

# Do bisphosphonates alter the clinico-radiological profile of children with Perthes disease? A systematic review and meta-analysis

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**Abstract.** – This meta-analysis is aimed to analyze the efficacy of bisphosphonates in the management of Perthes disease. A total of 8 animal and 7 human studies have been shortlisted for this analysis. In human studies, common variables for pain, Harris Hip Score (HHS), propensity for femoral head collapse, and total hip arthroplasty (THA), were assessed. In contrast, in animal studies, the data was recorded for epiphyseal quotient, trabecular volume, trabecular separation, trabecular thickness, and trabecular number. Meta-analysis of human studies on ONFH (Osteo-Necrosis of Femoral Head) revealed a statistically significant outcome in HHS [ $p < 0.001$ ; (95% CI: 4.79 – 8.87)], collapse of the femoral head [ $p = 0.079$ ; (95% CI: -0.16 – -0.01)], and THA [ $p = 0.002$ ; (95% CI: -0.19 – -0.04)] whereas the pain score showed an insignificant outcome [ $p = 0.067$ ; (95% CI: -0.62 – 0.04)]. The meta-analysis of selected variables in animal studies revealed a noteworthy outcome in bone volume ( $p < 0.001$ , 95% CI), trabecular number ( $p < 0.001$ , 95% CI), trabecular thickness ( $p < 0.013$ , 95% CI) and trabecular separation ( $p < 0.026$ , 95% CI) but not in epiphyseal quotient. Further, analysis of stratified datasets in animal studies revealed a contradictory outcome with significant observations described later in the paper. The use of bisphosphonates holds a promising treatment option in Perthes disease. Although, good quality RCTs are needed to validate it further.

*Key Words:*

Bisphosphonates, Legg-calve-perthes disease, Femur head.

## Introduction

Although being an age-old disease, Perthes disease or osteonecrosis of the femoral capital epiphysis still represents a challenge for the Pae-

diatric Orthopaedic surgeons<sup>1-5</sup>. It is a juvenile form of idiopathic osteonecrosis of the femoral head (ONFH). The uncoupling of the process of osteoblastic and osteoclastic activity leading to imbalance has been identified by numerous investigators as a potential target to address the issue, which could also help prevent deformity of the femoral head and alter the natural history of the disease. Several modalities are used to treat Perthes disease, including plaster cast, varus osteotomy and shelf acetabuloplasty. All of them aim to contain the soft femoral head within the acetabulum when it is most vulnerable. However, they are not designed to prevent the collapse of the femoral head due to increased osteoclastic activity<sup>6</sup>.

The current management to treat this condition by biological agents target the imbalance between excessive bone resorption and decreased bone formation. It has been hypothesized that these agents will reduce the osteoclastic activity, preserve the trabecular scaffold, and prevent the collapse of the femoral head. The trabecular scaffold, in turn, will provide channels for new bone formation to occur. Given this, various studies<sup>7-11</sup> have been conducted using bisphosphonates (BPs) in experimental models of ischaemic necrosis and adult cases having ONFH. The studies hypothesized that these agents would reduce the osteoclastic activity, thus favouring the osteoblastic activity.

The use of bisphosphonates to prevent the progression of the deformity and improve outcomes in patients with idiopathic aseptic ischaemic necrosis of femoral epiphysis in children is relatively new. Clinical evidence for their use in Perthes disease is limited. Therefore, a critical

appraisal of the available evidence in literature is essential before their use can be included in clinical practice. The present study aimed to analyze the efficacy of bisphosphonates in the management of Perthes disease.

## Materials and Methods

The search protocol for this meta-analysis was developed on July 20, 2019, as per the **PRI-SMA guidelines** and registered in the international prospective register of systematic reviews (PROSPERO-CRD42020165701) database. An electronic search was conducted online using appropriate search items/ keywords/Medical Search Headings (MeSH): Perthes or Perthes disease or Leg calve Perthes disease or Femoral head osteonecrosis or idiopathic osteonecrosis of the femoral head or idiopathic ischemic osteonecrosis of the femoral head or ischemic necrosis AND Bisphosphonates or Ibandronate or Diphosphonates or Alendronates or Risedronates or Zoledronic acid or Denosumab or Clodronate or Pamidronate, in all fields. A detailed search was performed in the following database: Medline/EMBASE/ PubMed/ Cochrane Library and Clinical Key (1995-2018). Additionally, a manual check was also performed for the reference lists of the retrieved papers. The two investigators independently identified all the possible studies which qualified for being included in the study. Any differences between them were resolved by discussion. The papers on human studies were evaluated for their quality by Modified Jaddad Score. Papers with scores of  $>4$  were considered good quality and were included for meta-analysis. The animal studies were also assessed for their quality.

### Study Selection

A total of 697 potentially relevant articles were found in the databases, and 03 were included from other sources. After the removal of duplicity, a total of 175 articles remained. After going through the title and abstracts of these studies, 146 articles were excluded due to irrelevant studies and 29 articles were selected for the further review process. Furthermore, 14 more studies were excluded because of the following reasons: no controls- 4; no relevant data- 4; review articles-4; mature ONFH model-2. The remaining 15 articles, including 08 animal and 07 human studies, were selected for meta-analysis (Figure 1).

### Data Collection and Extraction

In both the groups (animal and human studies), studies that were shortlisted for analysis were searched for similar variables (viz., study design, study period, study arm/drugs, the aim of the study, age of cases, route and dose of drug administration) and the outcomes (loss of follow-up, potential bias/ complications, limitation) noted (Tables I and II).

#### For animal studies

Data for statistical analysis were extracted and recorded under the following headings: mean epiphyseal quotients (EQ), trabecular bone volume (TV), trabecular separation (TS), trabecular thickness (TT), and trabecular number (TN). Due to the lack of relevant studies, data were also extracted from the studies having more than two study arms. The animal studies, based on their control groups, were further stratified into three groups viz., (A) experimental vs normal (control), (B) experimental vs saline (control) and (C) experimental vs untreated (control), to achieve a more homogenous data set for meta-analysis.

