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The effect of low-dose intravenous bisphosphonate treatment on osteoporosis in children with quadriplegic cerebral palsy

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Purpose: Quadriplegic children with cerebral palsy are more susceptible to osteoporosis because of various risk factors that interfere with bone metabolism. Pamidronate is effective for pediatric osteoporosis, but there are no guidelines for optimal dosage or duration of treatment in quadriplegic children with osteoporosis. We aimed to evaluate the efficacy of low-dose pamidronate treatment in these patients.

Methods: Ten quadriplegic patients on antiepileptic drugs (6 male, 4 female patients; mean age, 10.9±5.76 years), with osteoporosis and gross motor function classification system level V, were treated with pamidronate (0.5–1.0 mg/kg/day, 2 consecutive days) every 3–4 months in a single institution. The patients received oral supplements of calcium and vitamin D before and during treatment. The lumbar spine bone mineral density (BMD) z score and biochemical markers of bone metabolism were measured regularly during treatment.

Results: The main underlying disorder was perinatal hypoxic brain damage (40%, 4 of 10). The mean cumulative dose of pamidronate was 4.49±2.22 mg/kg/yr, and the mean treatment period was 10.8±3.32 months. The BMD *z*score of the lumbar spine showed a significant increase from -4.22±1.24 before treatment to -2.61±1.69 during treatment (P=0.008). Alkaline phosphatase decreased during treatment (P=0.037). Significant adverse drug reactions and new fractures were not reported.

Conclusion: Low-dose pamidronate treatment for quadriplegic children with cerebral palsy increased lumbar BMD and reduced the incidence of fracture.

Key words: Pamidronate, Osteoporosis, Cerebral palsy, Bone density, Quadriplegia

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Introduction

Cerebral palsy (CP) is defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to no progressive disturbances that occurred in the developing fetal or infant brain, with a prevalence rate of 2.11 per 1,000 people[1,2]. The severity of CP patients can be classified by the gross motor function classification system (GMFCS), and the higher the stage is, the lower the bone density of patients[3]. Although a study claims that the single factor of GMFCS has no correlation with fracture[4], a low bone density is the most direct indicator of bone metabolism inhibition, and can be the main target of intravenous bisphosphonate treatment[5].

In addition, CP patients have an epilepsy incidence of 15%–55%, which is much higher than that of general population[6]. Among antiepileptic drugs (AEDs), the cytochrome P450 enzyme-inducing AEDs and valproate, which is one of the enzyme-inhibiting AEDs cause hypocalcemia, elevate parathyroid hormone (PTH), and increase bone turnover, eventually leading to secondary osteoporosis. They act as a high risk factor for fracture[7-9]. Moreover, CP

patients have risk factors for osteopenia, such as less sunlight exposure, immobility and spasticity[10].

Bisphosphonate, pyrophosphate analogue, directly reduces bone resorption by decreasing the activity of osteoclasts, inhibiting recruitment of cells, increasing apoptosis, and it indirectly suppresses osteoclasts by increasing the activity of osteoblasts[11]. Pamidronate, which is an intravenous bisphosphonate, is an effective and safe treatment that increases the bone mineral density (BMD) in osteopenia of pediatric CP patients[5]. However, no clear treatment guidelines are available on the optimal dosage or the duration of use of pamidronate in quadriplegic children with CP.

In this study, we aimed to evaluate the efficacy of low-dose of cyclic IV pamidronate treatment on pediatric osteoporosis with CP GMFCS level V.

Materials and methods

This study was conducted between January 2005 and June 2017 on children with osteoporosis who had quadriplegic CP of GMFCS level V and AEDs treatment in one tertiary hospital. Osteoporosis was defined as less than BMD *z* score -2[12].

Pamidronate disodium (Panorin, Hanlim Pharm Co., Seoul, Korea) was diluted in 250 mL of isotonic saline and administered intravenously in cycles of 2 days at a dose of 0.5–1.0 mg/kg per infusion cycle given 3–4 months. Initial doses started at 0.5 mg/kg in patients with poor underlying diseases such as intractable epilepsy and chronic lung diseases. Some patients could start at 0.75 mg/kg considering their general condition. The duration of treatment was 6–15 months. All patients received a daily supplementation of calcium and vitamin D at least 4 weeks before initiation of pamidronate therapy and maintained oral supplemental medication. Dosages of calcium and vitamin D were given appropriately for age and weight.

