Original Article

Assessment of the Effect of Intravenous Pamidronate in the Treatment of Legg-Calve-Perthes Disease in Children

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Abstract

Background: Legg-Calvé-Perthes disease (LCPD) presents in childhood with idiopathic avascular necrosis of the femoral head(s), which can lead to disability and the need for corrective surgery at an early age. Bisphosphonates are a group of drugs that prevent osteoclastic bone resorption and may be helpful in the treatment of LCPD. So far, no trial has been conducted to investigate the effect of monthly intravenous pamidronate in the treatment of LCPD in children. Therefore, we assessed this issue in this study.

Materials and Methods: This study was conducted as a clinical trial on children with LCPD who were referred to Mofid Children's Hospital (Iran-Tehran) during 2022 and 2023. Pamidronate was injected monthly and intravenously at a dose of 1 mg/kg/dose. Both groups were the same in terms of the type of treatment received (except pamidronate), the number of visits, and other follow-up parameters. The study was conducted for one year. The significance level was considered less than 0.05.

Results: Forty-seven patients were included in the study. Twenty-one (60%) were in the pamidronate group, and 26 (40%) were in the control group. The mean age in the intervention group was 6.19 ± 1.69 years, and it was 6.15 ± 1.85 years in the control group (P-value=0.944). There was no statistically significant difference in children's gender (P-value = 0.731). Patients with pamidronate had a better overall score than the control group. The overall score in the pamidronate group was 2.37 more than the control group, but this difference was not statistically significant (P value=0.753). The scores of pain, lameness, walking, distance, squat, cross leg, and range of motion (ROM) in the pamidronate group were not significantly different from the control group (P value>0.05).

Conclusion: Pamidronate can improve the clinical results of children with Legg-Calve-Perthes disease, and it is recommended that this drug be used along with the usual treatments for these patients.

Keywords: Legg-Calve-Perthes Disease, Orthopedics, Pediatrics, Pamidronate

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Introduction

Legg-Calve-Perthes disease (LSPD) is idiopathic osteonecrosis or idiopathic avascular necrosis of the epiphysis of the femoral head[1]. The cause of LSPD is unknown. It may be idiopathic or due to other causes that impair blood flow to the femoral epiphysis, such as trauma (microtrauma, macrotrauma, or repetitive trauma), coagulopathy, and steroid use. Thrombophilia is present in approximately 50% of patients, and some form of coagulation disorder is present in 75%[2-6].

Treatment goals include managing pain and symptoms, restoring the hip range of motion, and immobilizing the femoral head in the acetabulum. Non-surgical treatment is recommended for children with bone age less than six years or lateral A column involvement. Activity restriction and protective weight bearing are recommended until ossification is complete[7,8].

Bisphosphonates are a class of drugs that prevent osteoclastic bone resorption. Bisphosphonate's therapeutic value comes from its ability to inhibit osteoclast-mediated bone resorption[9]. Recently, there has been increasing evidence for the use of bisphosphonates in the treatment of LCPD. In humans, there are few published reports, including one case report and one case series, of the use of bisphosphonate zoledronic acid (zoledronate). There are limited data about the use of Pamidronate (a second-generation bisphosphonate) in LCPD, but in children with inflammatory bone diseases, such as chronic relapsing multifocal osteomyelitis (CRMO), incomplete ossification, and bone-associated disease with malignancy have been useful reports[10-14]. This study aimed to assess the therapeutic effects of Pamidronate in LCPD.

Methods

In this study, which was conducted as a clinical trial on children with LCPD, all children with LCPD who were referred to the rheumatology clinic of Mofid Children's Hospital (Iran-Tehran) during 2022 and 2023 were evaluated.

The inclusion criteria were having LCPD and being under 18 years old. Exclusion criteria were receiving previous treatment, receiving other similar drugs, and not having consent to participate in the study.

