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ResearchArticle

ROLE OF ORAL RISEDRONATE IN CLINICAL OUTCOME OF LEGG-CALVE-PERTHES DISEASE, A RANDOMIZED CONTROL TRIAL

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ABSTRACT

In the present study, we aim to find out the effect of oral Risedronate a Bisphosphonate in clinical outcome of Perthes disease. In this randomized control trial, after ethical clearance and informed consent formalities, total 60 patients were analyzed. All the patients chosen in the study were in the Herrings A and B. The VAS score range of motion measured at different follow-ups and Deformity Index was measured at 2 years follow up. At 2 years final follow-up, Deformity index showed a statistically significant head shape preservation leading to increased range of motion of the involved hip. There was no statistically significant difference in pain by risedronate. Therefore we concluded that there is a definite role of oral risedronate in preservation of head shape with improved range of motion of hip joint in perthes disease.

INTRODUCTION

Perthes' disease is a self-limiting osteochondrosis of the capital femoral epiphysis that develops in children commonly between the ages of five and 12 years (Catterall A, 1982). The incident reported to be 8.5 to 29 per 100000 children per year (Randall *et al*., 2011). The blood supply to some part or entire epiphysis becomes compromised, that leads to necrosis of the involved epiphysis. The blood supply gets restored spontaneously in due course of time and the necrotic epiphysis heals in two to four years (Joseph B, 2011). The process of healing can be clearly appreciated on plain radiographs and the disease process can be quite reliably divided into definite stages on the basis of plain radiographic appearances. These stages are those of avascularity (stage I), fragmentation (stage II), regeneration (stage III) and complete healing (stage IV) (Joseph B, 2011). Prevention of deformation of the femoral head being the most important aim of treatment of Perthes disease. Weight-bearing and muscular contraction produce stresses that are transmitted across the acetabulum onto the avascular femoral capital epiphysis (SauloMartelli, 2011). The avascular epiphysis is particularly vulnerable to deformation when subjected to these stresses.

The logic behind using oral bisphosphonate (BP) therapy for Legg-Calvé-Perthes disease (LCPD) is the ability of the drug to prevent subsiquent femoral head deformity during the fragmentation phase by inhibiting osteoclast mediated bone resorption (Young ML, 2012). The aim of the study is to find out whether oral bisphosphonate prevents femoral head deformation. We hypothesise that weekly 35mg dose will inhibit osteoclasticresorption of avascular bone in the femoral head, thus preserving structural integrity and preventing collapse. New bone will then form over the preserve avascular bone, with improved healing at 24 months.

The primary aim of this study is to determine the efficacy of Oral Risedronateat preserving femoral head shape in Perthes disease. Secondary aim is to determine its effect on range of motion, hip pain and safety at 24 months.

MATERIALS AND METHODS

The study has been reviewed and approved by The Ethics Committee, King Georges Medical University Lucknow, Uttar Pradesh. Written informed consent is obtained from parents and assent from the young children prior to enrolment. Unblind, unicentric trial of 24 months risedronate in children with unilateral PD is designed. As this intervention is ment to

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prevent collapse of the femoral head those children who already had collapse were not eligible for study. All childeren undergone MRI scan of both the hip joints before inrollment in the study. The lateral pillar classification was used to define the population such that femoral heads with a lateral pillar >50% of the height of the unaffected side are included (lateral pillar A or B).

A randomised control trial recruiting 60 children (30 each treatment arm) 5 to 15 years old with unilateral PD. Subjects were randomized (a) Oral Risedronate and standard care or (b) Standard care. The primary outcome measure is deformity index (DI) (Fig-1), a radiographic parameter of femoral head roundness assessed at 24 months, following 24 months of Oral Risedronate 35 mg weekly treatment for 24 months observation (group A) or 24 months of observation only (group B). Secondary outcome measures are hip range of motion and pain measured by VAS scale, Harris hip score. Assessments are made at baseline, 3 month 6 months 12 months than 18 month, until the 24th month.