#### For human studies

Data for statistical analysis were extracted and evaluated for Pain score, Harris Hip Score, Femoral head collapse (FHC) and Total Hip Arthroplasty (THA). Based on treatment modalities, these studies were further re-analyzed by excluding the studies that had used other modalities in addition to bisphosphonates in the treatment group and thus creating a new group (Group-I) in order to achieve a more homogenous data set for meta-analysis.

### Statistical Analysis

This meta-analysis was conducted using MS-Excel. We analyzed the pooled results of the treated group with untreated, normal and saline groups for the animal studies. The proportion difference was used to measure the dichotomous outcomes, while the mean difference was used to analyze continuous outcomes, both with 95% confidence intervals (CI). Heterogeneity of the data was tested using  $\tau^2$  statistics, and a fixed or random-effect model was applied for meta-analysis. Publication bias was measured using Eggar's test by taking weighted and non-weighted mean differences as dependent variables.

**Table I.** Summary of the basic information of the included studies.

Author (year)	Country	Study design	Study model	Study Group			Control Group			Study duration
				n/hips	Age	Sex, M/F	n/hips	Age	Sex, M/F	
<b>ANIMAL STUDIES</b>										
Aruwajoye et al (2016) <sup>19</sup>	USA	Experimental	Piglet	10	5-8 w	Male	10	5-8 w	Male	8 weeks
Zou et al (2015) <sup>22</sup>	USA	Experimental (pilot study)	Piglet	6	2-3 w	Male	9	2-3 w	Male	6 weeks
Kim et al (2014) <sup>21</sup>	USA	Experimental	Piglet	6	6-8 w	Male	6	6-8 w	Male	8 weeks
Cheng et al (2014) <sup>20</sup>	Australia	Experimental (pilot study)	Piglet	4	6-8 w	Male	4	6-8 w	Male	8 weeks
Vandermeer et al (2011) <sup>23</sup>	USA	Experimental	Piglet	5	6-8 w	Male	5	6-8 w	Male	8 weeks
Aya-ay et al (2007) <sup>18</sup>	Germany	Experimental	Piglet	5	6-9 w	Male	4	6-9 w	Male	7 weeks
Kim et al (2005) <sup>6</sup>	USA	Experimental	Piglet	8	4-5 w	Male	8	4-5 w	Male	8 weeks
Little et al (2005) <sup>8</sup>	Australia	Experimental	Rat	16	14 w	Female	8	14 w	Female	6 weeks
<b>CLINICAL STUDY</b>										
*Jamil et al (2017) <sup>12</sup>	Australia	Multicentric RCT (Open-label)	Human	50/50	5-16	NR	50/50	5-16	NR	24 <sup>th</sup> month
Lee et al (2015) <sup>15</sup>	Korea	Multicentric RCT (Prospective, Level I)	Human	55/55	43.8±11.8 y	39/1	55/55	45.2±11.6	41/1	24 weeks
Kang et al (2012) <sup>14</sup>	China	Pilot study	Human	39/55	SG-43.8	6	40/52	45.3	4	63 weeks
Chen et al (2012) <sup>12</sup>	Taiwan	Multicenter, Prospective, Double-Blind-RCT	Human	26/32	48.4±11.4 y	22/4	26/33	44.2±9.2	19/7	24 weeks
Wang et al (2008) <sup>17</sup>	Taiwan	Prospective study	Human	23/30	35.7±4.7 y	13/10	25/30	38.6±12.6	20/5	25 weeks
Nishii et al (2006) <sup>16</sup>	Japan	Therapeutic study, (prospective comparative study, (Level-II)	Human	14/20	48 y	7/7	7/7	36	7/1	12 weeks
Lai et al (2005) <sup>11</sup>	Taiwan	Randomised control trial (Level-I)	Human	20/29	42.6 y	NR	20/25	42.4	NR	24 weeks

\*Perthes disease.

## Results

A total of 15 articles, including 08 animal and 07 human studies, were selected after a systematic review for meta-analysis (Figure 1). The median quality score of the reported animal studies was 4 (range, 3-5, Coefficient of variation- 13.36%), while the median of modified Jadad score of the clinical studies was 6 (range, 4-7, Coefficient of

variation-19.47%) ([Supplementary Materials](#)). No publication bias was observed in the human and animal studies as per Egger's test.

### Meta-Analysis of Study Variables

#### Epiphyseal quotient (%)

Meta-analysis of pooled data for analysis of EQ revealed that the positivity of effect size was

statistically significant ( $p=0.890$ ), whereas the meta-analysis of pooled data of stratified groups revealed a statistically significant result in all the groups [Group A (Experimental vs. Normal Group) -  $p=0.025$ ; Group B (Experimental vs. Saline Group) -  $p=0.012$ ; Group C (Experimental vs. Un-treated Group) -  $p=0.029$ ] (Figure 2 and Figure 3).

**Bone volume (%)**

Meta-analysis of pooled data for analysis of BV revealed that the positivity of effect size was statistically significant ( $p<0.001$ ). In contrast, the meta-analysis of pooled data of stratified groups revealed an insignificant result in Group A subjects ( $p=0.738$ ), but the results were statistically significant in the other two groups [Group B -  $p<0.001$ ; Group C -  $p<0.001$ ] (Figures 4 and 5).

**Trabecular number ( $mm^2$ )**

Meta-analysis of pooled data for analysis of TN revealed that the positivity of effect size was statistically significant ( $p<0.001$ ). In contrast, the meta-analysis of pooled data of stratified groups revealed an insignificant result in Group A subjects ( $p=0.515$ ), but the results were statistically significant in Group B subjects ( $p<0.001$ ). Analysis of Group C subjects could not be done as there was only one study in this group (Figure 6 and Figure 7).

