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ORIGINAL ARTICLE

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Utility of monthly minodronate for osteoporosis after gastrectomy: Prospective multicenter randomized controlled trials

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Abstract

Aim: Osteoporosis in patients after gastrectomy is increasing with the aging of gastric cancer patients. Bisphosphonates are effective treatments for osteoporosis; however, their safety or efficacy in postgastrectomy patients has not been established. The purpose of this multicenter prospective intervention study was to investigate the impact of monthly minodronate on osteoporosis after gastrectomy.

Methods: Of the 261 enrolled gastric cancer patients, 164 patients were diagnosed with osteoporosis based on criteria of the Japan Society of Osteoporosis. They were randomly assigned 1:1 to groups treated with active vitamin D (VD group) or monthly minodronate (MIN group). The primary endpoint was changes in lumbar bone mineral density (L-BMD) 12 mo after the start of administration. The secondary endpoints were changes in bone metabolism markers, adverse events (AEs), or treatment completion rates.

Results: There was no significant difference in patient background between the VD (n = 82) and MIN (n = 82) groups. In the MIN group, the increase in L-BMD was significantly higher than that in the VD group (4.52% vs 1.72%, $P = .001$), with a significant reduction in bone metabolism markers; blood NTX (−25.6% vs −1.6%, $P < .01$) and serum bone-specific alkaline phosphatase (−34.3% vs −20.1%, $P < .01$). AEs were observed in 26.8% and 9.3% of the patients and treatment completion rates were 77.5% and 89.3% in the MIN and VD groups, respectively. Serious AEs were not observed in either group.

Conclusion: This study demonstrated the safety and efficacy of monthly minodronate, suggesting that this treatment may be useful for osteoporosis after gastrectomy (UMIN000015517).

KEYWORDS

active vitamin D, bone metabolism disorders, gastrectomy, intervention, minodronate

1 | INTRODUCTION

The incidence of gastric cancer has been steadily declining worldwide in the last decades; nevertheless, it is still the fifth most common cancer worldwide, with more than 1 000 000 new cases and more than 780 000 deaths reported in 2018.[1] In Japan, more than 40 000 patients undergo gastrectomy for gastric cancer every year. After gastrectomy, patients are prone to bone metabolism disorders such as osteoporosis due to changes in the absorption of nutrients such as calcium and vitamin D.[2–5] The incidence of osteoporosis after gastrectomy was previously reported to have increased from 32% to 42%,[6–8] while that of osteoporotic fracture after gastrectomy was reported to be approximately 40%,[6,7,9,10] the majority of the fractures occurring several years postoperation.[9,11] Today, an increasing number of elderly patients are undergoing gastrectomy for gastric cancer and there has been an improvement in the survival rate of this condition; thus, securing quality of life after gastrectomy, including prevention of osteoporosis or osteoporotic fracture, is important.[12]

Currently, antiosteoporosis drugs, such as calcium gluconate, vitamin D3, and bisphosphonate, are available in Japan. Among them, bisphosphonates, such as alendronate[13–15] and minodronate,[16,17] exhibit strong efficacy for vertebral and hip fracture prevention and increasing bone mass. These agents have several administration regimens, such as daily, weekly, monthly, and yearly regimens, which can be selected according to the patient's preference to ensure excellent medication adherence. Therefore, bisphosphonate is widely used in the daily treatment of osteoporosis in Japan. Particularly, minodronate, a third-generation bisphosphonate, has a low frequency of side effects, such as digestive disorders, which was one of the drawbacks of conventional bisphosphonate preparations.[18,19] For osteoporosis after gastrectomy, some studies showed that alendronate might improve osteopenia[20] or might prevent bone mineral disorders and fractures.[5,21,22] However, these studies used a relatively small sample size, and no clear evidence has been established concerning their effectiveness. Particularly, bisphosphonates have various digestive complications, and the safety and feasibility of bisphosphonates in the special gastrointestinal environment after gastrectomy are still unclear. Under these circumstances, minodronate, which is likely to be less toxic and have less adverse events (AEs) of the gastrointestinal region, and is administered once a month, is widely used in clinical practice in Japan since 2012 as a therapeutic agent for osteoporosis.[19,16,23,24] After gastrectomy, patients often have gastrointestinal disorders, such as appetite loss, nausea, fullness, and abdominal pain; therefore, in the treatment of osteoporosis after gastrectomy, minodronate may be suitable to maintain medication compliance and be more effective. However, there have been no reports on the safety or efficacy of minodronate in osteoporosis after gastrectomy.

In this study, a randomized controlled trial using a group-administered activated vitamin D preparation as the control group was conducted to verify the efficacy and safety of minodronate in osteoporosis after gastrectomy.

2 | PATIENTS AND METHODS

2.1 | Patient enrollment

We first conducted a prospective observational multicenter study among the Clinical Study Group of Osaka University (CSGO), Upper GI Group, to evaluate the prevalence of osteoporosis and bone loss in elderly gastric cancer patients who had undergone gastrectomy. The eligibility criteria included: (a) no evidence of recurrence or metastasis over 3 y after curative gastrectomy for adenocarcinoma of the stomach; (b) males aged >70 y, or females aged >60 y; (c) a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale; (d) no history of bone fracture within the last 3 mo; (e) no liver or renal dysfunction; (f) no history of other malignancies during the last 5 y or diseases that cause bone loss, such as poorly controlled diabetes, hyperparathyroidism, osteomalacia, or multiple myeloma. We excluded patients who had been previously diagnosed with osteoporosis, and who had not taken any medication, such as estrogen, bisphosphonate, corticosteroid, or vitamin D. Among the 271 patients registered in this cohort, 164 patients had a bone mineral density (BMD) of less than 80% in the young adult mean (YAM) value, and they were confirmed to have bone metabolism disorders to be treated based on the diagnostic criteria of the Japan Society of Osteoporosis. These patients were enrolled in this study and they gave written informed consent before registration.

