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BONE MINERAL DENSITY IN CHILDREN WITH CEREBRAL PALSY AND *SPINA BIFIDA* TREATED WITH IBANDRONATE

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Background. Bisphosphonates have become a common method for the prevention and treatment of osteoporosis in children with neuromuscular diseases.
Aim. The aim of this study was to assess the mid-term changes of bone mineral density in patients with cerebral palsy and *spina bifida* treated with ibandronic acid.
Materials and methods. Thirty-four patients were examined and treated: 19 children with cerebral palsy (GMFCS levels III–IV) and 15 children with *spina bifida* (thoracic and upper lumbar neurosegmental levels), mean age 9.8 ± 2.9 years. Ibandronic acid was administered to all patients (3 consecutive intravenous infusions, 0.1 mg/kg every 3–4 months). The assessment of bone mineral density was performed using dual-energy X-ray absorptiometry.
Results. The Z-score increased from –2.55 to –2.1 (total body less head), and from –2.7 to –1.65 (lumbar spine). Improvement of the Z-score for the lumbar spine was noted after the first infusion, and for the whole body after the first two infusions.
Conclusion. Ibandronic acid infusions improved the bone mineral density in children with cerebral palsy and *spina bifida* for both the whole body and the lumbar spine. Given the data obtained, weight-bearing exercises can be recommended three months after the first infusion, and dynamic exercises can be performed, preferably after six months.

Keywords: densitometry; cerebral palsy; *spina bifida*; ibandronic acid.

ДИНАМИКА СРЕДНЕСРОЧНЫХ ПОКАЗАТЕЛЕЙ ОСТЕОДЕНСИТОМЕТРИИ У ПАЦИЕНТОВ С ДЕТСКИМ ЦЕРЕБРАЛЬНЫМ ПАРАЛИЧОМ И *SPINA BIFIDA*, ПОЛУЧАВШИХ ТЕРАПИЮ ИБАНДРОНОВОЙ КИСЛОТОЙ

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Обоснование. В последние годы для профилактики и лечения остеопороза у детей с нейромышечными заболеваниями все чаще применяют бисфосфонаты.
Цель — изучить динамику среднесрочных показателей денситометрии у пациентов с детским церебральным параличом и *spina bifida*, получавших терапию ибандроновой кислотой.
Материалы и методы. Проведено обследование и лечение 34 пациентов: 19 пациентов с детским церебральным параличом (GMFCS уровни III–IV) и 15 детей со *spina bifida* (грудной и верхнепоясничный нейросег-

ментарные уровни). Средний возраст пациентов составил 9,8 ± 2,9 года. Всем детям проводили последовательные инфузии ибандроновой кислоты (по 0,1 мг на 1 кг веса каждые 3–4 мес. на протяжении года). Минеральную плотность костной ткани оценивали с помощью двухэнергетической рентгеновской абсорбциометрии, которую выполняли на рентгеновском денситометре до первой инфузии, а также перед каждой последующей инфузией.

Результаты. Средние значения Z-критерия для всего тела увеличились с –2,55 до –2,1 и для поясничного отдела позвоночника с –2,7 до –1,65. Улучшение Z-критерия для поясничного отдела было отмечено уже после первой, а для всего тела — после первых двух инфузий.

Заключение. На фоне инфузий ибандроновой кислоты показатели минеральной плотности костной ткани у пациентов с детским церебральным параличом и *spina bifida* как для всего тела, так и для поясничного отдела позвоночника улучшались на протяжении среднесрочного периода наблюдения. С учетом выявленной динамики статические нагрузки на позвоночник рекомендуют увеличивать уже через 3 мес. после первой инфузии, а на нижние конечности — через 6 мес.

Ключевые слова: денситометрия; детский церебральный паралич; *spina bifida*; ибандроновая кислота.