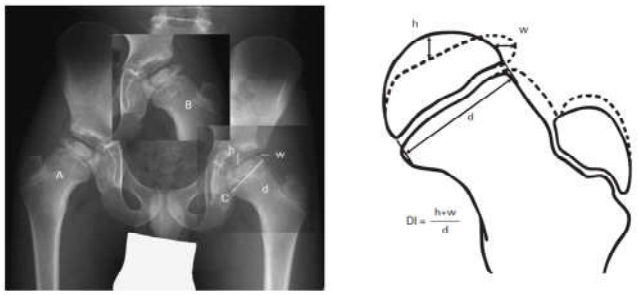

Fig1 Deformity index (DI) measurement

RESULTS

In the present study, total 60 patients were analysed, 30 in each group. All patients were treated on out-patient basis with regular follow-ups at specific duration (Table-1). Hip pain (VAS SCORE) and hip range of motion were observed during all follow up. Final outcome namely Deformity index (DI), Range of motion, VAS Score, Harris Hip Score were measured (Table-2).

Table1 Patients demographical data

Parameters		N	Percentage
Sex	Male	53	88.3
	Female	7	11.7
Laterality	Left	26	43.3
	Right	34	56.7
Lateral Pillar	A	44	73.3
	B	16	26.7
Harris Hip	Excellent	44	73.3
Score	Very Good	16	26.7

Table2 Patients descriptive data

Parameters	N	Minimum	Maximum	Mean	Std. Deviation
Age	60	5.00	14.00	7.1583	2.19493
Duration	60	2.00	12.00	4.9333	1.98184
Deformity index	60	0.11	0.76	0.3693	0.17284

30 patients were in each group with minimum age of 5 years and maximum age 14 years with mean age 7.15 years. Minimum duration from symptoms to first visit was 2 months and maximum was 1 year with mean duration 4.93 months. In our study there were 53 male patients accounting 88.3 % and 7 female patients accounting 11.7 %. 34 patients had right hip involvement accounting 56.7% and 26 patients with left hip involvement accounting 43.3%. 44 patients had Herrings lateral pillar A accounting 73.3%, 16 patients were classified under Herrings lateral pillar B accounting 26.7%. Initial mean VAS score was 4.52±1.41 at first visit that improved and became 0.62±0.98 and p value < 0.001.

Mean flexion at first visit was 111.50±10.22 degree that improved to 122.83±6.27and result was significant (Table-3).

Table 3 Patients clinical examination at different follow-ups

	N	Mean	Std. Deviation	p-value
Initial VAS Score	60	4.52	1.41	<0.001*
VAS @ 2 Years	60	0.62	0.98	
Flexion	60	111.50	10.22	<0.001*
Flexion at 2 yrs	60	122.83	6.27	
Extension	60	2.5000	2.52	<0.001*
Extension at 2 years	60	8.83	3.95	
Abduction	60	25.33	5.51	<0.001*
abd 2 yrs	60	30.75	5.35	
IR	60	16.33	5.36	<0.001*
IR After 2 Yrs	60	26.92	5.97	
IR IN 90 Flexion	60	3.33	4.08	<0.001*
IR 90 Flexion after 2 Years	60	15.00	6.51	
ER	60	22.58	6.34	<0.001*
ER 2 Years	60	28.58	5.97	
Adduction	60	12.50	4.06	<0.001*
Adduction at 2 years	60	19.58	5.84	

Mean Extension at first visit was 2.5±2.52 degree that improved to 8.83±3.95 and result was significant. Mean abduction at first visit was 25.33±5.51 degree that improved to 30.75±5.35 and result was significant. Mean adduction at first visit was 12.500±4.065 degree that improved to 19.583±5.843 and result was significant. Mean internal rotation at first visit was 16.33±5.36 degree that improved to 26.92±5.97 and result was significant. Mean internal rotation in 90 degree flexion at first visit was 3.33±4.08 degree that improved to 15.0±6.51 and result was significant. Mean external rotation at first visit was 22.58±6.34 degree that improved to 28.58±5.97and result was significant.