Serum calcium, phosphate, alkaline phosphatase (ALP), creatinine, serum 25-hydroxyvitamin D (25(OH)D), PTH, and osteocalcin levels were measured at baseline and before each infusion cycle. The urinary excretion of calcium and of *N*-telopeptide collagen cross-links (NTx) were measured on a urine sample and calcium/creatinine ratio was determined at each cycle. NTx was measured by enzyme linked immunosorbent assay. Renal ultrasound and plain x-ray of the KUB (kidneys, ureters, and bladder) were performed at baseline.

BMDs of the lumbar spine (LS) and femur neck were measured at 6–12 month intervals using dual-energy x-ray bone densitometry (General Electric Medical Systems Lunar, Madison, WI, USA). The femoral neck BMD was measured only 4 patients because of deformation of femur related to severe muscle contracture. Simple x-ray films of spine (anteroposterior and lateral views) were obtained at 6-month intervals. All available radiographs during treatment were assessed for evidence of fractures.

This study was based on the retrospective medical records review. This study was approved by the Institutional Review Board of Inha University Hospital (IUH-IRB 2017-03-016-002).

Descriptive statistics are indicated as the mean±standard deviation. The Wilcoxon signed-rank test was used to compare the changes in all indicators before and after the pamidronate treatment. IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis.

Results

The total number of patients was 10 subjects and mean age was 10.9±5.76 years (range, 2–18 years). The most common underlying disease was perinatal brain injuries (40%, 4 of 10), others were Lennox-Gastaut syndrome, Menkes disease, and Dandy-Walker

Table 1. Characteristics of the study population

Patient No.	Sex	Tanner stage	GMFCS level	Underlying disease	Age at first dose (yr)	Follow-up (mo)	Cumulative dose (mg/kg/yr)	First BMD at L1-L4 (*z* score)	Fracture before treatment (yes/no)	Fracture after treatment (yes/no)	AED medication
1	M	I	V	Menke's hair kinky syndrome	2	14	2.25	-4.1	Y	N	Y
2	F	I	V	Angelman syndrome	5	6	3.00	-4.9	Y	N	Y
3	M	IV	V	Spinal muscular atrophy	16	13	2.13	-2.3	N	N	Y
4	M	IV	V	Leigh's disease	18	15	2.30	-4.4	Y	N	Y
5	M	I	V	IVH with hydrocephalus	5	13	3.72	-3.9	Y	N	Y
6	F	I	V	Hypoxic brain damage	7	12	4.82	-2.2	N	N	Y
7	F	III	V	Prematurity with PVL	15	8	5.47	-5.5	N	N	Y
8	M	IV	V	Hypoxic brain damage	17	7	6.68	-5.2	Y	N	Y
9	M	I	V	Birth asphyxia, Lennox-Gastaut syndrome	11	9	8.80	-3.8	N	N	Y
10	F	III	V	Dandy-Walker syndrome	13	9	5.82	-5.9	Y	N	Y

GMFCS, gross motor function classification system; BMD, bone mineral densitometry; AED, antiepileptic drug; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

syndrome. The dosage of the pamidronate was adjusted depending on the patient's general health condition and the change of BMD. Overall, the children received a mean dosage of 4.49±2.22 mg/kg/yr (Table 1).

1. Change in LS BMD

All patients had low BMD in the LS, with *z* scores ranging from -2.3 to -5.9 at the baseline[13]. Patient 8 was unable to undergo the follow-up of BMD because the child died from worsening of the underlying disease during pamidronate treatment. The mean LS BMD *z* score of the remaining nine subjects showed a markedly improvement from -4.22±1.24 to -2.61±1.69 during treatment (*P*=0.008) (Fig. 1).

2. Change in biochemical findings, bone turn-over markers

Before treatment, all 10 subjects had normal serum levels of calcium and phosphate, excluding high ALP levels. A comparison of biochemical markers of bone metabolism showed a statistically significant decrease in ALP (*P*=0.037) and an increase in the 25(OH)D (*P*=0.036) (Table 2). Although there were increases in serum osteocalcin levels and decreases in Urine NTx concentration throughout the treatment periods, there were no significant changes.

3. Adverse drug effects and clinical outcome

There were nonspecific reactions such as fever and myalgia at the first treatment, but it was well controlled by the conservative management such as acetaminophen. No significant adverse effects were observed during treatment. Among the patients, 60% (6 of 10) experienced fracture a year before the pamidronate treatment, and no new fractures occurred during or after treatment.