2.2 | Randomization

The patients were randomly assigned 1:1 to the minodronate (MIN) group treated with the oral bisphosphonate formulation (monthly administration of minodronic acid hydrate Bonoteo 50 mg / Ricarbon 50 mg, 1 tablet/month) and the vitamin D (VD) group treated with the active vitamin D3 formulation (Eldecalcitol, EDIROL 0.75 μg, 1 capsule/d). The treatment was started within 8 wk after the BMD measurement and continued for 1 y in both groups. Randomization was performed by a computerized system and stratified by the extent of gastrectomy (nontotal gastrectomy / total gastrectomy) and gender. The improvement rate of lumbar spine bone density values in study subjects who were treated for 1 y was assumed to be 6% for the MIN group and 3% for the eldecalcitol group. If the detection period is 2 y and the follow-up period is 1 y and the one-sided significance level is $\alpha = 0.05$ and $\beta = 0.1$, the required number of cases is 59 cases per group, totaling 118 cases. Considering cases that would be deemed ineligible, the registered sample size was set to 150 cases.

2.3 | Study outcomes

The primary endpoint of the study was the rate of increase in lumbar BMD (L-BMD) values at 1 y after treatment. Secondary endpoints included the rate of increase in femoral BMD values at 1 y after

treatment, incidence of AEs associated with treatment, completion rate of treatment, occurrence of clinical fractures, and improvement rate of bone turnover markers. Because the 2015 Japanese Guidelines for Prevention and Treatment of Osteoporosis indicate that a +4.2% or higher change in L-BMD is the cutoff value for therapeutic effect, the related factors of cases with values of +4.2% or higher (effective treatment) were examined by univariate and multivariate analysis.

2.4 | BMD measurement

BMD values of the lumbar spine and femur neck were measured at study registration and 1 y after administration using dual-energy x-ray absorptiometry (DXA) scans. The BMD of the lumbar spine was evaluated as the average value of L2–L4. The BMDs were expressed as absolute values (g/cm^2), T scores (compared to young adults), and Z scores (compared to age-matched values) according to the GE-Lunar database.

2.5 | Assessment of bone turnover markers

Serum samples were collected at baseline, 6, and 12 mo after starting the drug administration, for measurement of serum bone turnover markers, including type I collagen N-telopeptide (NTX) and bone-specific alkaline phosphatase (BAP). Serum calcium, ionized phosphorus, and creatinine were also monitored.

2.6 | Assessment of AEs

The subjects visited the clinic or hospital every 4–8 wk during this study. All subjects were questioned about the occurrence of AEs of treatment at each visit, and all reported AEs were analyzed regardless of the investigators' assessments of causality. The Common Terminology Criteria for Adverse Events v. 4.0 (CTCAE-v4.0) was used to categorize the reported AEs.

2.7 | Statistical analysis

The improvement rate of L-BMD 1 y after drug treatment was assumed to be 6% for the minodronate group and 3% for the elcatcitol group. The estimated registration period was 2 y and the follow-up period was set as 1 y. The one-sided significance level was $\alpha = 0.05$ and $\beta = 0.1$ and the required sample size was 59 cases per group (total 118 cases). Considering cases that would be deemed ineligible, the required registered sample size was set to 150 cases.

Analysis of the increase in BMD values and the improvement rate of bone turnover markers was conducted in per-protocol subset (PPS). Among the intention-to-treat (ITT) population, subsets that were initiated with the treatment were used for analyzing the incidence of AEs associated with the treatment, the completion rate of treatment, and the occurrence of clinical fractures. All data were analyzed using a statistical software package (JMP 13, SAS Institute, Cary, NC) on a universal personal computer. For the comparison of two continuous variables, analysis of variance was used to compare parametric data. The Wilcoxon rank-sum test was applied to nonparametric data. The two categorical data were compared using Pearson's test or Fisher's test. Risk factors for L-BMD increase and treatment continuity were examined via univariate/multivariate analysis using a logistic regression model. In multivariate analysis, the factors of continuous variables were examined by dividing them into two groups based on the median cutoff. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient disposition

Patient disposition is shown in Figure 1. Among the 271 registered patients in the cohort from 14 institutions, 164 patients were diagnosed with bone metabolism disorders. The allocation of the 164 subjects (82 in the MIN group and 82 in the VD group) was randomized, and 146 subjects (71 in the MIN group and 75 in the VD group) received at least one dose of the study medication and were included in the safety analysis. The completion rate for 1-year treatment in the MIN group was 77.5% (55 of the 71 cases), which tended to be lower than the completion rate of 89.3% (67 of the 75 cases) in the VD group ($P = .0531$).

3.2 | Demographics and baseline characteristics

The baseline demographics of the subjects were well balanced; there was no significant difference in BMD and the level of bone turnover markers at the baseline between the two groups (Table 1). No significant difference was observed in surgical procedure and nutritional parameters.