The diagnosis and treatment of osteoporosis in pediatric patients with neuromuscular diseases has recently received increased attention [1, 2]. The desire of young patients and their parents to achieve a high quality of life necessitates the expansion of the range of rehabilitation measures and types of activities available to them. Quality of life is an inalienable right of the patient and, as such, medical workers are obligated to ensure this right. The quality of life of a pediatric patient with a neuromuscular disease is negatively affected by manifestations of osteoporosis, which include increased risk of pathological fractures, secondary pain syndrome, and increased risk of surgical interventions. Moreover, pediatric patients are prone to suffering from fractures in the postoperative period during orthopedic treatment. Pediatric patients with the most severe clinical forms of neuromuscular diseases are at extremely high risk of developing osteoporosis and its related complications. The manifestations of osteoporosis are most pronounced in patients with infantile cerebral palsy (ICP), those who are unable to move independently (GMFCS levels IV–V), and those with concomitant disorders (e.g., epilepsy and its related conditions, hydrocephalus) [3, 4]. Children with *spina bifida*, as pediatric patients with the most severe neurological and motor disorders at the thoracic and upper lumbar neurosegmental levels, are also highly susceptible to manifestations of osteoporosis, such as fractures of the lower extremities [5]. Patients of this category, besides already being prone to the above complications, most often receive large-scale surgical interventions, such as reconstructive surgery of the hip joints and stabilization of spinal deformities; unfortunately, these interventions may also lead to prolonged postoperative immobilization and contribute to the aggravation of osteoporosis.

Several attempts have been made over the last few decades to develop an optimal protocol for the management of such patients, and these efforts often describe the selection of optimal drugs or evaluation of the effectiveness and safety of a proposed approach. Rehabilitation and regular physical exercise are known to have positive effects on bone mineral density (BMD) [6]. The intake of supplements, such as calcium preparations, standard or high doses of vitamin D [7], growth hormone, and high doses of vitamin K [8] is often prescribed. Fehlings et al. [9] reported that vitamin D and calcium can improve the BMD of patients with ICP and osteopenia; however, the efficiency of this treatment in preventing fractures is insufficient. Moreover, approaches to treat osteoporosis in pediatric patients with *spina bifida* have scarcely been studied [10].

X-ray dual energy absorptiometry, hereinafter referred to as densitometry, is currently the most common method used to assess the state of bone tissue [11]. The accuracy and reproducibility of BMD measurements in pediatric patients with severe manifestations of cerebral palsy depend on the presence of contractures, spinal deformities, metal implants, positioning, and hyperkinesis.

Our clinic has treated osteoporosis in patients with ICP and *spina bifida* with bisphosphonates since 2009. In recent years, the use of ibandronic acid preparations has become more mainstream. Similar to other bisphosphonate preparations, ibandronic acid is administered to patients under 18 years of age for unregistered indications on the

basis of the findings of the medical commission and ethics committee. These restrictions exist in most European countries and the United States. Several studies presenting the authors' experience of the use of ibandronic acid in pediatric patients have been published. The literature data and our own studies have demonstrated the sufficient safety profile of this drug in patients with ICP and *spina bifida* [12].

Most studies on the BMD dynamics of pediatric patients with neuromuscular diseases during bisphosphonate therapy include the determination of BMD parameters before and 1 year after treatment [13, 14]. Few studies have demonstrated changes in densitometry indices several years after the start of treatment [15]. The available literature does not present studies reflecting the dynamics of medium-term (i.e., during the first year of therapy) changes in BMD in pediatric patients. In our opinion, this information is essential to formulate recommendations for increased motor activity in patients diagnosed with osteoporosis and after healing from injury and surgery. Since these changes in motor activity occur, as a rule, during the first year of therapy, we suggest that changes in BMD are non-linear and, therefore, the expansion or limitation of motor activities in this period would depend on the increase or decrease in BMD indices.

The present work aims to study the dynamics of middle-term densitometry indices in patients with ICP and *spina bifida* treated with ibandronic acid therapy.