**Trabecular thickness ( $\mu m$ )**

Meta-analysis of pooled data for analysis of TT revealed that the positivity of effect size was statistically significant ( $p=0.013$ ). In contrast, the meta-analysis of pooled data of stratified groups revealed an insignificant result in Group B subjects ( $p=0.200$ ), but the results were statistically signif-

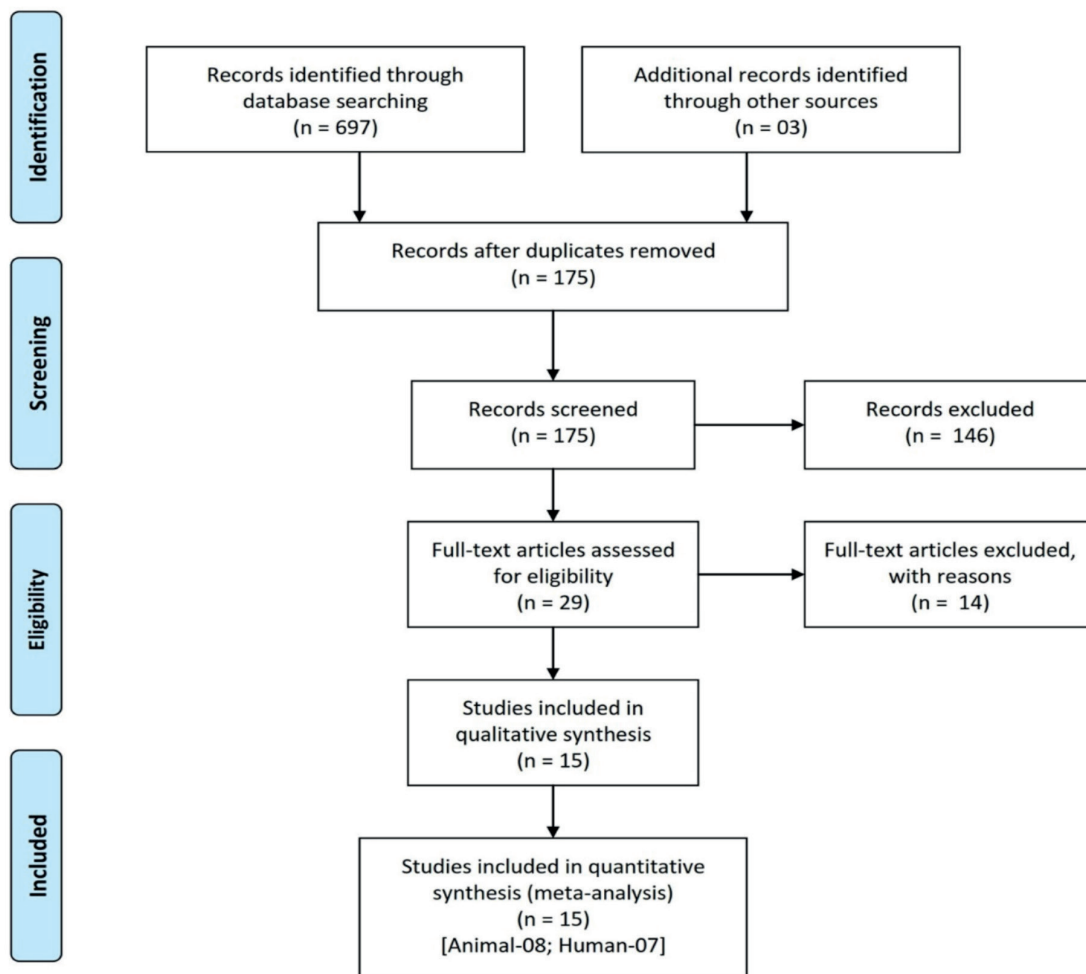


Figure 1. Flowchart of study selection.

[Epiphyseal Quotient] Study or subgroup	Experimental			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
Aya-ay J 2007 (280µg IB Vs Normal)	0.25	0.16	5	0.06	0.11	4	1.988	0.190	-0.010	0.390
Aya-ay J 2007 (560µg IB Vs Normal)	0.39	0.09	5	0.06	0.11	4	3.424	0.330	0.177	0.483
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	0.39	0.09	8	0.48	0.02	8	0.002	-9.200	-0.16	-0.028
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	0.39	0.09	8	0.28	0.10	8	0.001	0.11	-0.01	0.217
Kim HK 2014 (BMP+IB Treated Vs No Treatment)	0.44	0.06	6	0.39	0.06	6	14.406	0.050	-0.024	0.124
Kim HK 2014 (BMP+IB Treated Vs Normal)	0.44	0.06	6	0.49	0.02	6	25.931	-0.050	-0.105	0.005
Little DG 2005 (Weekly Treated Vs Saline)	0.47	4.20	40	0.44	3.23	40	0.029	0.030	-1.633	1.693
Little DG 2005 (Monthly Treated Vs Saline)	0.49	4.20	40	0.44	3.23	40	0.029	0.050	-1.613	1.713
Vandermeer JS 2011 (IB Treated Vs Saline)	0.37	0.03	5	0.29	0.11	5	6.383	0.080	-0.032	0.192
Vandermeer JS 2011 (IB+BMP-2 Treated Vs Normal)	0.44	0.03	6	0.47	0.04	6	41.490	-0.030	-0.074	0.014
Zou Y 2015 (Clod (IB) Treated Vs Normal)	0.22	0.12	3	0.43	0.03	3	2.937	-0.205	-0.370	-0.040
Zou Y 2015 (Clod+Sim (IB+BMP) Treated Vs Untreated)	0.39	0.05	3	0.21	0.10	3	3.428	0.177	0.025	0.329
Heterogeneity ( $\tau^2$ ) = 0, $I^2$ = 0.0 %; Test for overall effect $z = 0.138$ , $p = 0.890$							Overall	0.002	-0.026	0.030

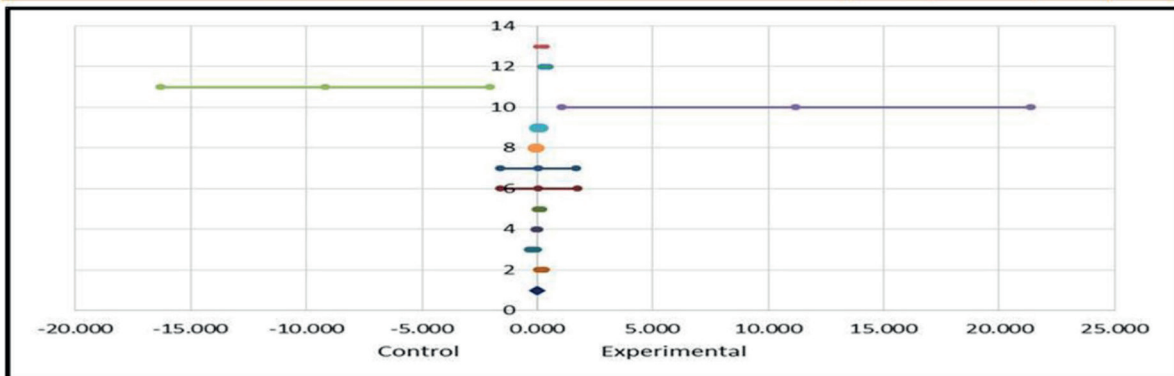


Figure 2. Forest plot of Epiphyseal Quotient.

icant in the other two groups [Group A –  $p=0.001$ ; Group C –  $p=0.008$ ] (Figures 8 and 9).