3.3 | Changes in BMD and bone turnover markers

Changes in BMD, including the primary endpoint, the increase in L-BMD values at 1 y after treatment, and bone turnover markers were analyzed in PPS (55 cases in the MIN group and 67 cases in the VD group; Figure 2). The increase in L-BMD was observed in both groups and the median increase rate was significantly higher in the MIN group than in the VD group (4.32% [−3.41-18.6] vs 2.14% [−12.8-12.0], $P = .0024$). The median increase in femoral BMD values, which was the secondary endpoint of this study, was also significantly higher in the MIN group than in the VD group (2.88% [−8.21-16.8] vs −0.775% [−13.4-25.0], $P < .0001$).

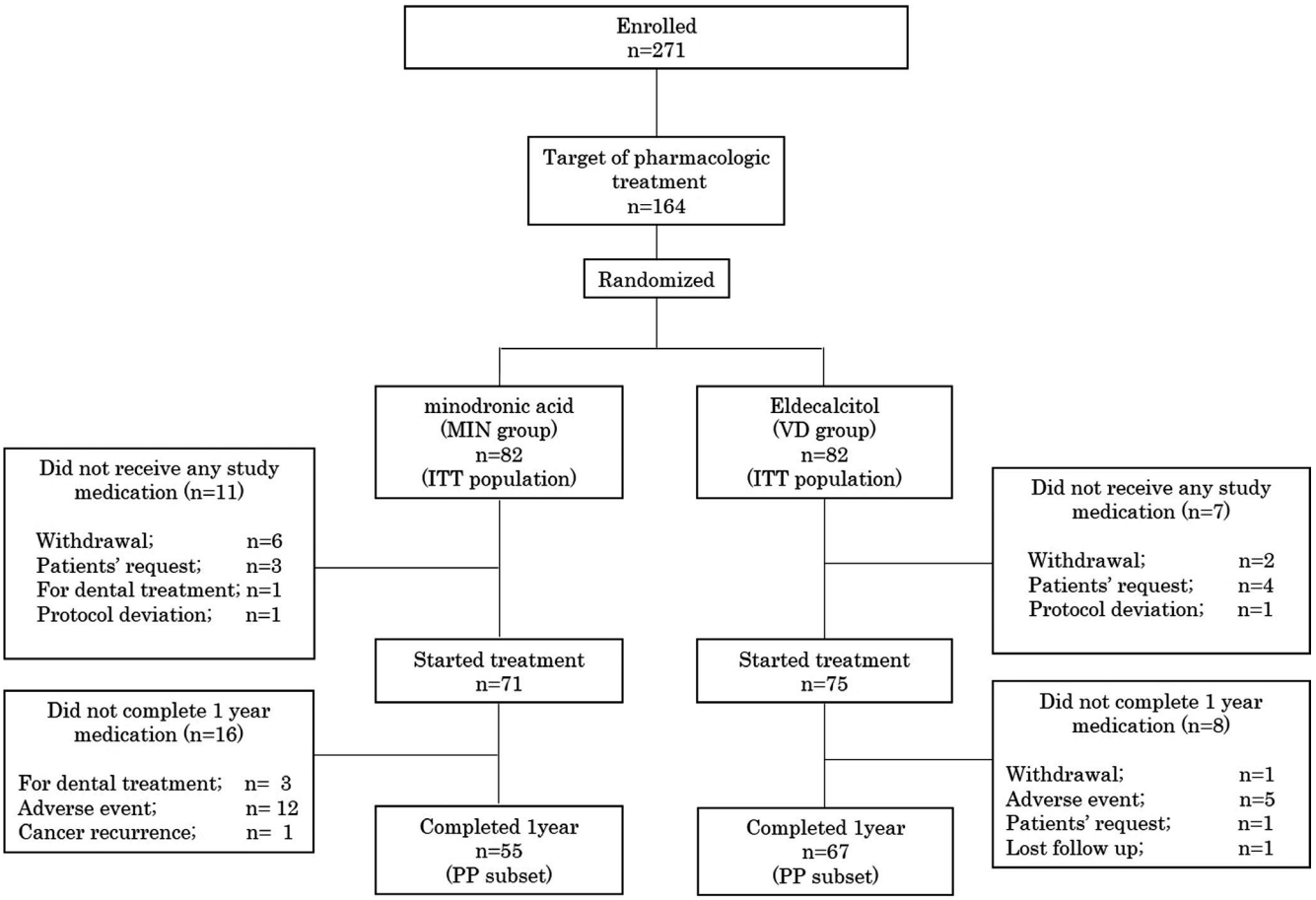


FIGURE 1 Patient disposition

Concerning the changes of bone turnover markers, both BAP (born formation marker) and NTX (born resorption marker) decreased in both groups and the decrease was significantly larger in the MIN group than in the VD group (BAP: −36.5% [−66.9-6.74] vs −22.0% [−62.2-89.2], $P = .0002$, and NTX: −30.2% [−64.5-32.8] vs −5.31% [−44.3-87.9], $P < .0001$). Figure 3 shows the rate of increase in L-BMD, which is the primary endpoint, for the stratifying factors gender and gastrectomy type. The rate of increase in L-BMD by gender was MIN 5.65% [−3.16-18.88] for females and VD 1.13% [−8.02-12.0] for females, showing a significantly higher rate of increase for MIN ($P = .0007$). Contrastingly, in males MIN 3.81% [−3.41-12.9] and VD 2.23% [−12.8-10.7] showed no significant difference in the rate of increase between the two groups ($P = .3155$). In comparison within the MIN group, females showed a higher rate of increase ($P = .0286$), whereas there was no significant difference between males and females within the VD group ($P = .7435$). Next, by the extent of gastrectomy, the comparison within nontotal gastrectomy (non-TG) was MIN 4.09% [−3.41-12.9] vs VD 1.17% [−8.02-12.0] ($P = .0358$). The comparison within total gastrectomy (TG) was MIN 6.37% [−2.55-18.6] and VD 2.26% [−12.8-11.8] ($P = .0327$), showing a significantly higher rate of increase in MIN for all gastrectomy types. In the comparison within the MIN group, TG showed a significantly higher rate of increase than in non-TG ($P = .0492$), but in the comparison within the VD group, there was no significant difference in the rate of increase between TG and non-TG ($P = .5285$).

3.4 | Factors for L-BMD improvement

