

Effect of pamidronate administration on bone in patients with acute spinal cord injury

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Abstract—Eleven subjects participated in a prospective placebo-controlled trial to address the efficacy of pamidronate in reducing bone loss in persons with acute spinal cord injury (SCI). We administered pamidronate (treatment) or normal saline (placebo) intravenously at baseline (22 to 65 days after injury) and sequentially over 12 months, with follow-up at 18 and 24 months. Regional bone mineral density (BMD) was lost over time, regardless of group. In the treatment group compared with the placebo group, we noted a mild early reduction in loss of total leg BMD. Significant bone loss from baseline occurred earlier in the placebo group at the regional sites than in the treatment group. However, by the end of the treatment and follow-up phases, both groups demonstrated a similar percent bone loss from baseline. Despite an early reduction in bone loss, pamidronate failed to prevent major, long-term bone loss in persons with acute neurologically complete SCI.

Key words: acute spinal cord injury, bisphosphonates, bone mineral content, bone mineral density, immobilization, N-telopeptide, osteocalcin, osteoporosis, pamidronate, paraplegia.

INTRODUCTION

Osteoporosis due to immobilization is an important and increasingly prevalent clinical condition in the aged and disabled populations. Persons with acute paralysis due to spinal cord injury (SCI) transition immediately

from a normal ambulatory lifestyle to markedly impaired mobility. Dramatic changes in bone and calcium metabolism are anticipated during the acute phase of SCI. Hypercalciuria occurs within days to weeks and persists for several months [1–2]. Stewart et al. demonstrated that the hypercalciuria is a manifestation of increased bone resorption, with suppression of the parathyroid hormone (PTH)-vitamin D axis [3].

Abbreviations: ASIA = American Spinal Injury Association, BMC = bone mineral content, BMD = bone mineral density, CV = coefficient of variation, mRNA = messenger ribonucleic acid, NS = not significant, NTx = N-telopeptide of type I collagen, PINP = N-terminal propeptide of type 1 procollagen, PTH = parathyroid hormone, SCI = spinal cord injury, VA = Department of Veterans Affairs.

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Intravenous bisphosphonates have been shown to be potent inhibitors of bone resorption in a wide variety of conditions associated with increased osteoclastic function. Intermittent intravenous pamidronate has been clinically used to treat hypercalcemia of malignancy, Paget's disease of bone, vitamin D intoxication, milk-alkali syndrome, hyperparathyroidism, and growth hormone-induced hypercalcemia in Acquired Immune Deficiency Syndrome (AIDS) [4–11]. Intravenous pamidronate has been reported to reduce the hypercalcemia of an immobilized child [12]. Thus, an intravenously administered bisphosphonate is potent in inhibiting bone resorption in a wide variety of conditions that are associated with increased osteoclastic function. Because of their multifactorial pharmacological effects on inhibition of the osteoclast, bisphosphonates may be hypothesized to be efficacious in reducing or preventing the osteoporosis associated with immobilization [13]. Bi-sphosphonate therapy has also reduced the increased urinary calcium excretion in able-bodied individuals restricted to bed rest [14]. A few investigators have addressed the role of bisphosphonates in preventing bone loss in persons with acute SCI, but these studies have not been double-blind, placebo-controlled prospective randomized trials [15–18]. In the acute period after SCI, an intravenously administered bisphosphonate may have potential advantage because it may be given soon after immobilization, whereas oral preparations require that the patient maintain upright posture, which may not be possible for weeks after sustaining an acute SCI. In this current study, we report the effect on bone mineral content (BMC) and density (BMD) and the metabolic markers of bone resorption and formation, following administration of a potent intravenous bisphosphonate (pamidronate, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey) that was administered within about 2 months of acute complete motor SCI and then administered sequentially over 12 months.