First, the steps of conducting the study, the type of injection of the drug, and its conditions were fully explained to the parents of the patients. Then, a written consent form was obtained from the parents of the patients to participate in the study. Children whose parents consented to pamidronate injection as a single dose monthly were considered the intervention group, and children whose parents did not consent to pamidronate injection were considered the control group. The patients of the control group received the routine treatment of the LCPD, and the patients of the intervention group received pamidronate injection in addition to the routine treatment.

Pamidronate was injected monthly and intravenously at 1 mg/kg/dose. Both groups were the same in terms of the type of treatment received (except pamidronate), the number of visits, and other follow-up parameters. Before starting the study, all patients underwent imaging to assess the condition of the femoral bone. Also, this imaging was repeated six months and one year later.

Patient information, including age, sex, imaging findings, physical examination findings, disease grade based on an expert rheumatologist's decision, and response to treatment, were recorded. Pre-protocol and intention-to-treat methods were used. Patients were followed up for one year, and at the end of the study, intervention, and control groups were assessed and compared.

Statistical analysis: Mean and standard deviation were used to describe quantitative data, and frequency and percentage were used for qualitative variables. Mann-Whitney, Chi-score, or Fisher's exact test are used to compare the results between the two groups depending on the type of response under investigation and the results of the data normality test. Analyzes were performed by SPSS 26 software. A P-value less than 0.05 was considered statistically significant.

Ethical issue: The ethical principles of the research were observed. This research has received the ethical code from the Ethics Committee of Shahid Beheshti Medical University (IR.SBMU.MSP.REC.1402.042).

The IRCT code was IRCT20230526058299N1.

Results

Forty-seven children were assessed in this study. Twenty-one (60%) were in the pamidronate group, and 26 (40%) were in the control group. The mean age in the intervention group was 6.19 ± 1.69 years, and it was 6.15±1.85 years in the control group (P-value=0.944). Nineteen patients (73.1%) in the control group were boys, and seven patients (26.9%) were girls in the control group. In the intervention group, there were 17 boys (81.0%) and four girls (19.0%). There was no statistically significant difference between the groups in terms of gender (P-value: 0.731).

The historical data are seen in Table 1. The deformity score was assessed based on the modified Harris hip score. Based on this system, each of the following sections receives one score: less than 30 ° fixed flexion contracture, less than 10 ° fixed abduction, less than 10 ° fixed internal rotation in extension, and less than 3.2 cm limb length discrepancy.

The results of imaging factors and interpreting the results of intervention and control groups according to the radiologist's decision are seen in Table 2.

The patient's abilities were assessed based on a modified Harris hip score questionnaire. The results are seen in Table 3.

Discussion

In this study, which was conducted with the aim of assessing pamidronate effects on the treatment of LCPD, 47 patients were assessed, of which 21 (60%) patients received pamidronate (intervention group), and 26 (40%) patients did not receive pamidronate and with the usual treatments as the control group. There were no statistically significant differences in terms of age and gender between the two groups. The two groups were similar in terms of other treatments received except for pamidronate. The group that received pamidronate (intervention group) had better interpretation results than the control group, and pamidronate has a positive and significant effect on the interpretation of children with LCPD. However, it does not have a significant effect on the findings of graphics and osteopenia. There was no significant difference between the two groups in the mean of various scores such as pain, lameness, crutches, walking distance, stairs, squats, walking, transportation, overall score, and ROM, as well as the

Table 1. Patients' historical data**.**

		Total	Control	Intervention	P value
Trauma	No	17 (36.2%)	5 (19.2%)	12 (57.1%)	0.007
	Yes	30 (63.8%)	21 (80.8%)	9 (42.9%)	
Using brace	No	8 (17.0%)	4 (15.4%)	4 (19.0%)	0.99
	Yes	39 (83.0%)	22 (84.6%)	17 (81.0%)	
Intra-articular corticosteroid injection	No	38 (80.9%)	21 (80.8%)	17 (81.0%)	0.99
	Yes	9 (19.1%)	5 (19.2%)	4 (19.0%)	
PAMIDRONAT use	No	11 (73.3%)	10 (100.0%)	1 (20.0%)	0.004
	Yes	4 (26.7%)	0 (0.0%)	4 (80.0%)	
History of gel injection	No	32 (68.1%)	16 (61.5%)	16 (76.2%)	0.28
	Yes	15 (31.9%)	10 (38.5%)	5 (23.8%)	
Deformity	No	9 (19.1%)	7 (26.9%)	2 (9.5%)	0.09
	2.00	2 (4.3%)	0 (0.0%)	2 (9.5%)	
	3.00	2 (4.3%)	2 (7.7%)	0 (0.0%)	
	4.00	34 (72.3%)	17 (65.4%)	17 (81.0%)	