#### Trabecular separation ( $\mu\text{m}$ )

Meta-analysis of pooled data for analysis of TN revealed that the positivity of effect size was statistically significant ( $p=0.026$ ). The meta-analysis of pooled data of stratified groups had similar findings, with statistically significant Group A ( $p=0.036$ ) and Group B ( $p=0.017$ ) dataset results. Analysis of Group C subjects could not be done due to a single study in this group (Figures 10 and 11).

#### Human Studies

##### Meta-analysis of pain score

The meta-analysis of selected human studies showed that the overall effect size (mean difference) of the treatment group compared to control was  $-0.29$  (95% CI:  $-0.62 - 0.04$ ). The negativity of the effect size was not found to be statistically significant ( $p=0.086$ ). The meta-analysis of pooled data of Group-I subjects continued to show insignificant results ( $p=0.067$ ) (Figures 12 and 12A).

Epiphyseal Quotient (Experimental Versus Control) Study or subgroup	Wt%	Mean Diff	95% CI	
			Lower	Upper
Aya-ay J 2007 (280µg IB Vs Normal)	2.173	0.190	-0.010	0.390
Aya-ay J 2007 (560µg IB Vs Normal)	3.743	0.330	0.177	0.483
Cheng TL 2014	2.012	0.130	-0.020	0.214
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	17.184	-0.092	-0.163	-0.021
Kim HK 2014 (BMP+IB Treated Vs Normal)	28.342	-0.050	-0.105	0.005
Vandermeer JS 2011 (IB+BMP-2 Treated Vs Normal)	45.347	-0.030	-0.074	0.014
Zou Y 2015 (Clod (IB) Treated Vs Normal)	3.210	-0.205	-0.370	-0.040
<b>Heterogeneity (<math>\tau^2</math>) = 0, <math>I^2</math> = 0.0 % Test for overall effect <math>z = 2.24</math>, <math>p=0.025</math></b>	<b>Overall</b>	<b>-0.034</b>	<b>-0.063</b>	<b>-0.004</b>

Epiphyseal Quotient (Experimental Versus Saline) Study or subgroup	Wt%	Mean Diff	95% CI	
			Lower	Upper
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	38.829	0.112	0.010	0.214
Little DG 2005 (Weekly Treated Vs Saline)	14.511	0.030	-0.136	0.196
Little DG 2005 (Monthly Treated Vs Saline)	14.511	0.050	-0.116	0.216
Vandermeer JS 2011 (IB Treated Vs Saline)	32.149	0.080	-0.032	0.192
<b>Heterogeneity (<math>\tau^2</math>) = 0, <math>I^2</math> = 0.0 % Test for overall effect <math>z = 2.50</math>, <math>p=0.012</math></b>	<b>Overall</b>	<b>0.081</b>	<b>0.017</b>	<b>0.144</b>

Epiphyseal Quotient (Experimental Versus Untreated) Study or subgroup	Wt%	Mean Diff	95% CI	
			Lower	Upper
Kim HK 2014 (BMP+IB Treated Vs No Treatment)	80.780	0.050	-0.024	0.124
Zou Y 2015 (Clod+Sim (IB+BMP) Treated Vs Untreated)	19.221	0.177	0.025	0.329
<b>Heterogeneity (<math>\tau^2</math>) = 0, <math>I^2</math> = 0.0 % Test for overall effect <math>z = 2.18</math>, <math>p=0.029</math></b>	<b>Overall</b>	<b>0.074</b>	<b>0.008</b>	<b>0.141</b>

Figure 3. Forest plot of Epiphyseal Quotient in stratified groups.

#### Meta-Analysis of Harris Hip Score (HHS)

The meta-analysis of pooled data for HHS showed that the overall effect size (mean difference) of the treatment group compared to control was 6.83 (95% CI: 4.79 – 8.87). The positivity of the effect size was found to be statistically significant ( $p < 0.001$ ). The meta-analysis of pooled data of Group-I continued to show significant results ( $p < 0.001$ ) (Figures 13 and 13A).

#### Meta-analysis of collapse of the femoral head

The meta-analysis of pooled data for analyzing the collapse of the femoral head showed that the overall effect size (mean difference) of the treatment group compared to control was -0.07 (95% CI: -0.16 – 0.01). The negativity of the effect size was not found to be statistically significant ( $p = 0.079$ ). The meta-analysis of pooled data of Group-I continued to show

insignificant results ( $p=0.186$ ) (Figure 14 and 14a).

*Meta-analysis of patients undergoing total hip arthroplasty (THA)*

The meta-analysis of pooled data for THA patients showed that the overall effect size (mean difference) of the treatment group compared to control was  $-0.12$  (95% CI:  $-0.19 - -0.04$ ). The negativity of the effect size was found to be statistically significant ( $p=0.002$ ). The meta-analysis

of pooled data of Group-I continued to show significant results ( $p<0.001$ ) (Figure 15 and Figure 15A).