The results of univariate and multivariate analyses for factors involved in better L-BMD improvement of +4.2% or more are summarized in Table 2. The administration of MIN was the only independent factor that improved L-BMD by 4.2% or more (odds ratio [(OR] 2.91, 95% confidence interval [CI] 1.33 - 6.35, $P = .0072$).

3.5 | Adverse events

Details of AEs are shown in Table 3. All grades of AE occurred in 19 of 71 cases (26.8%) in the MIN group and in 7 of 75 cases (9.3%) in the VD group. Most of observed events were minor AE of Grade 1–2. Appetite loss was the most common AE observed, with three cases in the MIN group and one case in the VD group. There was no difference in the incidence of Grade 3 or higher AE in the two groups: four in the MIN group (pneumonia, hyponatremia, ileus, peritoneal infection) and three in the VD group (pneumonia,

TABLE 1 Patient characteristics

	MIN group (n = 82)	VD group (n = 82)	*P* value
Sex; male/female	42/40	40/42	.7548
Age (y. o); median (range)	74 (60–92)	74 (62–89)	.6530
The extent of gastrectomy; non-TG/TG	56/26	59/23	.6088
BMI (kg/m^2); median (range)	19.5 (14.9–29.3)	19.5 (14.7–28.5)	.9580
Adjuvant chemotherapy; yes/no	14/68	12/70	.6690
% of postoperative BW; median (range)	91.0 (65.9– 116.2)	87.1 (67.1–113.4)	.1534
Serum albumin level (g/dL); median (range)	4.1 (2.9–4.7)	4.1 (3.0–5.2)	.1857
Lymphocyte count (/m^3); median (range)	1648 (764–3952)	1668 (819–4192)	.6654
Duration after gastrectomy (year); median (range)	3.8 (3.0–11.4)	4.1 (2.6–18.3)	.3039
Lumbar BMD (YAM value, %); median (range)	79 (45–164)	77.5 (47–109)	.9629
Femoral BMD (YAM value, %); median (range)	66 (37–81)	66.5 (31–91)	.5602
NTx (nmolBCE/L); median (range)	17.7 (6.4–430)	18.7 (9.7–57.4)	.9366
BAP (μg/L); median (range)	16.6 (8.0–75.9)	17.0 (6.9–59.3)	.3736

Note: Median values (ranges) are shown for continuous variables.

Abbreviations: BAP, bone-specific alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; non-TG, non-total gastrectomy; NTx, type I collagen N-telopeptide; TG, total gastrectomy; y.o, years old; YAM, young adult mean.

thrombocytopenia, kidney stones). There was no treatment-related death in either group.

3.6 | Fracture rate

The frequency of fracture occurrence during the observation period in the ITT analysis was 2.4% in the MIN group (two cases among a total of 82 cases: humerus fracture one, unknown details one), and 0% (no event was observed) in the VD group. There was no significant difference between the groups ($P = .1548$).