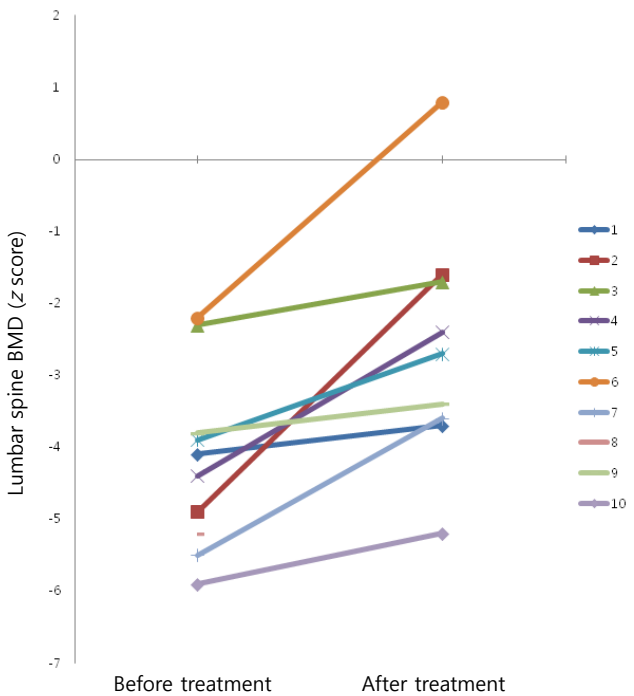

Fig. 1. Change in lumbar spine bone mineral density (BMD) in children with severe cerebral palsy. Significant increase in bone mineral density *z* scores was observed with low-dose pamidronate treatment in children with cerebral palsy.

Discussion

This study demonstrated that the administration of low-dose pamidronate in severe CP patients was effective in increasing the BMD. Regarding the appropriate dose of pamidronate, many studies have introduced various doses and treatment periods (Table 3), but no definition of "low dose" is available[5,14-17]. On the basis of the studies published so far, Plotkin et al. reported that using the dose of 0.75 mg/kg/day for 2 consecutive days every 16 weeks (4.5 mg/kg/yr), which is smaller than the frequently used typical dose of 1 mg/kg/day for 3 consecutive days every 12–16 weeks (9–12 mg/kg/yr), was effective in increasing the BMD of pediatric CP patients of GMFCS levels IV–V. In addition, the low-dose administration could be advantageous in various aspects by citing a previous study on administrating pamidronate to osteogenesis imperfecta patients[14,18].

The fracture incidence in pediatric CP patients has been reported to be 4% per year, and the probability of refracture in patients with a previous fracture was 7% per year[4]. Although Bachrach et al.[19] reported that fracture incidence in pediatric CP patients certainly decreased after pamidronate treatment for 1 year, refracture occurred after discontinuation of treatment in some cases. The metaphyseal lines that are generated like annual rings in growing bones by the cyclic administration of pamidronate are called zebra lines[20] or pamidronate bands. The parts between these bands where the density decreases could act as a stress riser and cause refractures. To prevent this possibility, low-dose treatment was suggested[21]. In this study, the average cumulative dose was 4.49±2.22 mg/kg/yr, which is lower than the general dose (Table 3). In terms of the welfare of

Table 2. Changes in biochemical markers of bone metabolism during low-dose pamidronate treatment in quadriplegic children with cerebral palsy

Biochemical marker	Before treatment	After treatment	*P* value
Calcium (mg/dL)	8.7±1.2	9.5±0.3	0.092
Phosphorus (mg/mL)	3.6±0.9	4.0±0.7	0.201
Alkaline phosphatase (IU/L)	861.7±845.2	318.3±264.6	0.037
Parathyroid hormone (pg/mL)	91.3±102.8	29.9±27.7	0.153
25(OH)D (ng/mL)	9.1±6.4	20.8±10.4	0.036
Osteocalcin (ng/mL)	7.9±4.4	9.7±4.0	0.444
Urine NTx	403.2±252.9	342.9±303.5	0.161

Values are presented as mean±standard deviation.
25(OH)D, 25-hydroxyvitamin D; NTx, cross-linked N-terminal telopeptide of type I collagen.