**Discussion**

There is plenty of literature emphasizing bisphosphonates in treating Perthes disease in experimental models and adult ONFH. To date, there has been no proven medical treatment,

**Table II.** Detail information about treatments given in the studies.

Author	Kind of ONFH/Perthes	[Study Arm] Drugs	Dosage	Route	Study Period
<b>ANIMAL STUDIES</b>					
Aruwajoye et al (2016) <sup>19</sup>	Traumatic	[5] Ibandronate vs placebo BMP+Ibandronate vs BMP Zoledronic acid vs placebo	0.6 mg, once	Intraosseous	8 weeks
Zou et al (2015) <sup>22</sup>	Traumatic	[4] Clodronate vs Placebo Clodronate+ Sim vs Sim	2.2 mg, once	Intraosseous	6 weeks
Kim et al (2014) <sup>21</sup>	Traumatic	[2] Ibandronate+ BMP vs BMP	0.6 mg, once	Intraosseous	8 weeks
Cheng et al (2014) <sup>20</sup>	Traumatic	[2] Zoledronic+BMP vs BMP	0.25 mg, once	Intraosseous	8 weeks
Vandermeer et al (2011) <sup>23</sup>	Traumatic	[2] Ibandronate vs Placebo	0.56 mg, once	Intraosseous	8 weeks
Aya-ay et al (2007) <sup>18</sup>	Traumatic	[2] Ibandronate vs Placebo	0.28 mg or 0.56 mg, once	Intraosseous	7 weeks
Kim et al (2005) <sup>6</sup>	Traumatic	[2] Ibandronate vs Placebo	44.4 µg/kg, 3 × per/w × 6 w	Intraosseous	8 weeks
Little et al (2005) <sup>8</sup>	Traumatic	[2] Zoledronic acid vs placebo	0.1 mg/kg/w × 3 w	Subcutaneous	6 weeks
<b>CLINICAL STUDIES</b>					
*Jamil et al (2017) <sup>12</sup>	--	[2] Zoledronic acid + vit-D vs vit D	0.025 mg/kg at a 3-monthly interval for five doses	Intravenous	24th month.
Lee et al (2015) <sup>15</sup>	Alcohol,steroid, Idiopathic	[2] Zoledronate+Ca+vitD vs Placebo+Ca+vit D	5 mg/year for 2 year	Intraosseous	24 weeks
Kang et al (2012) <sup>14</sup>	Alcohol,steroid, Idiopathic	[2] Alendronate+MD(Multiple drilling)+Ca+vitD vs Placebo+MD+Ca+vit D	10 mg/day or 70 mg/w for 24 weeks	Oral	63 weeks
Chen et al (2012) <sup>13</sup>	Alcohol, steroid	[2] Alendronate +Ca+vitD vs placebo +Ca+vit D	70 mg/w for 2 year	Oral	24 weeks
Wang et al (2008) <sup>17</sup>	Alcohol, steroid	[2] ESWT+Alendronate vs ESWT	70 mg/w for 1 year	Oral	25 weeks
Nishii et al (2006) <sup>16</sup>	Alcohol,steroid, Idiopathic	[2] Alendronate vs placebo	5 mg/day for 1 year	Oral	12 weeks
Lai et al (2005) <sup>11</sup>	Alcohol,steroid, Idiopathic	[2] Alendronate vs placebo	70 mg/w for 25 week	Oral	24 weeks

which could alter the natural history of the disease and prevent future deformity and complications. The current review was executed to know whether bisphosphonates could represent a valid medical treatment option for such patients. We chose to review the studies analyzing the role of bisphosphonates, taking advantage of the fact that the basic pathophysiology or the critical culprit of this disease is well known (i.e., disruption of the vascularity to the femoral head leading to pathological and structural changes in the growing femoral head). However, the exact aetiology remains unsubstantiated. Bisphosphonate group of drugs (especially nitrogen-containing) can inhibit

osteoclastic bone resorption. In addition to their inhibitory effect on osteoclasts, they appear to have a beneficial effect on osteoblasts.

In a detailed literature search, we could find only one human study in the paediatric age group (that too an ongoing study). So, considering the similar underlying pathology of Perthes disease and adult ONFH, we planned to include both Perthes and ONFH related clinical studies for further analysis as per the PRISMA guideline (PRISMA checklist). We also came across a meta-analysis published in the year 2017<sup>12</sup>, analysing the efficacy of bisphosphonates in femoral head osteonecrosis.

[Bone Volume] Study or subgroup	Experimental			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
Aruwajiye OO 2016 (IB Treated Vs Normal)	1.40	1.40	5	2.20	0.70	5	34.396	-0.800	-2.334	0.734
Aruwajiye OO 2016 (IB+BMP Treated Vs Untreated)	3.40	1.60	5	0.48	0.40	5	30.982	2.920	1.304	4.536
Aya-ay 2007 (560µg IB Treated Vs Normal)	19.60	9.70	5	20.30	1.40	4	0.871	-0.700	-10.337	8.937
Aya-ay 2007 (560µg IB Treated Vs Saline)	19.60	9.70	5	4.50	4.20	4	0.717	15.100	4.472	25.728
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	13.70	5.80	8	19.70	1.30	8	4.174	-6.000	-10.403	-1.597
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	13.70	5.80	8	7.10	3.90	8	3.019	6.600	1.422	11.778
Kim HK 2014 (BMP+IB Treated Vs No Treatment)	19.70	6.50	6	3.30	1.70	6	2.334	16.400	10.511	22.289
Kim HK 2014 (BMP+IB Treated Vs Normal)	19.70	6.50	6	16.90	1.90	6	2.297	2.800	-3.136	8.736
Little DG 2005 (Weekly Treated Vs Saline)	69.20	8.60	40	62.80	8.50	40	5.620	6.400	2.605	10.195
Little DG 2005 (Monthly Treated Vs Saline)	69.90	8.40	40	62.80	8.50	40	5.753	7.100	3.349	10.851
Vandermeer JS 2011 (IB Treated Vs Saline)	19.60	9.70	5	5.60	3.20	5	0.808	14.000	3.990	24.010
Vandermeer JS 2011 (IB+BMP-2 Treated Vs Normal)	28.00	3.30	6	21.40	1.30	6	8.373	6.600	3.491	9.709
Zou Y 2015 (Clod (IB) Treated Vs Normal)	47.85	17.00	3	31.08	3.00	3	0.141	16.770	-7.155	40.695
Zou Y 2015 (Clod+Sim (IB+BMP) Treated Vs Untreated)	34.40	1.00	3	45.61	9.00	3	0.514	-11.210	-23.760	1.340
Heterogeneity ( $\tau^2$ ) = 24.38, $I^2$ = 99.31 %; Test for overall effect $z = 5.51$ , $p < 0.001$							Overall	2.527	1.628	3.427