METHODS

Fourteen subjects with acute SCI (less than 2.5 months) were enrolled and randomized into a double-blind, placebo-controlled study for determining the effect of bisphosphonate administration on loss of bone following acute injury. Subjects were recruited from the Kessler Institute of Rehabilitation, West Orange, New Jersey, and the SCI Service Department of Veterans Affairs (VA) Medical Center, Bronx, New York. Three subjects voluntarily withdrew

before the first time-point (month 3) measurements were performed. Eleven subjects completed the study: five had tetraplegia and six, paraplegia; mean age was 35 ± 12 years (range: 21–61 years); and 8 were Caucasian, 2 were African American, and 1 was Hispanic. The average duration of injury for the study group ($N = 11$) at the time of entry was 44 ± 18 days (range: 22–65 days). All subjects were classified as American Spinal Injury Association (ASIA) Impairment Scale A classification (motor complete injury) and were mobilized according to their own rehabilitation regimen and ability, which was not documented by the study investigators. The three females who completed the study were premenopausal. Institutional Review Board approval and informed consent was obtained at Kessler Institute of Rehabilitation (West Orange, New Jersey) and the VA Medical Center (Bronx, New York).

At baseline and subsequently at 1, 2, 3, 6, 9, and 12 months, either pamidronate (60 mg) (treatment group: $n = 6$) or normal saline (placebo group: $n = 5$) was administered intravenously. None of the patients or investigators had knowledge of whether drug or placebo was administered. Subjects received a “normal” calcium diet (at least 700 mg calcium/d) during their inpatient rehabilitation, but intake was not monitored; patients received a multivitamin with the recommended daily allowance of vitamin D. After discharge, patients were on an ad lib calcium intake without administration of a calcium supplement.

Dual X-ray absorptiometry (DPX) was performed by investigators to determine total (minus the skull) and regional BMC and BMD (Lunar Model DPX, version 3.6, Madison, Wisconsin) [19]. Day-to-day DPX variation determined over a 12-month period with a phantom scanned 38 consecutive times was less than 1 percent (coefficient of variation [CV] = 0.06). In our unit, 15 subjects were studied four times during a 2-week period. The day-to-day variability was found to be less than 1.5 percent (CV = 1.493 ± 0.014 ; 95% confidence interval [CI]: lower = 1.11%, upper = 1.9%). Measurements were performed at baseline, during the treatment phase (1, 3, 6, and 12 months), and during the follow-up phase (18 and 24 months). The body was divided into the lower limbs and pelvis with the application of software algorithms as reported (Lunar instrumentation manual) [19]. These regions were graphically displayed, and the operator adjusted the final cut lines for each division. To prevent variation from individual to individual, a single-blinded investigator performed all cuts to avoid interrater variability.

To measure densitometry of the knee, an anterior-posterior software program was used by investigators to obtain the image of the left knee. For the femur, regional cuts were made proximal to the patella and continued for 20 lines (distal femur); for the tibia, regional cuts were made distal to the growth plate and continued for 15 lines (proximal tibia).

Markers for bone metabolism were obtained prior to pamidronate administration at baseline and at 1, 3, 6, 12, 18, and 24 months. Twenty-four-hour urine calcium with powdered boric acid in a sample container was collected by investigators to acidify the specimen to prevent precipitation. To evaluate resorption, before administering the drug, aliquots for the 24 h urine samples were assayed by investigators for N-telopeptide of type I collagen (NTx) with a kit by Osteomark™ (Ostex International, Inc., Seattle, Washington) that has about a 6 percent intra-assay variability and a 4 percent interassay variability. To evaluate formation, serum osteocalcin (Diagnostic Systems Laboratories, Inc., Webster, Texas) and intact N-terminal propeptide of type 1 procollagen (PINP) (Orion Diagnostica, Espoo, Finland) were performed by a technician. Metabolic markers of bone were performed in a subset of 10 individuals with acute SCI (43 ± 17 , range of 22–65 days): 5 had paraplegia and 5 had tetraplegia.

An unpaired *t*-test was used by investigators to test for significant differences between the groups for the continuous demographic variables. Chi-squared analysis was used by investigators to test for distribution differences in the categorical variables between the groups. Difference and percent change from baseline were calculated for each time point for each of the bone variables. An analysis of variance for the factors was performed by investigators (group and time) to test for main effects on difference or percent change from baseline for the BMD, BMC, bone markers, and calcium variables. Within-group analyses were performed for the determination of significant change from baseline with each time point by a paired *t*-analysis for the BMD and NTx variables. Results are expressed as mean \pm standard deviation (SD) in the text and tables.