*P value based on Fisher Exact test and chi-square

Table 2. Imaging factors and interpretation of results of the groups.

		Total	Control	Intervention	P value
interpretation	Weak	13 (27.66%)	9 (34.6%)	4 (19%)	0.04
	Good and excellent	34 (72.34%)	17 (65.4%)	17 (80.19%)	
Graphy	Normal	30 (63.83%)	17 (65.4%)	13 (61.9%)	0.75
	Decrease	10 (21.28%)	6 (23.1%)	4 (19.0%)	
	Fusion	7 (14.89%)	3 (11.5%)	4 (19.0%)	
result	Normal	33 (70.21%)	17 (65.4%)	16 (76.2%)	0.68
	Osteopenia	14 (29.79%)	9 (34.6%)	5 (23.8%)	

*P value based on Fisher Exact test and chi-square

Table 3. The results of patients' abilities in the groups based on the modified Harris hip score questionnaire.

	Total	Control	Intervention	P value
Pain	35.62 ± 9.88	35.92 ± 7.17	35.24 ± 12.66	0.816**
Claudication	7.57 ± 2.71	7.88 ± 1.34	7.19 ± 3.79	0.388**
walking stick	8.98 ± 3.61	8.73 ± 3.65	9.29 ± 3.62	0.606**
Walking distance (m)	9.98 ± 1.91	10.08 ± 1.41	9.86 ± 2.41	0.699**
Stairs (number)	3.13 ± 1.21	2.96 ± 1.18	3.33 ± 1.24	0.3*
Squat (number)	2.89 ± 1.54	3.08 ± 1.49	2.67 ± 1.59	0.368**
cross leg	3.6 ± 1.88	3.81 ± 1.77	3.33 ± 2.03	0.397*
Using public transportation	0.85 ± 0.36	0.88 ± 0.33	0.81 ± 0.4	0.518*
total	80.64 ± 25.36	79.58 ± 19.23	81.95 ± 31.83	0.753**
Range of motion	4.36 ± 1.15	4.29 ± 1.12	4.43 ± 1.21	0.695*

* P value based on T-test, **P value based on Mann-Whitney

mean overall score. Of course, the mean score of the questionnaire in the pamidronate group was 2.37 higher than the control group, but it was not statistically significant. The small sample size can cause the non-significance of this score. The remarkable point about this score is the clinical significance and not the statistical significance because the statistical significance depends on the sample size. However, based on our findings, it was seen that clinically, treatment with pamidronate improved the functional scores of children with Legg-Calve-Perthes.

In a review by Young et al., only one study-initiated treatment with bisphosphonates (BPs) in the pre-collapse stage of osteonecrosis and reported prevention of femoral head deformity in 9 of 17 patients. All studies reported improvement in pain and gait in patients treated with intravenous BPs. Of the eight experimental studies reviewed, seven reported a reduction in femoral head deformity. It was concluded that the clinical evidence lacks consistent patient groups and drug protocols to definitively conclude that the treatment with BPs can reduce femoral head deformity in juvenile osteonecrosis conditions. Experimental studies show that bisphosphonate treatment protects the infarcted femoral head from deformity but has no effect on bone anabolic metabolism[١٠]. One of the advantages of the current study is that, according to our information, no clinical trial study has been conducted on the effect of pamidronate on Legg-Calve-Perthes disease. In our study, it was seen that pamidronate, as a member of the bisphosphonate family, has a good effect on the treatment and performance of children with Legg-Calve-Perthes. Based on our findings, pamidronate improved the overall performance score of the patients, but it did not have a significant effect on radiographic findings. In terms of radiographic findings, the results of our study were different from

those of Young et al.'s study. However, regarding the improvement of performance, the results of these two studies were similar.