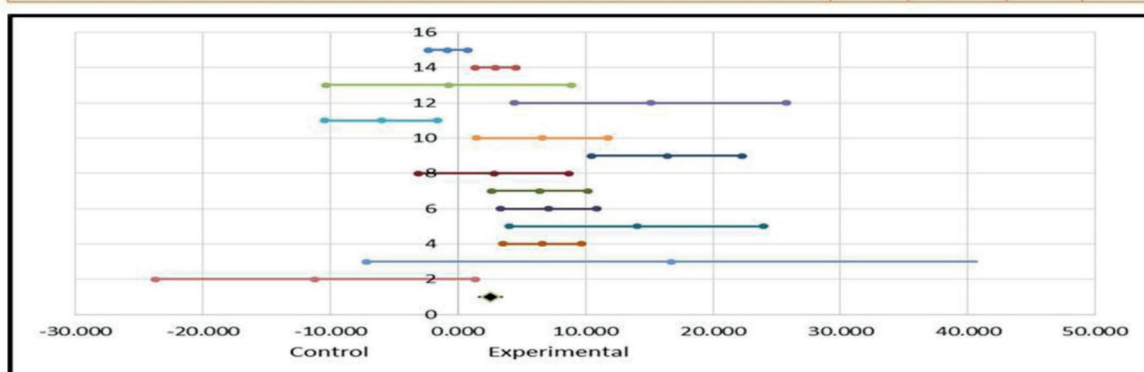


Figure 4. Forest plot of Bone Volume.

Bone Volume (Experimental Versus Control) Study or subgroup	Wt%	Mean Diff	95% CI	
			Lower	Upper
Aruwajiye OO 2016 (IB Treated Vs Normal)	68.455	-0.800	-2.334	0.734
Aya-ay 2007 (560µg IB Treated Vs Normal)	1.734	-0.700	-10.337	8.937
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	8.307	-6.000	-10.403	-1.597
Kim HK 2014 (BMP+IB Treated Vs Normal)	4.571	2.800	-3.136	8.736
Vandermeer JS 2011 (IB+BMP-2 Treated Vs Normal)	16.665	6.600	3.491	9.709
Zou Y 2015 (Clod (IB) Treated Vs Normal)	0.281	16.770	-7.155	40.695
<b>Heterogeneity (<math>\tau^2</math>) = 23.77, <math>I^2</math> = 99.58 % Test for overall effect <math>z</math> = 0.33, <math>p</math>=0.738</b>	<b>Overall</b>	<b>0.217</b>	<b>-1.052</b>	<b>1.486</b>

Bone Volume (Experimental Versus Saline) Study or subgroup	Wt%	Mean Diff	95% CI	
			Lower	Upper
Aya-ay 2007 (560µg IB Treated Vs Saline)	4.502	15.100	4.472	25.728
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	18.967	6.600	1.422	11.778
Little DG 2005 (Weekly Treated Vs Saline)	35.306	6.400	2.605	10.195
Little DG 2005 (Monthly Treated Vs Saline)	36.147	7.100	3.349	10.851
Vandermeer JS 2011 (IB Treated Vs Saline)	5.075	14.000	3.990	24.010
<b>Heterogeneity (<math>\tau^2</math>) = 7.59, <math>I^2</math> = 99.26 % Test for overall effect <math>z</math> = 6.50, <math>p</math>&lt;0.001</b>	<b>Overall</b>	<b>7.468</b>	<b>5.213</b>	<b>9.723</b>

Bone Volume (Experimental Versus Untreated) Study or subgroup	Wt%	Mean Diff	95% CI	
			Lower	Upper
Aruwajiye OO 2016 (IB+BMP Treated Vs Untreated)	98.367	2.920	1.304	4.536
Zou Y 2015 (Clod+Sim (IB+BMP)Treated Vs Untreated)	1.631	-11.210	-23.760	1.340
<b>Heterogeneity (<math>\tau^2</math>) = 99.43, <math>I^2</math> = 99.69 % Test for overall effect <math>z</math> = 3.29, <math>p</math>=0.001</b>	<b>Overall</b>	<b>2.689</b>	<b>1.086</b>	<b>4.292</b>

Figure 5. Forest plot of Bone Volume in stratified groups.

### Meta-Analysis on Human Studies

We were able to narrow down our search to seven studies, out of which one is an ongoing study on Perthes disease<sup>12</sup>, and the remaining six studies are on adult ONFH<sup>11,13-17</sup>. For the meta-analysis, only completed studies of adult ONFH were included. Of these six studies reviewed, four studies were solely based on giving bisphosphonates to cases with idiopathic/non-traumatic osteonecrosis of the femoral head<sup>11,13,15-16</sup>. In contrast, the remaining two studies have given bisphosphonate as an adjuvant to other modalities of treatment<sup>14,17</sup>. Of all the six included studies, oral Alendronate was gi-

ven in all cases except one<sup>15</sup>, where Zolendronate was the test drug. Although being a level-1 study, this study had a weak study design due to its being an open-label study and thus had a drawback of introducing bias in the study. The outcome analysis using Zolendronate in the cases with osteonecrosis of the femoral head revealed that it did not prevent the collapse of the femoral head, and neither did it reduce the need for future THA. The second level 1 study conducted by Chen CH et al<sup>13</sup> had Alendronate as the test drug, which neither showed any advantage in preventing the future need of THA nor any improvement in the quality of life.