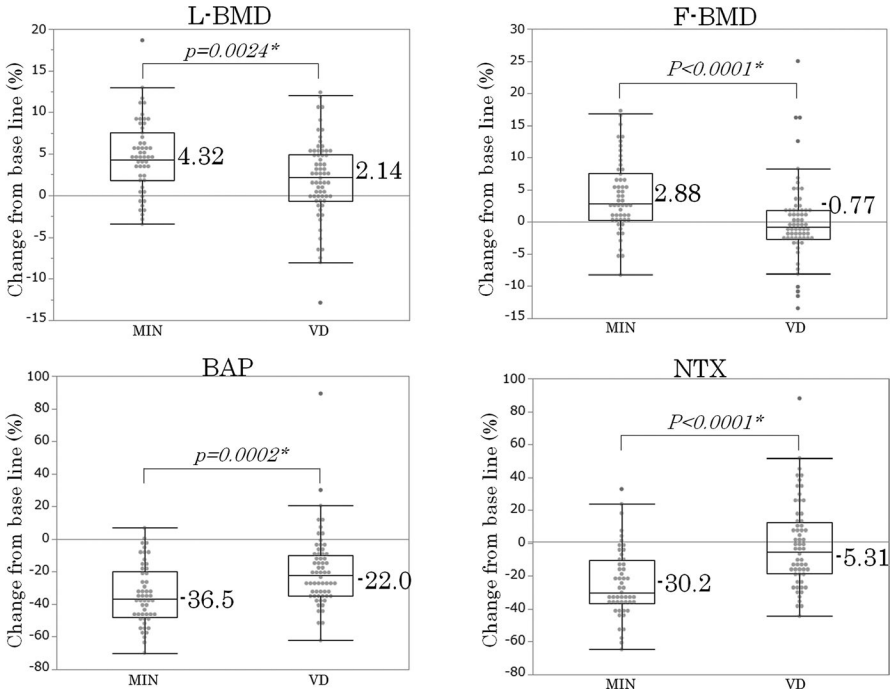
3.7 | Treatment continuity

The change in the number and proportion of patients who continued treatment is shown in Figure 4. The treatment continuation rate 12 mo after the start of treatment was 81.7% in the VD group and 67.0% in the MIN group in the analysis by the ITT population, which was lower in the MIN group than in the VD group ($P = .0318$) (Figure 4A). Analysis by the PP subset also showed that the VD group was 89.3% and the MIN group was 77.5%, which tended to be lower in the MIN group ($P = .0531$) (Figure 4B). The reason for discontinuing treatment was the side effects of 62.5% of the treatments, followed by 16.7% of patients' offers (Figure 4C). The only important risk factor for discontinuation of treatment was Alb ≤4.1 (hazard ratio [HR] 4.97, 95% CI 1.5310–16.172, $P = .0076$). Administration of minodronate was not a statistically significant risk factor, but was more likely to be discontinued than vitamin D (HR 2.57, 95% CI 0.9934–6.6969, $P = .0516$) (Table 4).

4 | DISCUSSION

This study is the first randomized controlled trial to examine the safety and efficacy of interventions with a relatively new bisphosphonate agent, minodronate, for impaired bone metabolism after gastrectomy. We compared and examined a relatively large sample size of patients who completed treatment (55 in the MIN group and 67 in the VD group). It is likely that this study may have the largest sample size compared to previously reported drug intervention studies for impaired bone metabolism after gastrectomy.

The primary endpoint of this study, the median rate of increase in L-BMD values after 1-y medication, was 4.32% in the MIN group and 2.14% in the VD group. The effect was significantly higher in the MIN group than in the VD group, although an



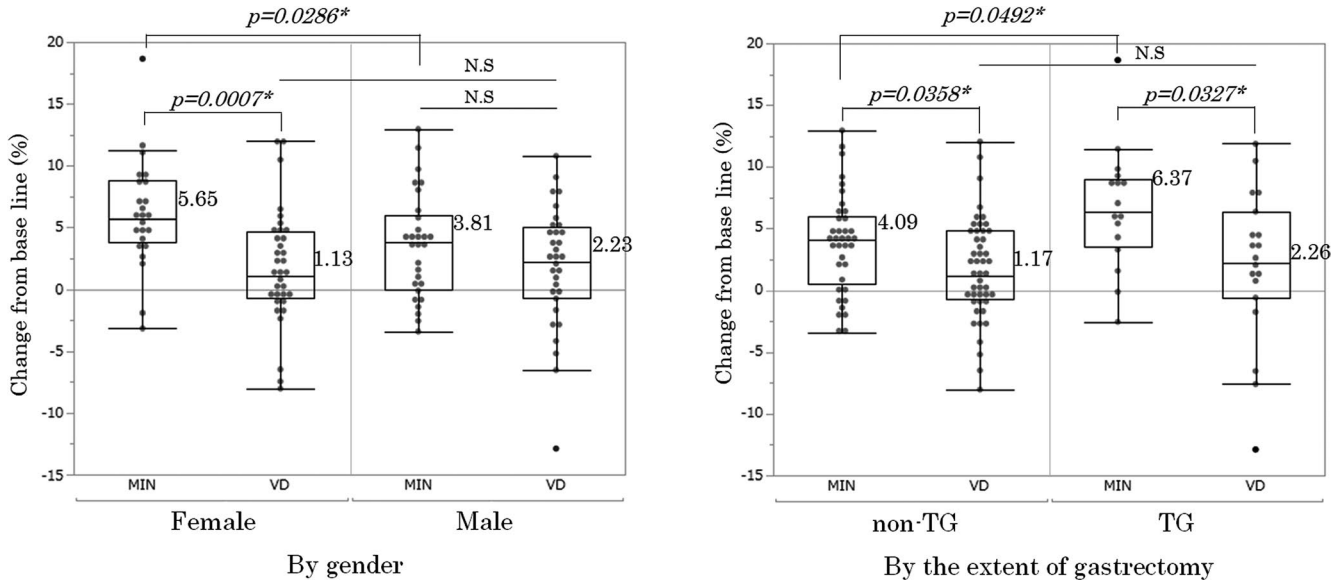


FIGURE 2 Changes in parameters. The figure shows the changes in parameters at 12 mo after administration (% of the measured value before the treatment). Analysis was performed on the per-protocol subset and the Wilcoxon test was used for the significant difference test between the two groups. L-BMD; lumbar bone mineral density, F-BMD; femoral bone mineral density

FIGURE 3 Changes in the primary endpoint; L-BMD, by randomized stratification factor ("gender" and "extent of gastrectomy")

increase was confirmed with both drugs. In the MIN group, both the bone formation marker BAP and the bone resorption marker NTX showed a significant decrease compared to the VD group after 1 y. The decrease observed in the MIN group suggested that minodronate had a medicinal effect and strongly inhibited bone metabolism in patients with bone metabolism disorders after gastrectomy, as in other patients with bone metabolism disorders. The increase in BMD values is reported to be related to the fracture-suppressing effect in the Japanese guidelines of 2015[25] and references cited therein. And we defined +4.2% of BMD as a cutoff, which is reported to be clinically useful in the Japanese guidelines of 2015.[25] Additionally, the L-BMD increase of 4.32% in the MIN group may have the effect of reducing the relative risk of fractures of the body by approximately 30%-40%.