Cheng et al. investigated the effect of surgery with and without zoledronic acid (ZA) on the pig model of Legg-Calve-Perthes and the effect of these two methods on idiopathic osteonecrosis of the femoral head (ONFH). They concluded that recombinant human bone morphogenetic protein-2 (rhBMP-2) without adding bisphosphonate is ineffective in preventing femoral head collapse[۱۵]. Actually, according to Cheng et al.'s study, adding bisphosphonate to femoral head surgery in Legg-Calve-Perthes causes the improvement of the effect of this surgery. One of the differences between this study and the current study was that our study examined the effect of pamidronate. However, the study by Cheng et al. examined the effect of zoledronic acid on Legg-Calve-Perthes disease. Zoledronic acid and pamidronate are both bisphosphonates. Studies have shown that zoledronic acid is more effective than pamidronate in the treatment of bone cancers[۱۶،۱۷]. However, according to our knowledge, no study has investigated these two drugs in the treatment of Legg-Calve-Perthes. Based on the current study, bisphosphonate can be useful in the treatment of Legg-Calve-Perthes.

Logan et al. presented a case report of an 11-year prospective clinical and radiological course of a 6-year-old boy with bilateral Legg-Calvé-Perthes disease treated with intravenous pamidronate (IV-PAM). The patient received nine courses of monthly IV-PAM (1 mg/kg/dose, monthly) over 13 months, along with Petrie/broomstick casting and physical therapy. Over time, his femoral head healed[۱۸]. In our study, which was conducted as a clinical trial, it was seen that monthly and intravenous pamidronate injection of 1 mg/kg/dose during 12 months improves the clinical and interpretative findings of patients with Legg-Calvé-Perthes. One of the advantages of our study compared to Logan et al.'s study was that Logan et al.'s study was conducted as a case report. However, our study was a clinical trial, which indicates that the present study is valuable. Despite this difference, the findings of two studies showed the effectiveness of pamidronate in the treatment of Legg-Calvé-Perthes disease.

Sivakumar et al. recommended a single dose of zoledronic acid (2 mg) in the epiphysis to two children (7 years old with Catterall Stage II unilateral affection and 11 years old with Catterall Stage III bilateral affection). Both children were followed up every three months with clinical and radiological examinations. At the last 4-year follow-up, both had satisfactory results. The conclusion was that the local administration of a single dose of zoledronic acid within the epiphysis is a relatively harmless method and is effective in preventing the progression of the pathology of the disease, especially in children aged 6 to 10 years[۱۹]. In the current study, it was seen that pamidronate in the treatment of Legg-Calvé-Perthes disease, monthly and intravenously at 1 mg/kg/dose for one year, had acceptable clinical results. However, it did not improve the test scores related to this disease, and the score of the overall questionnaire was also statistically non-significantly better in the pamidronate group.

The meta-analysis by Kumar et al. showed a statistically significant effect of bisphosphonates in Harris hip score (HHS) and femoral head collapse in Legg-Calvé-Perthes disease. However, the effect on pain score was not significant. It was concluded that the use of bisphosphonates is a promising treatment option for LCPD. However, good-quality RCTs are needed for further validation[۲۰]. Our study, which was conducted as a clinical trial, showed that pamidronate, as a bisphosphonate, can have a good effect on the scores of the overall clinical questionnaire as well as the interpretation of LCPD, which, from this point of view, these two studies were similar.

Conclusion

It is concluded that monthly and intravenous pamidronate 1 mg/kg/dose for one year can be a valuable treatment for children with Legg-Calvé-Perthes disease. This drug improved the interpretation status and the overall score of the questionnaire but did not statistically change the status of radiological findings or osteopenia. In children who receive Legg-Calvé-Perthes treatments, adding pamidronate to their treatment improves the patient’s outcome.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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