Trabecular number (mm <sup>2</sup> ) Study or subgroup	Experimental			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
	Aya-ay 2007 (560µg IB Treated Vs Normal)	2.40	1.10	5	2.60	0.10			4	2.913
Aya-ay 2007 (560µg IB Treated Vs Saline)	2.40	1.10	5	0.60	0.40	4	2.504	1.800	0.631	2.969
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	2.20	0.90	8	2.40	0.30	8	6.930	-0.200	-0.903	0.503
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	2.20	0.90	8	1.20	0.60	8	5.331	1.000	0.199	1.801
Kim HK 2014 (BMP+IB Treated Vs No Treatment)	2.30	0.70	6	0.40	0.20	6	8.405	1.900	1.262	2.538
Kim HK 2014 (BMP+IB Treated Vs Normal)	2.30	0.70	6	2.10	0.20	6	8.405	0.200	-0.438	0.838
Little DG 2005 (Weekly Treated Vs Saline)	12.30	1.70	40	9.00	2.10	40	4.760	3.300	2.452	4.148
Little DG 2005 (Monthly Treated Vs Saline)	13.40	2.70	40	9.00	2.10	40	2.970	4.400	3.326	5.474
Vandermeer JS 2011 (IB Treated Vs Saline)	2.40	1.10	5	1.60	0.70	5	2.096	0.800	-0.478	2.078
Vandermeer JS 2011 (IB+BMP-2 Treated Vs Normal)	2.70	0.20	6	2.60	0.20	6	55.686	0.100	-0.148	0.348
Heterogeneity ( $\tau^2$ ) = 1.64, $I^2$ = 92.36 %; Test for overall effect $z = 6.52, p < 0.001$							Overall	0.615	0.430	0.800

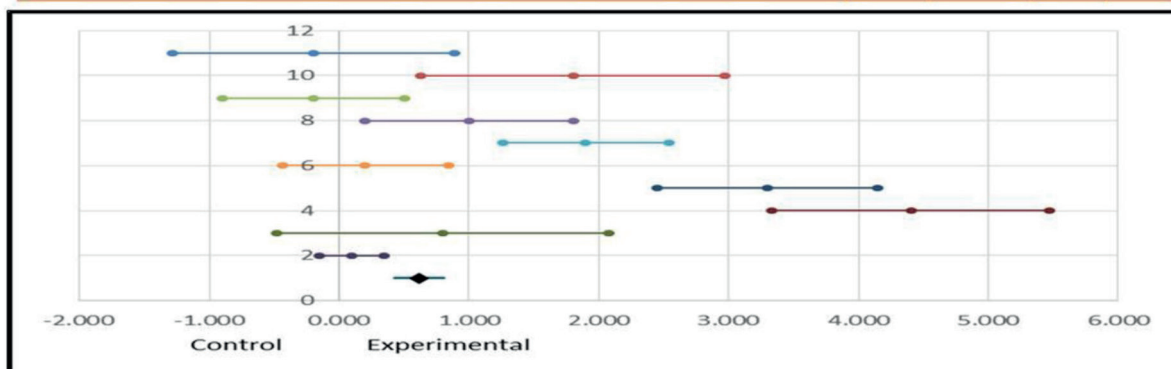


Figure 6. Forest plot of Trabecular Number.

In contrast, the study conducted by Lai et al<sup>11</sup> concluded that Alendronate might help prevent the collapse of the femoral head in hips with Steinberg stage II and III C non-traumatic osteonecrosis. The major limitation in both the above studies was the small sample size and short follow-up, leading to inefficacy to determine the effect of confounding risk factors. The study conducted by Nishii et al<sup>16</sup> was a level 2 study with small sample size and short follow up. This study suggests Alendronate as a potential drug in preventing the collapse of the femoral head. With meagre follow-up data, it is unwise to comment on the efficacy of bisphosphonate, if any, in delaying or preventing the collapse of the femoral head.

The two other studies by Wang et al<sup>17</sup> and Kang et al<sup>14</sup> focussed on using Alendronate and another modality of treatment to treat cases with osteonecrosis of the femoral head. One of them used multiple drilling in addition to Alendronate therapy, with the conclusion favouring the combined treatment modality in reducing pain and delaying the progression of the early stage of the disease<sup>14</sup>. This study simultaneously emphasised the ineptitude of the combination therapy to prevent it. In contrast, the other study by Wang et al<sup>17</sup> used Alendronate in addition to ECSWT (Extra Corporeal Short Wave Therapy) and found no difference in outcomes of either group in the early stages of the disease. Data were extracted for meta-analysis on human cli-

anical studies on adult ONFH. They were evaluated for pain score, HHS, the future propensity of femoral head collapse and future total hip arthroplasty (THA). The analysis revealed statistically significant results having improved HHS [ $p < 0.001$ ; case/controls = 163/166 in a total of five studies] and the decreased need for future THA [ $p = 0.002$ ; case/controls = 221/226 in a total of six studies] in the experimental group as compared to the control group. The results obtained through the analysis of pooled data for these variables are subject to the heterogeneity of interventions in the two groups in selected studies. A further analysis was performed on the pooled data obtained from four studies<sup>11,13,15,16</sup>, having only bisphosphonates as the test drug in the experimental group to make the pooled data set more homogenous

concerning the intervention given. Analysis of extracted data revealed statistically significant improvement in HHS [ $p < 0.001$ ; case/controls = 101/101 in a total of three studies] and in future need for THA [ $p < 0.001$ ; case/controls = 113/113 in a total of three studies] whereas there was no statistically significant improvement in the pain score [ $p = 0.067$ ; case/controls = 73/71 in a total of seven studies] and the propensity of future femoral head collapse [ $p = 0.186$ ; case/controls = 81/71 in a total of three studies]. Although the outcomes were similar to those with the previous pooled dataset, the results of clinical trials were contradictory considering statistically insignificant results in the propensity of femoral head collapse and significant need for future THA. There was high heterogeneity in clinical trials allowing the bias to be introduced



Figure 7. Forest plot of Trabecular Number in stratified groups.