In the analysis of factors related to the L-BMD increase in multivariate analysis, minodronate administration was a significant independent factor for a BMD increase in all cases. According to the results of the stratified analysis of the L-BMD increase rate (Figure 3), minodronate showed a higher BMD increase rate in females than in males, and in patients who had undergone surgical procedures, especially TG; therefore, females and patients who had undergone TG were expected and speculated to be good targets for minodronate.

TABLE 2 Factors for L-BMD increase; ≧4.2%

		Univariate			Multivariate		
	n	OR	95% CI	*P*	OR	95% CI	*P*
Sex							
Male	63	0.7447	0.3595–1.5424	.4276			
Female	59						
Age							
≦74	65	1.0821	0.5221–2.2425	.8319			
>74	57						
BMI							
>19.3	61	1.8095	0.8677–3.7773	.1137	1.8087	0.8275–3.9532	.1374
≦19.3	61						
Extent of gastrectomy							
TG	38	1.9296	0.8691–4.2843	.1062	1.8431	0.7833–4.3370	.1613
non–TG	84						
Serum albumin level							
>4.1	56	0.8712	0.4205–1.8047	.7106			
≦4.1	66						
Lymphocyte count							
>1667	61	1.2656	0.6115–2.6194	.5256			
≦1667	61						
History of bone fracture							
Yes	40	0.6508	0.2959–1.4313	.2855			
No	82						
Familial history of bone fracture							
Yes	15	0.7125	0.2235–2.2711	.5666			
No	107						
Smoking							
Yes	12	0.7416	0.2049–2.6835	.6487			
No	110						
History of steroid administration							
Yes	7	0.6530	0.1148–3.7120	.6308			
No	115						

(Continues)

TABLE 2 (Continued)

		Univariate			Multivariate		
	n	OR	95% CI	*P*	OR	95% CI	*P*
Drinking habits							
Yes	13	1.6439	0.5169–5.2275	.3997			
No	109						
Creatinine							
≦0.73	62	1.0400	0.5030–2.1499	.9157			
>0.73	60						
Calcium							
>9.1	50	1.3269	0.6348–2.7732	.4520			
≦9.1	72						
Phosphate ion							
>3.4	54	1.1566	0.5438–2.4596	.7055			
≦3.4	60						
Post-op chemotherapy							
Yes	20	2.6813	0.9716–7.3992	.0569	2.2816	0.7741–6.7244	.1347
No	102						
Duration after surgery (year)							
≦4.1	64	0.9805	0.4742–2.0273	.9578			
>4.1	58						
Treatment							
MIN	55	2.7950	1.3195–5.9204	.0073*	2.9138	1.3356–6.3569	.0072*
VD	67						

Note: Factors with a *P*-value of < .2 in univariate analysis were examined in multivariate analysis.

Abbreviations: CI, confidence interval; OR, odds ratio.

*Statistically significant $P < .05$.

TABLE 3 Summary of adverse events

	MIN group (N = 71)	VD group (N = 75)
Grade ≤2		
Anorexia	3	1
Joint pain	2	
Abdominal pain	2	
Fever	2	
Rash	2	
Tooth decay	2	
Sweet itch	1	
Hypocalcemia	1	
Hypoalbuminemia	1	
AST elevation	1	
Muscle pain	1	
Periodontal disease	1	1
Fracture	1	
Diarrhea	1	
Fatigue	1	
Anemia		1
Leukocytopenia		1
Creatinine elevation		1
Hives		1
Blurring of eyes		1
Total	22	7
Grade ≥3		
Pneumonia	1	1
Hyponatremia	1	
Ileus	1	
Peritoneal infection	1	
Thrombocytopenia		1
Nephrolith		1
Total	4	3

Note: All grades of adverse events occurred in 19 of 71 cases (26.8%) in the MIN group and in 7 of 75 cases (9.3%) in the VD group. Most of them were minor adverse events of Grade 1–2, and appetite loss was the most common adverse event observed three in the MIN group and one in the VD group.

The patients who had undergone TG could have stronger nutritional disorders/sarcopenic changes than those who had undergone distal or proximal gastrectomy, and the patients who had undergone chemotherapy might have a tendency to suffer from malnutrition/sarcopenic changes/frailty, owing to a high degree of cancer progression or as side effects of chemotherapy.[26–29] These conditions are indicative of nutritional disorders and are likely to cause abnormal bone metabolism. If the improvement effect is high in patients with such backgrounds, they may be appropriate candidates for intervention and should be actively treated with drugs that improve bone metabolism.

Sugiyama et al[21] used a second-generation bisphosphonate preparation, andronate (a weekly medication), to study the time course of changes in bone density in patients after gastrectomy. The rate of increase in BMD was higher than that of the formulation group from the early stage of administration (9.3% vs 3.5% at 2 y after the initiation of administration). Although the study had a small sample size, with 20 people in each group, this report shows an increase in the rate of bone density over 2 y after the start of administration, whereas the andronate group showed an increase over time. In the vitamin D group, the rate of increase almost reached a plateau 1 y after the start of administration. Based on this report, in this study the effects of the agents were evaluated according to the increase in the rate of BMD 1 y after the start of administration.