RESULTS

The treatment and placebo groups were not significantly different for age, height, weight, and days since injury, or distributions of gender or level of lesion (**Table 1**). At baseline, no significant differences were found between

Table 1.

Characteristics of subjects.

Characteristic	Treatment (Mean \pm SD)	Placebo (Mean \pm SD)
Count (<i>n</i>)	6	5
Age (yr)	39 \pm 15	30 \pm 8
Height (cm)	176 \pm 9	175 \pm 8
Weight (kg)	81.9 \pm 18.4	71.2 \pm 11.3
Days Injured	41 \pm 17	45 \pm 16
Males/Females (<i>n</i>)	4/2	4/1
Tetraplegia/Paraplegia (<i>n</i>)	3/3	2/3

SD = standard deviation

the treatment and placebo groups for total leg BMD (1.466 ± 0.139 vs. 1.514 ± 0.171 g/cm²), pelvis BMD (1.237 ± 0.140 vs. 1.265 ± 0.107 g/cm²), or leg BMC ($1,408 \pm 317$ vs. $1,275 \pm 148$ g/cm²) (**Table 2**). A significant main effect for time was noted for BMD of the total leg, pelvis, distal femur, proximal tibia, and leg BMC (**Table 2**). No significant main effect was found for group in any of the variables, suggesting that the groups were not different overall. A mild treatment effect was noted for total leg at months 1 ($F = 5.9$, $p < 0.05$), 3 ($F = 4.6$, $p < 0.07$), and 6 ($F = 5.7$, $p < 0.05$), indicating a slight sparing of total leg BMD in the treatment group compared with the control group. Additionally, significant bone loss from baseline occurred earlier in the placebo group in the pelvis (months 3, 6, and 12: $p < 0.05$), distal femur (months 3, 6, and 12: $p < 0.05$), and proximal tibia (month 3: $p < 0.05$) than in the treatment group for these same time points (**Figure 1(a) and 1(b)** and **Figure 2 (a)**). By the end of the treatment phase (month 12), both the treatment and placebo groups demonstrated a similar percentage of bone loss from baseline in total leg BMD ($-9\% \pm 7\%$ and $-12\% \pm 7\%$), total leg BMC ($-16\% \pm 9\%$ and $-16\% \pm 9\%$), pelvis BMD ($-8\% \pm 9\%$ and $-13\% \pm 4\%$), distal femur BMD ($-9\% \pm 11\%$ and $-14\% \pm 11\%$), and proximal tibia BMD ($-24\% \pm 19\%$ and $-29\% \pm 13\%$) (**Table 2**). This loss persisted through the end of the follow-up phase (**Table 2**). Arm BMD (not shown), for the total group, remained unchanged at 24 months (difference from baseline = 0.280 ± 0.720 g/cm², not significant [NS]).

No significant differences were found for serum total or ionized calcium over the course of the study (**Table 3**). The treatment group had significantly lower NTx values at month 1 compared with the placebo group (113 ± 77 vs. 273 ± 123 nM BCE/mM creatinine, $p < 0.05$) and lower 24 h urinary calcium excretion (141 ± 87 vs. 337 ± 143 mg/d, $p < 0.05$). The treatment group demonstrated a reduction in

Table 2.Results of bone mineral density (BMD) and bone mineral content (BMC) (mean \pm standard deviation).