Initial vas score in interventional group was 4.5±1.33 while in noninterventional group was 4.533 ±1.50 p value 0.928 that improved and became 0.66±1.03 in interventional group and 0.60±0.93 p value 0.896 in non interventional group and this signifies no effect of drug in improving pain in perthes disease patients. Deformity index at end of treatment in risedronate group was 0.3083±0.168 and non interventional group was 4.303±0.157 with p value 0.005 that signifies definite improvement in deformity index. Sphericity of the head is definitely preserved and improved with the use of risedronate weekly.

Flexion in resedronate group at first visit was 111.0 ±9.321 and non interventional group was 112.0±11.181 with p value 0.78. At the end of two years flexion in risedronate group 125.50±5.14 and in non interventional group was 120.17±6.226 with p value 0.001. Patient taking risedronate has better sphericity so the improvement in flexion is morew in this group

which is statistically significant. Extension in resedronate group at first visit was 2.166 ±2.520 and non interventional group was 2,833.0±2.520 with p value 0.310. At the end of two years extension in risedronate group is 10.00±4.152 and in non interventional group is 7.667±3.407 with p value 0.021. Patient taking risedronate has better sphericity so the improvement in extension in this group is statistically significant.

Abduction in resedronate group at first visit was 111.0 ±9.321 and non interventional group was 26.166±5.971 with p value 0.245. At the end of two years abduction in risedronate group 33.833±4.488 and in non interventional group was 27.666.17±4.310 with p value 0.001. Patient taking risedronate has better sphericity so the improvement in abduction in this group is statistically significant. Adduction in resedronate group at first visit was 13.8333 ±3.13031 and non interventional group was 11.1667±4.488 with p value 0.010. At the end of two years Adduction in risedronate group 22.666±5.20 and in non interventional group was 16.500±4.761 with p value< 0.001 (Table-3).

Table4 Patients clinical examination in two groups at different follow-ups

	GROUP	N	Mean	SD	p-value
Initial VAS Score	Intervention (Risedronate)	30	4.5000	1.33261	0.928
	Noninterventional	30	4.5333	1.50249	
VAS @ 2 Years	Intervention (Risedronate)	30	0.6333	1.03335	0.896
	Noninterventional	30	0.6000	.93218	
Deformity index	Intervention (Risedronate)	30	0.3083	.16824	0.005*
	Noninterventional	30	0.4303	.15740	
Flexion	Intervention (Risedronate)	30	111.00	9.32183	0.708
	Noninterventional	30	112.00	11.18805	
Flexion at 2 yrs	Intervention (Risedronate)	30	125.50	5.14446	0.001*
	Noninterventional	30	120.17	6.22610	
Extension	Intervention (Risedronate)	30	2.1667	2.52003	0.310
	Noninterventional	30	2.8333	2.52003	
Extension at 2 years	Intervention (Risedronate)	30	10.0000	4.15227	0.021*
	Noninterventional	30	7.6667	3.40723	
Abduction	Intervention (Risedronate)	30	26.1667	5.97168	0.245
	Noninterventional	30	24.5000	4.97407	
abd 2 yrs	Intervention (Risedronate)	30	33.8333	4.48817	<0.001*
	Noninterventional	30	27.6667	4.30183	
IR	Intervention (Risedronate)	30	17.1667	5.20002	0.231
	Noninterventional	30	15.5000	5.46935	
IR After 2 Yrs	Intervention (Risedronate)	30	30.5000	4.01506	<0.001*
	Noninterventional	30	23.3333	5.46672	
IR in 90 Flexion	Intervention (Risedronate)	30	4.5000	4.01506	0.026*
	Noninterventional	30	2.1667	3.86927	
IR 90 Flexion After 2 Years	Intervention (Risedronate)	30	17.6667	5.83292	0.001*
	Noninterventional	30	12.3333	6.12138	
ER	Intervention (Risedronate)	30	23.1667	6.62848	0.481
	Noninterventional	30	22.0000	6.10257	
ER 2 Yrs	Intervention (Risedronate)	30	32.0000	3.85066	<0.001*
	Noninterventional	30	25.1667	5.79586	
Adduction	Intervention (Risedronate)	30	13.8333	3.13031	0.010*
	Noninterventional	30	11.1667	4.48817	
Adduction at 2 years	Intervention (Risedronate)	30	22.6667	5.20830	<0.001*
	Noninterventional	30	16.5000	4.76156	