Materials and methods

This prospective study included 34 patients [19 ICP patients (GMFCS levels III–IV) and 15 pediatric patients with *spina bifida* (thoracic and upper lumbar neurosegmental levels)] who underwent staged infusion with ibandronate throughout the year.

The inclusion criterion was the presence of at least two of the following factors:

- Z-score according to densitometry lower than 2.0;
- Low-energy fracture of a long tubular bone 1 year before the start of therapy;
- Reconstructive surgery of the hip joint or corrective osteotomy of two or more bones of the lower extremities; or
- Pain associated with osteoporosis.

We used an ibandronic acid preparation (Bonviva) at a dosage of 0.1 mg per 1 kg of weight (maximum dose, 2 mg) every 3–4 months for therapy. We selected this drug because of its infusion regimen (one infusion per treatment cycle). Earlier studies indicated that ibandronic acid is well tolerated by adult patients as well as pediatric patients with imperfect osteogenesis and cerebral palsy. Following a standard examination, the drug was administered to each patient by drop infusion at a rate of 100 ml/h with an infusion pump in the hospital.

The average age of the patients at the time of the first infusion was 9.8 ± 2.9 years. BMD was assessed by dual energy X-ray absorptiometry using a Lunar Prodigy X-ray densitometer (GE Medical Systems, USA). Z-scores determined according to the densitometry of the whole body, excluding the head, and lumbar spine (LS), were taken into account when analyzing the results of the examinations.

Densitometry was performed before the first and all subsequent infusions. Thus, in this study, 124 examinations were performed in 34 patients, with three examinations were conducted for each of all patients and four examinations for each of 22 patients. To simplify data capture, we designated intervals between examinations as intervals after infusion. The average recommended time interval between infusions is 3 months; in fact, in the present study, the time interval between infusions was 3.3 months. Therefore, the intervals after infusions 1, 2, and 3 were 3, 6, and 9 months, respectively. The total follow-up duration (time interval from the first to the final examination) was 9.3 ± 1.8 months (minimum, 7 months; maximum, 14 months).

The statistical data were processed according to our analysis of the normality of the distribution of indicators in different groups of patients at different follow-up periods. Data processing using the Shapiro–Wilk test showed statistically significant differences with a normal distribution; therefore, non-parametric criteria were applied. The Wilcoxon signed rank test was used to assess changes at different terms of treatment in the groups of patients. Here pairs of variables were formed between each group at different stages of treatment (15 pairs in total). A decrease in Z-score relative to that in the previous stage of treatment was considered a negative rank, and an increase in Z-score was considered a positive rank. No change

was considered a coincident case. Changes between related patient groups were considered statistically significant at $p < 0.05$.

Results

Table 1 presents Z-score indicators (descriptive statistics) for the whole body and lumbar spine at different stages of treatment.

Table 1 reveals that the average (median) and quartile values of the initial Z-score indicators for both the whole body and LS were beyond the normal range (less than 2.0) and improved over the follow-up period. Moreover, the Z-score increased more significantly for the LS than for the whole body (whole body, from −2.55 to −2.1; LS, from −2.7 to −1.65). Three months after the first infusion, the median Z-score for the whole body did not change but that for the LS improved significantly. The median Z-score for the lumbar region reached −1.9, which is within the normal limit, prior to the third infusion (i.e., 6 months after the start of therapy) and improved after infusion 3. Figures 1 and 2 present the data of the whole body and LS, respectively, as box diagrams.

The indicators of the Wilcoxon signed rank test were analyzed to assess the significance of changes in Z-score at different treatment stages. Table 2 presents the results of the analysis of these changes for the whole body.

The increase in BMD (Z-score) for the whole body peaked after the first two infusions. The Z-score also increased after infusion 3 but the increase observed was less pronounced compared with that observed in the previous stages. Statistically significant differences between the Z-score parameters were observed after each of the subsequent infusions ($p < 0.05$).