Bone Region		Baseline	Treatment Phase				Follow-Up Phase	
		Month 0	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
BMD (g/cm²)								
Total Leg*	Treatment	1.466 \pm 0.139	1.481 \pm 0.147 [†]	1.448 \pm 0.168 [‡]	1.403 \pm 0.176 [†]	1.339 \pm 0.172	1.245 \pm 0.166	1.208 \pm 0.180
	%Ch	—	1 \pm 1	-1 \pm 3	-5 \pm 4	-9 \pm 7	-15 \pm 8	-18 \pm 9
	Placebo	1.514 \pm 0.171	1.494 \pm 0.116	1.423 \pm 0.126	1.374 \pm 0.111	1.328 \pm 0.078	1.240 \pm 0.085	1.223 \pm 0.062
	%Ch	—	-1 \pm 5	-6 \pm 7	-9 \pm 8	-12 \pm 7	-17 \pm 9	-19 \pm 9
Pelvis*	Treatment	1.237 \pm 0.140	1.231 \pm 0.127	1.191 \pm 0.110	1.190 \pm 0.151	1.135 \pm 0.167	1.073 \pm 0.134	1.043 \pm 0.126
	%Ch	—	0 \pm 2	-4 \pm 3	-4 \pm 4	-8 \pm 9	-13 \pm 6	-15 \pm 8
	Placebo	1.265 \pm 0.107	1.215 \pm 0.123	1.204 \pm 0.091	1.171 \pm 0.95	1.102 \pm 0.061	1.075 \pm 0.063	1.029 \pm 0.058
	%Ch	—	-4 \pm 3	-5 \pm 3	-7 \pm 1	-13 \pm 4	-17 \pm 5	-18 \pm 5
Distal Femur*	Treatment	0.957 \pm 0.167	0.988 \pm 0.129	0.920 \pm 0.132	0.889 \pm 0.128	0.853 \pm 0.068	0.772 \pm 0.107	0.756 \pm 0.060
	%Ch	—	4 \pm 5	-3 \pm 4	-7 \pm 7	-9 \pm 11	-18 \pm 12	-19 \pm 17
	Placebo	1.071 \pm 0.266	1.046 \pm 0.235	0.988 \pm 0.264	0.983 \pm 0.263	0.915 \pm 0.203	0.806 \pm 0.073	0.754 \pm 0.098
	%Ch	—	-2 \pm 5	-8 \pm 4	-8 \pm 5	-14 \pm 11	-22 \pm 14	-28 \pm 10
Proximal Tibia*	Treatment	1.107 \pm 0.253	1.073 \pm 0.219	1.015 \pm 0.166	0.924 \pm 0.180	0.821 \pm 0.203	0.665 \pm 0.196	0.654 \pm 0.217
	%Ch	—	-2 \pm 6	-7 \pm 8	-16 \pm 7	-24 \pm 19	-36 \pm 26	-36 \pm 29
	Placebo	1.089 \pm 0.205	1.060 \pm 0.196	0.995 \pm 0.203	0.892 \pm 0.178	0.771 \pm 0.162	0.651 \pm 0.102	0.619 \pm 0.111
	%Ch	—	-2 \pm 5	-8 \pm 3	-18 \pm 9	-29 \pm 13	-38 \pm 14	-42 \pm 14
BMC (g)								
Total Leg*	Treatment	1,408 \pm 317	1,351 \pm 271	1,300 \pm 261	1,259 \pm 281	1,179 \pm 272	1,105 \pm 249	1,067 \pm 251
	%Ch	—	-3 \pm 11	-7 \pm 9	-10 \pm 9	-16 \pm 9	-21 \pm 9	-24 \pm 9
	Placebo	1,275 \pm 148	1,267 \pm 152	1,191 \pm 217	1,161 \pm 190	1,114 \pm 175	1,001 \pm 127	980 \pm 110
	%Ch	—	-1 \pm 2	-7 \pm 8	-9 \pm 6	-16 \pm 9	-21 \pm 6	-23 \pm 6

* $p < 0.0001$ significant main effect for time for total leg, pelvis, distal femur, and proximal tibia† $p < 0.05$ for treatment vs. placebo‡ $p < 0.07$ for treatment vs. placebo

%Ch = percent change from baseline

NTx excretion from baseline to month 1 (217 ± 268 vs. 113 ± 77 nM BCE/mM creatinine, NS) The placebo group had a similar fall in NTx excretion from baseline to month 6 (289 ± 190 vs. 114 ± 30 nM BCE/mM creatinine, NS) (**Figure 3** and **Table 3**). At 6 months, average urinary NTx values fell and thereafter were fairly constant until month 24, but persisted just above the normal range (68 ± 39 nM BCE/mM creatinine, normal range from 3 to 65 nM BCE/mM creatinine). No significant changes were demonstrated for markers of bone formation, osteocalcin, or propeptide of type I pro-collagen (PINP) over the length of the study (**Table 3**).