Internal rotation in resedronate group at first visit was 17.166±5.201 and non interventional group was 15.50±5.466 with p value 0.231. At the end of two years internal rotation in risedronate group 30.50±4.015 and in non interventional group was 23.333±5.466 with p value < 0.001. Patient taking risedronate has better sphericity so the improvement in internal rotation is more in this group which is statistically significant. Internal rotation in 90 degree flexion in resedronate group at first visit was 4.500±4.015 and non interventional group was 2.166±3.869 with p value 0.026. At the end of two years internal rotation in 90 degree flexion in risedronate group 17.666±5.832 and in non interventional group was 12.333±6.121 with p value < 0.001 (Table-4). Patient taking risedronate has better sphericity so the improvement in internal rotation in 90 degree flexion is more in this group which is statistically significant. External rotation in resedronate group at first visit was 23.166±6.628 and non interventional group was 22.000±6.102 with p value 0.481. At the end of two years internal rotation in risedronate group 32.00±3.850 and in non interventional group was 25.166±5.795 with p value < 0.001. Patient taking risedronate has better sphericity so the improvement in external rotation is more in this group which is statistically significant.

DISCUSSION

For the past many years it was thought that treatment should be aimed at preventing weight bearing as weight transferred through avascular head would lead to increased head deformity. However, the validity of the above concept is not yet proven. As the goal of Perthes' disease treatment is to prevent deformation of femoral head, it becomes very important to start the treatment before any complication develops. Containment should be achieved before the disease progresses to the stage of late fragmentation (stage IIb) or early stage of regeneration (stage IIIa).In our study we have chosen patients in early stage with Herrings lateral pillar A or B. Deformation of avascular femoral head occurs due to weakening of bones mediated by osteoclasts. Hence, the use of bisphosphonates in perthes disease leads to reduced bone resorption and preservation of femoral head roundedness

We have done extensive search in the literature and couldn't get much data on use of bisphosphonate in perthes disease. Two major studies have shown the effect of bisphosphonates, one is a large animal study and another is on children.

Little, David G *et al*. (2007) did a large animal piglet study and found better preservation of the femoral head shape with systemic and local bisphosphonate administration, and stated "if the goal of treatment is to prevent deformity, then the window of therapy may be limited to an early stage of the disease before the significant collapse of the head". In their study they did a histomorphometric assessment that revealed changes in the trabecular bone volume, trabecular number, and separation were preserved in the femoral heads of the animals treated with prophylactic and postischemic doses of ibandronate compared with the animals that received saline only (P<0.05).

Several experimental studies suggest ischemic necrosis of the immature femoral head produces mechanical weakening of the cartilage and bone. The likelihood of bisphosphonates therapy to have an immediate effect on restoring the mechanical

properties of the necrotic femoral head is small as this restoration depends on new bone formation that occurs over time. Since the healing process can be prolonged, especially in older patients with LCPD, a treatment regimen that combines protected weightbearing with a biologic agent to control bone resorption and formation may offer the best solution to avoiding mechanical collapse and ensuring good long-term results.