Administration of bisphosphonates requires attention to AEs, such as gastrointestinal disorders, osteonecrosis of the jaw/bone marrow inflammation, bone pain, arthritis, renal dysfunction, and liver dysfunction. Particularly, gastrointestinal disorders are the most common complications associated with bisphosphonate use.[30] In a phase III study of Japanese patients with primary osteoporosis, the incidence of gastrointestinal disorders was 7.4% for monthly minodronate,[23] 10.7% for weekly alendronate,[14] and 12.0% for weekly risedronate regimens.[31] The incidence of gastrointestinal disorders in the MIN group observed in this study was 9.9% (anorexia in three patients, abdominal pain in two, diarrhea in one, and ileus in one) and the result was comparable to the incidence previously reported for bisphosphonate agents. When compared with vitamin D preparations, the incidence of grade 2 or lower AEs was certainly higher in the MIN group (19 of 71 cases, 26.8%); however, grade 3 or higher AE were infrequent in both groups, and the causal relationship with the drug was presumed to be low. The results of multivariate analysis of risk factors for treatment discontinuation also showed that administration of minodronate was not a significant risk factor and the administration of minodronate for bone metabolism disorders after gastrectomy did not pose a major safety problem. The risk factor for discontinuing treatment was the serum albumin level. It is easy to speculate that cases with low serum albumin levels may be poorly tolerated for side effects, such as digestive disorders, of medication owing to malnutrition. Regardless of the drug used, careful attention to side effects is important to ensure treatment continuation.

In this study, 11 patients (13.4%) in the MIN group and 7 (8.5%) in the VD group were unable to begin drug administration mainly due to the postassignment patient preference, resulting in the 1-y completion rate of treatment in the ITT analysis was lower in the MIN group than VD group (67% vs 81.7%, $P = .0318$). It was suggested that the general public's interest and awareness of the importance of therapeutic intervention for an osteoporotic disorder may still be low and it will be necessary for those of us who treat gastric cancer to proactively provide information and encourage activities regarding bone metabolism disorders after gastrectomy. The convenience of the drug may also be important for the acceptance of treatment, and minodronate, a third-generation bisphosphonate formulation selected in this study, can be taken once a month and is more patient-acceptable than other conventional daily or weekly

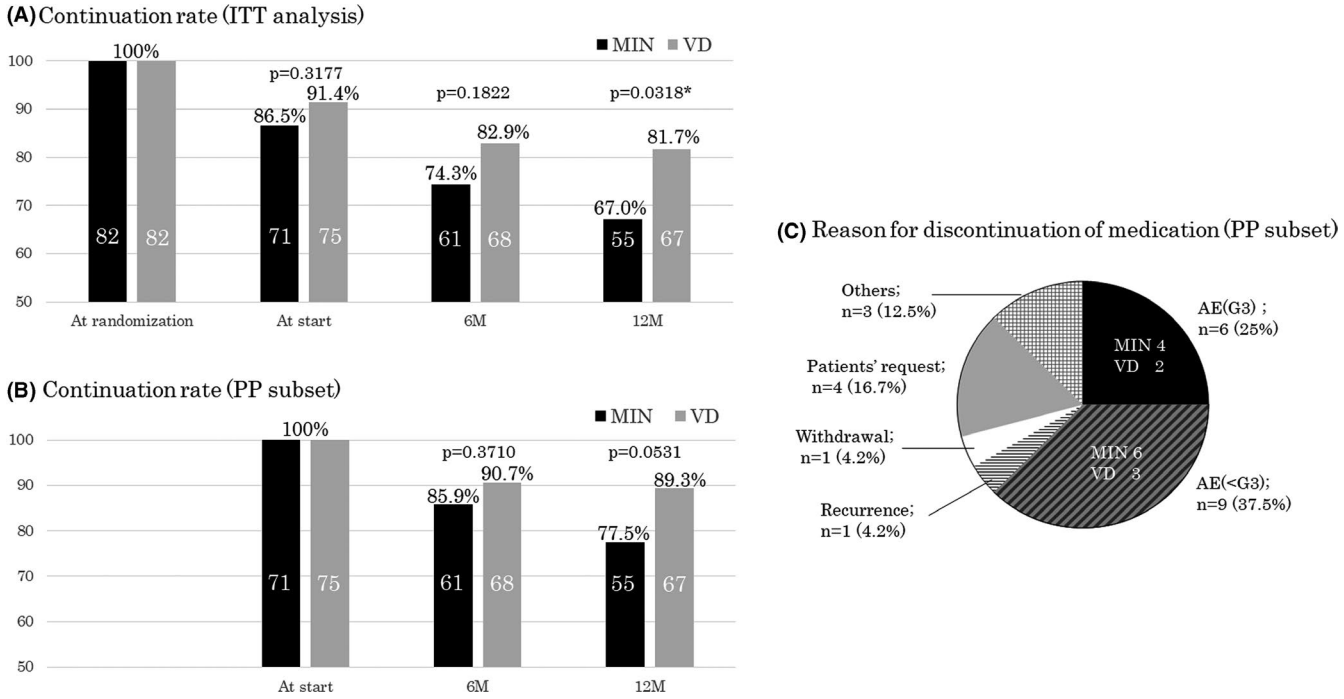


FIGURE 4 Continuation summary. The changes of continuation rate are shown; analysis by ITT population (A), and by PP subset (B). The numbers on the bar chart show the number of people who continued treatment, and the continuation rate (%) is shown at the top. The *P*-value presented is the result of a comparison between the two groups of continuation rates (Pearson test)