DISCUSSION

In any condition that causes immobilization, loss of bone occurs and is correlated to the severity of unweight-

ing. In patients with acute SCI, skeletal resorption causes an elevation of serum calcium and suppression of both PTH release and associated 1,25-dihydroxyvitamin D ($1,25[\text{OH}]_2\text{D}$) production [3]. Because of suppression of the PTH-vitamin D axis, urinary excretion of calcium and the serum calcium levels are unaffected by wide fluctuations in the dietary calcium [3]. Urinary calcium excretion has been demonstrated to rise over the first several days, to be elevated for 3 to 6 months after acute injury, and then to return to or below baseline values by 12 months [1–2]. In our study, urine calcium values were elevated in both groups at baseline and fell in the treatment group at 1 month, with a trend for lower values at 3 months compared to the control group.

A dramatic loss of BMD and BMC occurs within the initial months following acute SCI. Histomorphometry of bone in patients with acute SCI has demonstrated an

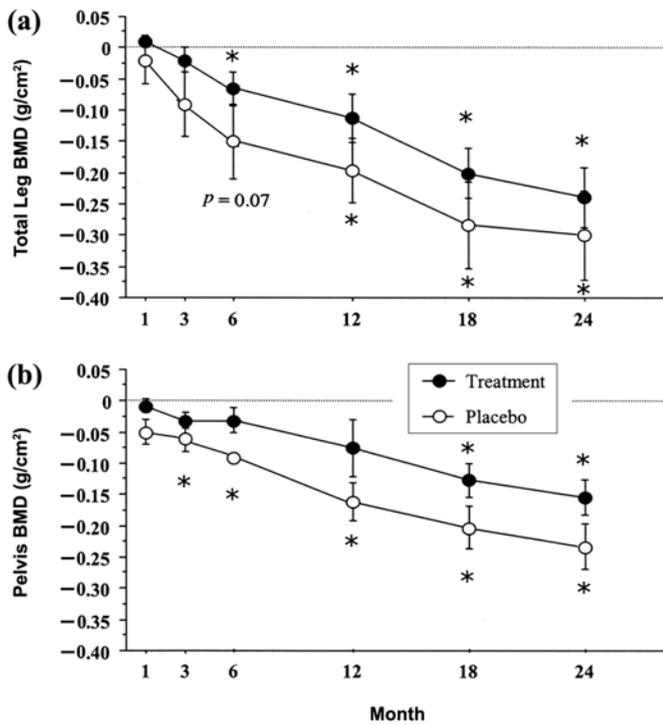


Figure 1. Difference (g/cm^2) from baseline for bone mineral density (BMD) for each time point: (a) total leg and (b) pelvis in treatment and placebo groups. * $p < 0.05$ for bone loss from baseline within each group.