Table 3. Studies of pamidronate treatment for pediatric cerebral palsy patients

Study	Year	Subject	Number of patients	Protocol	Cumulative dose	Change in BMD	Change in biochemical marker	New fracture
Henderson et al.[5]	2002	Nonambulatory children with quadriplegic CP	12 (6 pairs)	1 mg/kg/day, 3 consecutive days every 3 months over 18-month period	12 mg/kg/yr	Distal femur BMD *z* score: -4.0±0.6 →-1.8±1.0 (increased 89%± 21%) L-spine BMD *z* score: -3.4±0.4→-2.2 ±0.4 (increased 33%±3%)	Decreased serum NTx	-
Grissom et al.[16]	2005	Spastic quadriplegic CP	12	1 mg/kg/day, 3 consecutive days every 4 months over 12- to 18-month period	9 mg/kg/yr	Lateral distal femur BMD *z* score: -4.0±1.1→-2.1±2.5 (increased 65.7%±55.2%) L-spine BMD z score: -4.1±1.1→-2.5 ±0.6 (increased 47.4%±39.0%)	-	No fracture
Allington et al.[17]	2005	Severe quadriplegic CP or neuromuscular disorder	18 (11 CP)	1 mg/kg/day, 3 consecutive days every 4 months over 12-month period	9 mg/kg/yr	L-spine BMD *z* score: increased 31%± 15%	-	No fracture
Plotkin et al.[14]	2006	GMFCS IV, V	23	0.37 mg/kg/day, first day 0.75 mg/kg/day, 2 consecutive days every 4 months over 12-month period	4.12 mg/kg/yr	Femur neck BMD *z* score: -4.5±1.2 → -2.6±0.9 L-spine BMD *z* score: -3.8±1.4→-2.3± 1.2	Increased PTH Decreased serum NTx	One fracture during treatment
Present study	2017	GMFCS V	10	0.25–0.5 mg/kg/day, first day 0.5–1.0 mg/kg/day, 2 consecutive days every 3–4 months over 6- to 12-month period	4.49±2.22 mg/kg/yr	L-spine BMD *z* score: -4.2±1.2→-2.6± 1.6	Decreased serum ALP Increased VitD	No fracture

CP, cerebral palsy; BMD, bone mineral densitometry; NTx, cross-linked N-terminal telopeptide of type I collagen; GMFCS, gross motor function classification system; PTH, parathyroid hormone; ALP, alkaline phosphatase; VitD, vitamin D.

patient with chronic illness, the low-dose treatment has a greater significance compared to the general dose treatment because it can decrease adverse reactions and improve quality of life while preventing fracture. The optimal dose of pamidronate can be defined by achieving the effects as increased BMD while minimizing the adverse reactions.

In the patient 6, the LS BMD improved after a 1-year treatment, but the BMD *z* score of the femur remained at -4.0. After a 1-year additional treatment, *z* score of the LS BMD increased further to 0.8, but the BMD *z* score of the femur was -3.8. Although the patient had no fracture before, because the femur is the most frequent site of fracture in CP[22], a closer assessment of the therapeutic effect and the continuous monitoring of the patient are required.

Among the biochemical markers of bone metabolism, ALP decreased significantly. Bone-specific ALP is the important bone turnover marker of bone formation; unfortunately, it was not measured in this study. Urine NTx clearly decreased in 7 of 8 subjects, but patient 10 showed an increase in urine NTx even though her BMD increased. No statistically significant result could be obtained (P=0.069). Moreover, no consistent change patterns were observed in other bone markers, such as calcium, phosphorus, PTH, and osteocalcin (Table 2).

Most patients showed nonspecific systemic symptoms from the first infusion of pamidronate, but their symptoms improved in one to 2 days with antipyretic analgesics (e.g., acetaminophen). All the patients were taking calcium before treatment, and their doses were increased by 1.5–2.0 times during hospitalization to prevent against symptomatic hypocalcemia. A temporary decreasing pattern for calcium immediately after treatment was observed frequently in each cycle, but the symptomatic or continuous hypocalcemia did not appear, and no significant adverse reactions were observed.

Bisphosphonate is known to accumulate in bone and act in the body for a long time[23]. In addition, some studies have reported improved bone density in a single cycle of treatment and in most cases BMD could be expected to improve within a year[14,24]. Considering the duration of action of the drug in the body, the timing of drug withdrawal can be determined by monitoring BMD within the treatment period of 1 to 2 years.

The study for low-dose therapy on severe CP children has been reported outside Korea, but there were no similar studies in Korea thus far[14]. There are 4 limitations in this study; the small sample of patients, the omission of femur BMD measurement, and the fact that the end point of treatment and the number of infusion cycle were not exactly unified. Nevertheless, this study emphasized the efficacy of low-dose pamidronate treatment in severe pediatric CP group, and proposed a direction for practical treatment of pamidronate and contributes to improving the quality of life for severe CP children. Appropriate guidelines for pamidronate treatment for this group should be developed through a large-scale study.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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