To determine the significance of changes in the Z-scores of the LS at different stages of treatment, we studied the indicators of the Wilcoxon signed rank test (Table 3).

The data presented in Table 3 reveal that the number of positive ranks, i.e., the improvement

Table 1

Z-score indicators (descriptive statistics) for the whole body and lumbar spine at different stages of treatment

Study time	Number of cases	Z-score — whole body		Z-score — lumbar spine	
		median	quartile	median	quartile
Before treatment	34	−2.55	−2.1; −3.2	−2.7	−2.08; −3.4
After the infusion 1	34	−2.55	−1.98; −3.1	−2.1	−1.6; −3.0
After the infusion 2	34	−2.2	−1.78; −2.7	−1.9	−1.4; −2.83
After the infusion 3	22	−2.1	−1.53; −2.82	−1.65	−1.1; −2.83

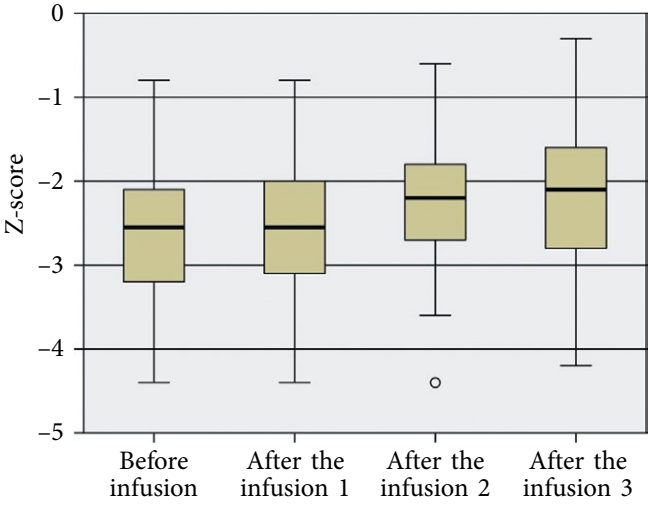

Fig. 1. Changes in Z-score for the whole body at different stages of treatment

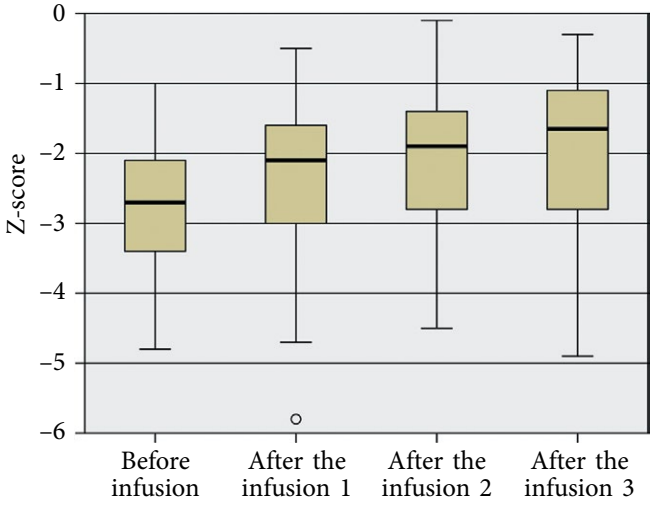

Fig. 2. Changes in Z-score for the lumbar spine at different stages of treatment

Table 2

Z-test ranks for whole-body densitometry at different stages of treatment

Interval	Positive ranks	Negative ranks	Coincident cases	Asymptotic significance (bilateral)
Before treatment — after the infusion 1	24	6	4	$p < 0.001$
Before treatment — after the infusion 2	30	2	2	$p < 0.001$
Before treatment — after the infusion 3	19	3	0	$p < 0.001$
Between the infusions 1 and 2	21	4	9	$p < 0.001$
Between the infusions 1 and 3	17	4	1	$p = 0.001$
Between the infusions 2 and 3	16	4	2	$p = 0.001$