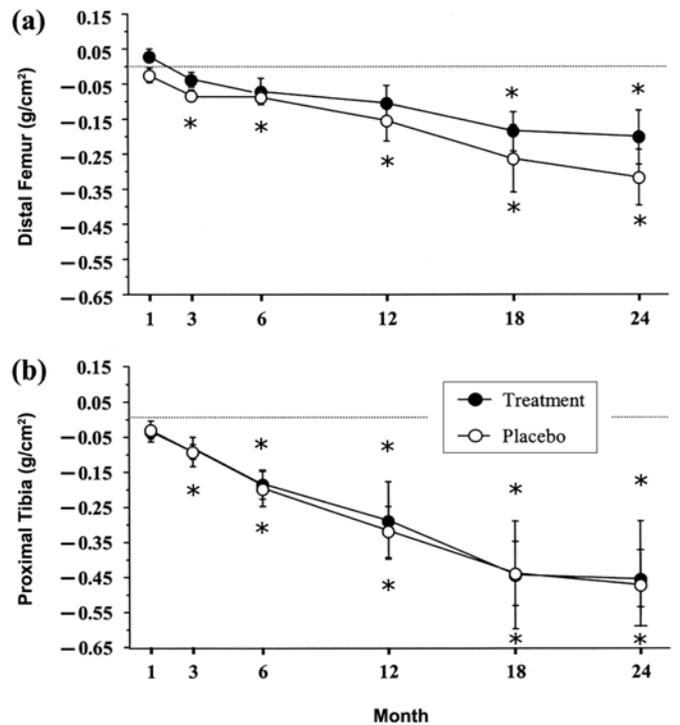


Figure 2. Difference (g/cm^2) from baseline for bone mineral density for each time point: (a) distal femur and (b) proximal tibia in treatment and placebo groups. * $p < 0.05$ for bone loss from baseline within each group.

Table 3. Results (mean \pm standard deviation) of bone markers and calcium values.

Bone and Calcium Values	Normal Range	Group	Month 0	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
NTx (nM BCE/ mM creatinine)	3–65	Treatment	217 \pm 268	113 \pm 77*	116 \pm 82	129 \pm 55	108 \pm 60	85 \pm 21	56 \pm 36
		Placebo	289 \pm 190	273 \pm 123	213 \pm 126	114 \pm 30	96 \pm 44	86 \pm 41	80 \pm 42
Osteocalcin (ng/mL)	1.7–25.0	Treatment	3.4 \pm 3.5	4.8 \pm 5.5	3.3 \pm 2.1	4.4 \pm 4.1	4.0 \pm 3.0	2.9 \pm 2.5	3.1 \pm 2.9
		Placebo	3.5 \pm 1.5	4.4 \pm 1.4	6.2 \pm 2.8	4.9 \pm 3.3	4.1 \pm 2.5	2.8 \pm 1.6	3.3 \pm 2.1
PINP (Intact) (ng/mL)	21–78	Treatment	35 \pm 26	53 \pm 75	25 \pm 23	52 \pm 94	65 \pm 80	58 \pm 77	57 \pm 73
		Placebo	13 \pm 3	20 \pm 15	36 \pm 42	16 \pm 14	42 \pm 49	41 \pm 46	21 \pm 24
Urine Calcium (mg/dL)	100–300	Treatment	285 \pm 166	141 \pm 87*	203 \pm 42	189 \pm 94	205 \pm 82	202 \pm 9	172 \pm 46
		Placebo	337 \pm 93	337 \pm 143	268 \pm 120	249 \pm 68	157 \pm 44	167 \pm 51	144 \pm 15
Serum Calcium (mg/d)	8.5–10.5	Treatment	9.2 \pm 0.4	9.3 \pm 0.8	9.3 \pm 0.4	9.4 \pm 0.6	9.4 \pm 0.3	9.2 \pm 0.3	9.4 \pm 0.3
		Placebo	9.1 \pm 0.6	9.2 \pm 0.1	9.3 \pm 0.5	9.3 \pm 0.5	9.1 \pm 0.9	9.2 \pm 0.2	9.7 \pm 0.5
Ionized Calcium (mg/dL)	4.5–5.4	Treatment	5.1 \pm 0.8	5.3 \pm 0.2	4.4 \pm 1.6	4.9 \pm 0.8	4.6 \pm 1.7	5.2 \pm 0.2	4.4 \pm 1.9
		Placebo	5.5 \pm 0.2	5.4 \pm 0.1	5.5 \pm 0.1	4.6 \pm 1.9	4.5 \pm 1.8	5.1 \pm 0.4	5.5 \pm 0.0

