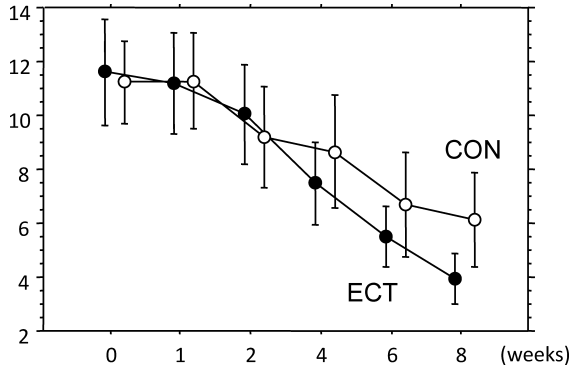

Fig. 3. Changes in RDQ Scores

Data are expressed as mean±95% confidence interval. n total, 5 patients withdrew from the study. Of these 5 patients, 4 withdrew within 2 weeks and 1 within 4 weeks. The intention to treat analysis was adopted. The one-way ANOVA with repeated measurements was used to examine the significance of longitudinal changes in the parameter in either group (Table 3). The two-way ANOVA with repeated measurements was used to compare longitudinal changes in the parameter between the two groups (Table 3). The unpaired *t*-test and Mann–Whitney's *U*-test were used to compare data at each time point between the two groups. There were no significant differences in RDQ scores at any time points between the two groups. ECT, elcatonin; CON, control; RDQ, Roland–Morris Disability Questionnaire; ANOVA, analysis of variance.

by 28.9–33.7% and increased lumbar BMD by 1.74–4.21%, which results were comparable with the previous results.[22,23] No additional effect of ECT and risedronate on urinary NTX and lumbar BMD was observed probably due to the non-significant or modest effect of ECT on bone metabolism.

The present open-label prospective study has notable limitations. First, the study was not a double-blind trial. Therefore, some of the results might be biased. Second, the number of study subjects may not be sufficient, although we obtained a significant finding regarding back pain at movement. Thus, a large double-blind randomized placebo-controlled trial is needed to confirm the results of the present study.

In conclusion, the present prospective study showed that ECT in combination with risedronate was more effective than risedronate alone for reducing back pain at movement, but not back pain at rest and function, in postmenopausal women with osteoporosis. Thus, there was a beneficial effect of ECT on back pain in postmenopausal women with osteoporosis during bisphosphonate therapy.

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