Three Level IV clinical studies met there inclusion criteria. Only one study initiated BP therapy during the precollapsed stage of osteonecrosis and reported prevention of femoral head deformity in nine of 17 patients. All studies noted subjective improvements of pain and gait in patients treated with intravenous bisphosphonates. Of the eight experimental studies reviewed, seven reported reduced femoral head deformity and six found better preservation of trabecular framework.

Ramchandran*et al*. (2007) evaluated bisphosphonate therapy for femoral head osteonecrosis following trauma in adolescents. They established a protocol for identifying adolescents with osteonecrosis of the femoral head with use of bone scans immediately after surgical treatment of hips at risk for the development of osteonecrosis following trauma. In a consecutive group of twenty-eight patients with an unstable slipped capital femoral epiphysis (twenty-two patients), femoral neck fracture (four), or traumatic hip dislocation (two), seventeen patients with osteonecrosis were identified. These patients received treatment with intravenous bisphosphonates. The average duration of the bisphosphonate treatment was 20.3 months. All patients were followed clinically and radiographically for a minimum of two years.

After a mean duration of follow-up of 38.7 months, fourteen patients were pain-free. Clinically, all seventeen patients had a good or excellent outcome. On the average, the Harris hip score was 91.2 points. They concluded Bisphosphonate therapy may play an adjunctive role in the treatment of adolescents with osteonecrosis of the femoral head following trauma. Bisphosphonates are available in both oral and injectable forms.We, in our study, we have used Risedronate 35 mg weekly preparation and followed our patients at scheduled intervals and noted down the data for our study. After completion of the study, we applied statistics and derived our results which is as given below.

We have found a good clinical outcome of Perthes disease at the end of two years. Patients taking oral risedronate had a statistically significant difference in Deformity index and range of motion, VAS score was minimally affected by risedronate. Deformity index at the end of treatment in risedronate group was 0.3083±0.168 and in non interventional group was 4.303±0.157 with p value< 0.005 that signifies definite improvement in deformity index. Sphericity of the head is definitely preserved and improved with the use of risedronate.

There has not been any similar study previously regarding Perthes disease and use of oral bisphosphonate. This study has been undertaken for the first time. In our patients there is significant improvement in hip range of motion in patients taking oral bisphosphonate in comparison to those taking standard care only. VAS score is not affected much with the use of this drug. There is a natural course of perthes disease where with the passage of time improvement in symptoms occurs. Pain is not a significant feature of perthes disease and pain improves with the time.

None of our patients have developed any bisphosphonate related complications. Osteonecrosis of jaw is a well-known complication of bisphosphonates, especially in patients taking bisphosphonates in cancer treatment and those having recent tooth extraction. To date, no reported cases have occurred in children Little, David G *et al*. (2007). In our study none of the patients developed any of the bisphosphonate related complications.

Zeitlin*et al*. (2003) have documented increased height in children with OsteogenesisImperfecta after 4 years therapy with pamidronate. In a cohort of children treated for fibrous dysplasia with pamidronate, growth was normal after 1 to 9 years of treatment. A recent review of patients with osteonecrosis and LCPD treated with bisphosphonates noted maintenance of height Z scores. The impairment in longitudinal growth seen in some rapidly growing animals has not been seen in studies of children on bisphosphonates. Out of these previous studies none of the studies have shown any serious drug related side effects on children. Bisphosphonates are relatively safer in children in comparison to adults and old age patients.

CONCLUSION

This is an important study towards improving the treatment protocol of Perthes disease with the hope of proving the efficacy, safety and outcome of bisphosphonates in a randomised controlled group of patients, and can be used as an effective treatment in Perthes disease. Deformity index (DI) at 24 months is the primary outcome measure. Deformity index is a tool developed specifically for the assessment of femoral head roundness in unilateral Perthes disease using an AP radiograph of the pelvis, the DI compares the affected hip to the unaffected side, providing a continuous variable that correlates well with long-term outcome using the Stulberg classification, the standard measure of femoral head shape at skeletal maturity.

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