* $p < 0.05$ for treatment vs. placebo
NTx = N-telopeptide of type I collagen

BCE = bone collagen equivalent
PINP = N-terminal propeptide of type I procollagen

increase in trabecular osteoclastic resorptive surfaces and an early depression of osteoblastic bone formation [15]. The change in total bone mass was reported in 25 acutely injured individuals at a mean of 114 days after injury compared with 10 healthy, able-bodied, age-matched controls [20], and 12 of the acutely injured subjects were reexamined 16 months after injury. By about 4 months after acute injury, BMD of the legs had declined by an average of 35 percent compared with that of age-matched controls, and particularly at the knee (distal femur and proximal tibia), BMD reached the fracture threshold [20]. In a longitudinal study, Biering-Sorensen et al. made several measurements of BMC in eight subjects with acute SCI over a period of 31 to 53 months (median of 41 months) [21]. After approximately 2 years, the BMD of the proximal tibia lost 50 to 60 percent and of the femoral neck lost 30 to 40 percent [21]. Within the period of observation, the femoral shaft appeared to have a slower loss of BMD and had not reached steady state [21].

Numerous studies have described the effect of bisphosphonates on bone loss in animal and human models of immobilization. Bisphosphonates inhibit osteoclast recruitment, adhesion, and activity and reduce the life span of the osteoclast. Animal models of immobilization have shown that paralysis, casting of limbs, prolonged bed rest, or weightlessness causes substantial bone loss due to an initial phase of accelerated bone resorption and a prolonged phase of decreased formation [22–23]. In rat models of immobilization, administration of bisphosphonates reduced bone loss [24–26]. To address the mechanism of disuse osteoporosis induced by weightlessness, Kurokouchi et al. demonstrated an increase in rat tartrate-resistant acid phosphatase mRNA (messenger ribonucleic acid), a marker of bone resorption, within 3 days and a decrease in osteocalcin and alkaline phosphatase mRNA, markers of bone formation, after 3 days [27].

Tiludronate was studied in 20 patients with acute SCI (6 placebos, 7 tiludronate 200 mg/d, and 7 tiludronate 400 mg/d) [16]. Histomorphometric analysis was performed on transiliac bone biopsies before and after treatment for 3 months. The number of osteoclasts increased in the placebo group but decreased in the groups receiving tiludronate. However, osteoid parameters were not significantly different among the three groups [16]. Of note, in an uncontrolled trial in 21 patients with complete motor SCI studied for at least 6 months with a 3.5-month treatment period, Minaire et al. showed that disodium dichloromethylene diphosphate administered within an

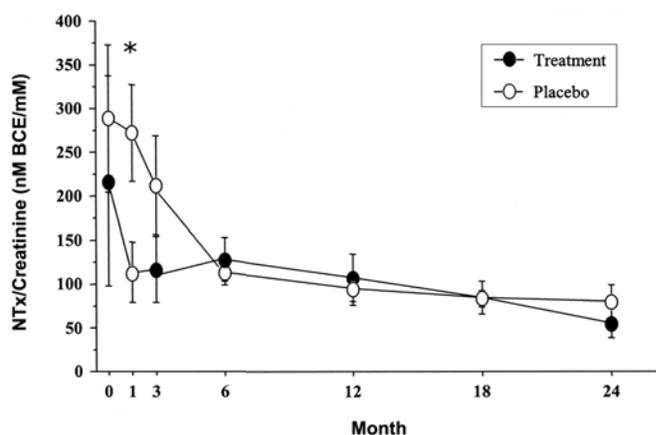


Figure 3.

Urinary N-telopeptide of type I collagen (NTx) excretion for treatment and placebo groups, expressed in nanomolar per bone collagen equivalents (BCEs). * $p < 0.05$ for treatment versus placebo at month 1.

average of 17.6 days after injury prevented the elevation in serum calcium, as well as the rise in urinary calcium and hydroxyproline [15].

Bisphosphonate therapy has also been studied in patients with incomplete lesions. In a prospective, randomized trial of 13 subjects, Pearson et al. compared the effects of cyclical etidronate ($n = 6$) or conventional rehabilitation without etidronate ($n = 7$) administered within 6 weeks of acute SCI and then followed BMD over a 12-month period [17]. Only patients who became ambulatory and received etidronate had preservation of BMD compared to all other subgroups. In a nonrandomized trial of 24 patients with acute injury, Nance et al. demonstrated that pamidronate infused monthly was effective in those with ASIA D classification (ambulatory), whereas those with ASIA A classification (nonambulatory) had no significant effect [18].