TABLE 4 Risk factors for discontinuation of treatment

		Univariate			Multivariate		
	n	HR	95% CI	*P*	HR	95% CI	*P*
Sex							
Male	76	1.1067	0.4600–2.6628	.8208	1.0946	0.4150–2.8870	.8551
Female	70						
Age							
≦74	78	1.0363	0.4306–2.4940	.9365	1.5994	0.5968–4.2862	.3504
>74	68						
Extent of gastrectomy							
TG	45	0.9102	0.3485–2.3771	.8477	0.6740	0.2433–1.8667	.4479
non-TG	101						
Serum albumin level							
>4.1	60	0.2357	0.0760–0.7304	.0123*	0.2009	0.0618–0.6531	.0076*
≦4.1	86				(4.9760)	(1.5310–16.172)	
Treatment							
MIN	71	2.4363	0.9703–6.1170	.0580	2.5793	0.9934–6.6969	.0516
VD	75						

*Statistically significant $P < .05$.

bisphosphonates.[24] Poor compliance and continuity of oral bisphosphonates in osteoporosis treatment, not only after gastrectomy, has long been a problem. According to Silverman et al,[32] the reasons for patients' poor compliance and discontinuity were due to forgetting to refill a prescription (24%), concern about side effects (20%), cost issues (17%), and lack of understanding of treatment necessity (14%). In osteoporosis, the fractures prevention effect increases as the oral compliance increases,[33] and these facts should be carefully

introduced to patients to educate them on the importance of treatment compliance. In contrast, recently an anti-RANKL antibody preparation, which has a strong inhibitory effect on bone resorption and a strong preventive effect on both lumbar fractures and fractures, has been developed. Among them is denosumab, which has a once-every 6-mo administration cycle,[34–36] and may be more effective in improving patient acceptance and medication compliance in bone metabolism disorders after gastrectomy. In general, osteoporosis management, active vitamin D3 preparations, and a selective estrogen receptor modulator are used for patients in their 50s and 60s, who have many vertebral body fractures. Bisphosphonates or anti-RANKL antibody drugs will often be selected for patients aged 70 y and older, who have many femur fractures. However, in patients after gastrectomy, who are often elderly and tend to have poor nutritional status, bisphosphonate preparations and anti-RANKL antibody drugs, which are administered infrequently, are preferable in terms of therapeutic compliance and therapeutic effects. Additionally, it is stated that the "patient's own management style" is important, and that patients who have a "sense of control" may have good medication compliance and continuity.[32] This is not a problem that can be solved only by increasing the oral intake interval, but a problem, like in other chronic diseases such as hypertension and hyperlipidemia, that requires a strengthening of the interaction between the healthcare provider and the patients, to emphasize the need for treatment and improve the motivation and encouragement for treatment. If there is a relationship of trust between the patient and the medical staff that has been built up through the treatment of the serious illness that is gastric cancer, this point may be improved by devising a better way to interact with the patients.

The present study had several limitations. First, the sample size and observation period of this study might not have been sufficient to draw accurate conclusions, especially to judge whether minodronate is effective in suppressing fractures, which is the most important clinical outcome. Additionally, there were cases in which BMD measurement data 1 y later could not be obtained because the administration was not started or the administration was interrupted in the middle. The per-protocol analysis was another limitation. To clarify this issue, another study with a larger sample size and longer observation period is required. Second, the progress of bisphosphonate preparations is remarkable, administration intervals and administration routes are simplified, and drugs that can be expected to improve compliance are emerging. These new drugs may be more appropriate and effective bisphosphonate preparations to be used in patients with impaired bone metabolism who have unstable ingestion and intestinal absorption after gastrectomy. Finally, this study included gastric cancer patients who had undergone surgical treatment and had been oncologically stable, cancer-free for at least 3 y, to prevent the effects of gastric cancer itself or interventions, such as chemotherapy. However, especially in patients with advanced gastric cancer, it is considered that there is a high risk of developing bone metabolic disorders in the oncologically unstable period, that is, in the early postoperative period or in a situation wherein the patient would not be undergoing surgery. This is because chemotherapy for gastric cancer in perioperative adjuvants therapy and advanced/recurrence treatment often uses cytotoxic drugs with a high risk of vomiting, and supportive care, such as steroids, are often used to reduce the side effects of chemotherapy. Especially in the treatment of advanced/recurrent gastric cancer, the administration period of anticancer drugs tends to be longer as the chemotherapy regimen progresses and the overall survival period is extended. Considering the long-term effects of steroids, the nutritional disorders caused by cancer and gastrectomy, and the catabolic effects of anticancer drugs, more attention should be paid to the occurrence of bone metabolism disorders in patients with oncologically unstable gastric cancer, that is, patients who require chemotherapy. This would be an important target in future research.

In conclusion, monthly minodronate treatment was feasible in patients with bone metabolism disorders who had a history of gastrectomy and was effective in improving BMD in the lumbar spine and thigh. This convenient therapy showed an improvement effect of +4.32% in lumbar spine BMD 1 y later, which was a clinically significant result with respect to prevention of fractures. Healthcare professionals should be aware that there are a significant number of osteoporotic patients after gastrectomy and should consider interventions for those who do have osteoporosis, and monthly minodronate treatment may be a promising option.

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