Table 3

Z-test ranks for lumbar-spine densitometry at different stages of treatment

Interval	Positive ranks	Negative ranks	Coincident cases	Asymptotic significance (bilateral)
Before treatment — after the infusion 1	27	7	0	$p = 0.001$
Before treatment — after the infusion 2	31	2	1	$p < 0.001$
Before treatment — after the infusion 3	19	3	0	$p < 0.001$
Between the infusions 1 and 2	26	7	1	$p < 0.001$
Between the infusions 1 and 3	17	5	0	$p = 0.005$
Between the infusions 2 and 3	13	6	3	$p = 0.098$

in Z-score, increased after infusion 1 and peaked after infusion 2. By contrast, Z-scores for the whole body showed no statistically significant difference between infusions 2 and 3 ($p = 0.098$), although the significance of improvement at this stage persisted compared with the initial indicator.

Discussion

The treatment of osteoporosis in pediatric patients with neuromuscular diseases is a complex problem that remains unresolved. We believe that the treatment of such patients should begin with the elimination of known risk factors. Choosing the minimum dose of the most effective drug to maintain BMD, increasing the duration of insolation, and ensuring adequate intake of calcium and vitamin D are essential to enhance treatment success. The most significant breakthrough in this field involves the use of antiresorptive drugs, primarily bisphosphonates. The literature provides extensive information on this issue. However, most protocols are empirical in nature, and treatment efficacy studies are largely limited to evaluations of the basic parameters of bone metabolism, such as blood alkaline phosphatase activity. However, osteoporosis represents a combination of clinical disorders in the form of pathological fractures and certain results of evaluation (decrease) of BMD. In this case, to follow these criteria, BMD must be determined at each stage of a patient's examination and treatment.

Osteodensitometry in pediatric patients with neuromuscular diseases presents a number of limitations, including a wide range of anthropometric variations in patients with ICP and the consequences of spinal hernia associated with eating habits, comorbidity, puberty, and various medical and non-medical circumstances. Moreover, patients with ICP and *spina bifida* often present contractures and deformities of the extremities, malpositions, and surgical hardware after orthopedic intervention. In patients with *spina bifida*, congenital spinal deformities characteristic of the disease can cause additional difficulties. These factors are widely discussed in the literature, but their presence is not considered as a direct obstacle to obtaining and interpreting densitometry data in pediatric patients

with ICP and *spina bifida*. However, in all cases, this fact is specified as a certain restriction.

Literature data on the dynamics of densitometry in ICP patients treated with bisphosphonates are very limited. A previous meta-analysis [8] published in May 2015 found only four studies evaluating the effect of bisphosphonates on BMD using densitometry before and after treatment. In all studies, the Z-score for the LS significantly improved after treatment with bisphosphonates. Henderson et al. [13] conducted a randomized double-blind placebo-controlled study in which six patients were administered intravenous pamidronate and found that Z-scores ranged from −3.4 to −2.2 ($p = 0.005$). Bachrach et al. [14] performed a case–control retrospective study in which seven patients were administered intravenous pamidronate and found that Z-scores changed from −4.0 to −2.8 ($p = 0.03$). Plotkin et al. [15] also reported a prospective case–control study in which a group of 19 pediatric ICP patients received intravenous pamidronate; Z-scores in this group improved from −3.8 to −2.3 ($p < 0.01$). A case–control prospective study in which oral alendronate was administered to 26 patients revealed an improvement in BMD from−3.45 to−2.4 ($p < 0.001$) [16].