The rate of formation or degradation of bone matrix may be determined with the quantification of bone cell enzymatic activity or by measuring bone matrix components released into the circulation during the process of resorption. It should be noted that these markers of bone activity are somewhat nonspecific. Intact PINP is the aminoterminal extension peptide of type 1 collagen before cleavage and fibril formation; it measures total body collagen synthesis, the bulk of which is related to bone matrix [28–29]. Osteocalcin is a noncollagenous protein that is predominantly synthesized by the osteoblast but is also found in dentin [28–29]. Osteocalcin may also be released during osteoclastic degradation and

thus may indicate either formation when resorption and formation are coupled or turnover when they are uncoupled [30]. Measurement of urinary excretion of the pyridinoline cross-links of collagen has been increasingly recognized as a sensitive marker of bone resorption for clinical investigation. [31–32]. Currently, popular pyridinoline assays include the measurement of the aminotelopeptide (or NTx) and the carboxytelopeptide (CTx) linkages to helical sites. Each of these assays appears to provide a reliable measure of bone resorption [31–33]. Roberts et al. studied the markers of bone metabolism for 6 months after acute SCI; serum ionized calcium rose above the upper limit of normal, and serum PTH was suppressed [34]. The markers of bone resorption (total pyridinoline, deoxypyridinoline [free and total], and NTx) demonstrated a striking rise (up to 10 times the upper limit of normal) after acute immobilization, with highest values between 10 to 16 weeks after injury. The markers of bone formation (total alkaline phosphatase and osteocalcin) displayed a nonsignificant rise that remained within the normal range [34]. Nance et al. observed that urinary NTx values were lower during the first several months in the pamidronate-treated patients than in the control patients, but this finding did not reach significance [18].

In our study in persons with motor complete acute SCI, we noted a significant suppression of urinary excretion of NTx at 1 month after bisphosphonate treatment, which may have been expected to be associated with some reduction in bone loss compared to the placebo group. The NTx values were lower for the treatment group at 3 months but, because of the fall in values in the control group, the difference between the groups at this time point failed to reach significance. Thus, bone resorption, as reflected in NTx values, appears to fall regardless of bisphosphonate administration approximately 3 to 6 months after the acute immobilizing event. Despite the fall of NTx values in both groups, net bone loss continued, probably also due to a failure of bone formation, albeit this could not be confirmed by a suppression below the normal range of the bone markers of formation.

CONCLUSIONS

In this study in patients with acute complete motor lesions, the relatively early and sequential administration

of pamidronate, a parenteral bisphosphonate, failed to prevent clinically significant bone loss. Pamidronate treatment may have temporarily reduced the degree of bone loss, as reflected in lower urinary NTx and 24 h urinary calcium values at 1 month compared with the control group, and the percent change in BMD from baseline over the first several months for leg, pelvis, and distal femur. This drug effect appeared to be due to inhibiting early bone resorption. However, this salutary effect of pamidronate essentially disappeared at the later time points, perhaps when any beneficial mechanical effects of normal ambulation on bone have passed. The persistent elevated metabolic marker of resorption, urinary NTx, even after 24 months of observation, suggests that the osteoclast is partially free of inhibition, which may be the result of the absence of mechanical forces per se or related to an uncoupling from inhibitory stimuli from the osteoblast. Markers of bone formation were relatively low, and the sensitivity of these assays may not have permitted the appreciation of a further reduction. The apparent lack of efficacy of pamidronate may be related to the length of time between acute injury to initial administration of drug. Conceivably, earlier administration of a bisphosphonate may have enhanced its efficacy. The choice of drug, the dosage, and the timing of administration may all be relevant and should be addressed in future investigations. However, the possibility exists that antiresorptive therapy alone may have limited efficacy in those with complete motor lesions. Because of the apparent effect of pamidronate to reduce bone resorption early but not eventual bone loss, the possibility that the prompt and sustained reduction in bone formation should be considered as a major cause for the osteoporosis in patients with more complete neurological deficits.

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