A later study in 2017 [4] analyzed the data of 10 patients with quadriplegia (GMFCS level V) who received antiepileptic drugs. Pamidronate was prescribed to the patients (0.5–1.0 mg/kg per day, 2 consecutive days) every 3–4 months to treat osteoporosis. The authors evaluated the Z-score for the LS and revealed improvements from −4.22 to −2.61. A unique aspect of this study is its inclusion of patients suffering from syndromic diseases with the clinical presentations of ICP (e.g., Angelman syndrome, Li syndrome, Dandy–Walker disease, Lennox–Gastaut syndrome) who received antiepileptic therapy. Thus, extremely low indicators of the Z-score may be associated with this feature.

The optimal duration of therapy for osteoporosis with bisphosphonates remains unknown, and the limited numbers of studies on this topic prevent the formulation of clear conclusions. The present study revealed that three consecutive infusions of ibandronic acid at intervals of 3 months positively influence the increase in BMD, due to which it can be increased to the minimum borderline indicators of the norm (Z-score −2.0). However, additional studies are required to determine the effectiveness of subsequent infusions.

The X-ray dose applied when examining pediatric patients is an important consideration. The effective radiation dose for densitometry of the whole body on a Lunar Prodigy device in a pediatric patient aged 10 years is 0.14 μSv for boys and 0.16 μSv for girls [17]. According to Sanitary Rules SP 2.6.1.758-99 "Ionizing radiation, radiation safety. Radiation safety standards (RSS-99)," an equivalent radiation dose not exceeding 1 mSv per year is permissible during examination, including for scientific purposes.

Thus, even if examination is performed every 3 months, the total annual radiation dose received by the patient will be hundreds of times lower than the permissible dose. Nevertheless, despite the fact that radiation safety standards were observed in the present study, densitometry without serious clinical grounds is not recommended in everyday practice.

Conclusion

Bisphosphonates are increasingly used to prevent and treat osteoporosis in pediatric patients with neuromuscular diseases. The optimal dose of drugs resulting in the best effects with the fewest adverse reactions can be determined by assessing BMD. Thorough assessment of the therapeutic effect and constant monitoring of the patient's condition are required. Comparative analysis of our own findings with the literature data has enabled us to draw several important conclusions. Published studies have confirmed the positive effect of ibandronic acid therapy on BMD indices in pediatric patients with cerebral palsy and *spina bifida*. Ibandronic acid, which was first studied as the drug of choice in this category of patients, demonstrated sufficient safety and effectiveness in our earlier studies. In the present work, densitometry revealed that ibandronic acid produces more pronounced improvements in the LS compared with that in the whole body. The finding may indicate some imbalance in the improvement of BMD between the axial and appendicular skeleton. Both indicators changed most significantly approximately 6 months after the first infusion. The data obtained can serve as a basis for practical recommendations to

expand the motor activity of patients receiving antiresorptive therapy. For example, static loads on the spine can be increased 3 months after the first infusion of ibandronic acid and dynamic loads on the lower extremities could be increased after two stages of infusion, that is, after 6 months.

Despite the availability of clinical material for this type of research, a significantly larger number of cases is required to address issues related to the influence of age-related, clinical (e.g., diagnosis of ICP or *spina bifida*, history of surgeries and fractures), anthropometric, and neurological factors, as well as dosage options for the drug. Further research in this field and generalization of literature data could improve and personalize the care of this complex category of patients.

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Ethical statement. The examination and treatment protocols of the pediatric patients were approved by the local ethics committee of the Turner Scientific and Research Institute for Children's Orthopedics, Ministry of Health of Russia (protocol of the meeting No. 3 of 10/28/2009). Patients (or their representatives) provided consent to the treatment and processing and publication of personal data.

Author contributions

V.M. Kenis developed the study concept, collected and analyzed the scientific material, and wrote the article.

A.V. Sapogovsky collected and analyzed the scientific material and performed statistical data processing.

T.N. Prokopenko, S.V. Ivanov, and *T.I. Kiseleva* collected and analyzed the clinical material.

A.N. Bergaliev collected and analyzed the densitometry material.

All authors made significant contributions to the research and preparation of this article, read, and approved the final version before publication.

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