Trabecular Thickness (µm) Study or subgroup	Experimental			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
Aya-ay 2007 (560µg IB Treated Vs Normal)	80.00	9.00	5	78.00	5.00	4	7.29	2.000	-8.479	12.479
Aya-ay 2007 (560µg IB Treated Vs Saline)	80.00	9.00	5	51.00	43.00	4	0.33	29.000	-20.452	78.452
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	64.00	15.00	8	85.00	15.80	8	3.07	-21.000	-37.139	-4.861
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	64.00	15.00	8	57.00	16.40	8	2.95	7.000	-9.465	23.465
Kim HK 2014 (BMP+IB Treated Vs No Treatment)	85.90	6.10	6	77.90	3.60	6	20.76	8.000	1.791	14.209
Kim HK 2014 (BMP+IB Treated Vs Normal)	85.90	6.10	6	79.80	3.30	6	21.66	6.100	0.021	12.179
Little DG 2005 (Weekly Treated Vs Saline)	55.20	20.00	40	72.60	16.20	40	12.27	-17.400	-25.478	-9.322
Little DG 2005 (Monthly Treated Vs Saline)	57.80	14.20	40	72.60	16.20	40	17.51	-14.800	-21.561	-8.039
Vandermeer JS 2011 (IB Treated Vs Saline)	80.00	9.30	5	33.10	5.80	5	6.94	46.900	36.159	57.641
Vandermeer JS 2011 (IB+BMP-2 Treated Vs Normal)	103.50	13.10	6	82.30	4.60	6	5.40	21.200	9.030	33.370
Zou Y 2015 (Clod (IB) Treated Vs Normal)	240.00	12.43	3	133.00	17.31	3	0.92	107.000	77.465	136.535
Zou Y 2015 (Clod+Sim (IB+BMP) Treated Vs Untreated)	147.00	12.43	3	133.00	17.31	3	0.92	14.000	-15.535	43.535
Heterogeneity ( $\tau^2$ ) = 454.21, $I^2$ = 99.97 %; Test for overall effect $z = 2.47$ , $p = 0.013$							Overall	3.568	0.739	6.397

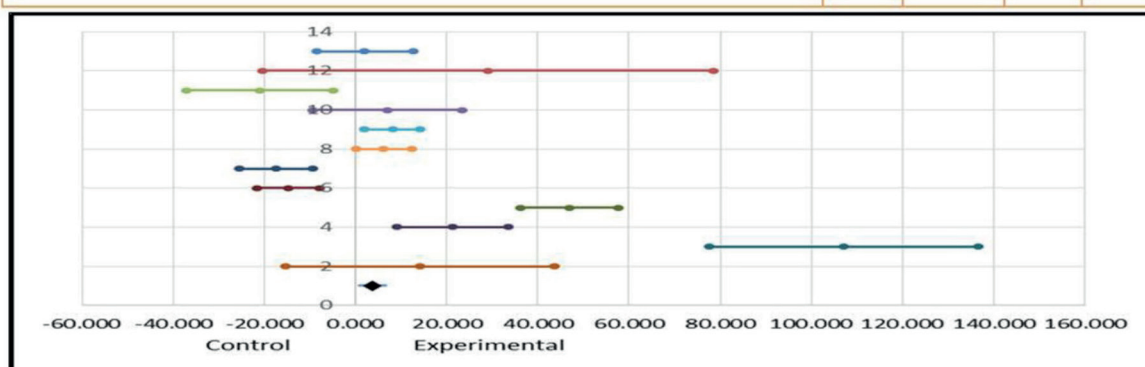


Figure 8. Forest plot of Trabecular Thickness.

at various levels affecting the results obtained, limiting the power of the study and the conclusion drawn. Good clinical outcomes were not reported in any of the studies that could prevent the collapse of the femoral head.

Moreover, there were no significant side effect or complications noted or reported with cases undergoing therapy with bisphosphonate in isolation or combination therapy. Improved clinical outcomes may be more important in short term evaluation. However, the deformity index is an essential long-term entity that entails preventing collapse/ deformity and needs to be considered.

### Meta-Analysis on Animal Studies

We included animal studies in our analyses since there were no completed clinical trials available in the literature on the use of bisphosphonates in Perthe's disease and limited clinical trials were available using bisphosphonates in adult ONFH. In our search of the literature, we retrieved 700 studies from the database. Finally, we were able to narrow down our search to eight studies<sup>6,8,18-23</sup>. The included studies evaluated the effect of bisphosphonates on femoral head sphericity and bone mass of femoral head in experimental models. Seven<sup>6,18-23</sup> out of eight shortlisted studies had piglet as the study model with the in-

traosseous route of test drug administration. The study by Little et al<sup>8</sup> was on rat models, and the route of drug administration was subcutaneous. All the studies were matched for age and sex, with the study duration varying from 6-8 weeks. Four [Kim et al<sup>6</sup> and Little et al<sup>8</sup>, Aya-ay et al<sup>18</sup>, Vandermeer et al<sup>23</sup>] out of eight studies had a similar study design (test drug and placebo). In all these studies, the test drug was Ibandronate, except the study by Little et al<sup>8</sup>, where they used Zolendronate as the test drug. The most noticeable variation in all eight studies was a different dosage regime which posed a significant limitation in the pooling of the data for analysis. Another limitation was that of multiple study arms in a few

studies<sup>19,22</sup> posing difficulties in creating a homogenous pooled data set for analysis. The pooled data results from a meta-analysis on animal studies did not show any significant improvement in epiphyseal quotient (EQ) [ $p=0.890$ ], which is a measure of femoral head sphericity but the bone volume (BV) [ $p<0.001$ ], trabecular number (TN) [ $p<0.001$ ], trabecular thickness (TT) [ $p=0.013$ ] and trabecular separation (TS) [ $p=0.026$ ] which are a measure of bone mass of the femoral head, showed a statistically significant improvement in experimental group cases.

Further, the results obtained on analysing the pooled data set of stratified groups (A, B and C) revealed an antithetic outcome, with EQ having



Figure 9. Forest plot of Trabecular Thickness in stratified groups.

Trabecular Separation (µm) Study or subgroup	Experimental			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
Aya-ay 2007 (560µg IB Treated Vs Normal)	557	646	5	306	12	4	0.32	251.0	-382.2	884.2
Aya-ay 2007 (560µg IB Treated Vs Saline)	557	646	5	1131	215	4	0.28	-574.0	-1252.2	104.2
Kim HK 2005 (Post-Ischemia Treatment Vs Normal)	489	273	8	347	53	8	3.02	142.0	-64.0	348.0
Kim HK 2005 (Post-Ischemia Treatment Vs Saline)	489	273	8	1043	799	8	0.33	-554.0	-1179.5	71.5
Kim HK 2014 (BMP+IB Treated Vs No Treatment)	195.1	46.6	6	222.7	58.8	6	29.61	-27.6	-93.4	38.2
Kim HK 2014 (BMP+IB Treated Vs Normal)	195.1	46.6	6	254.6	23.9	6	60.77	-59.5	-105.4	-13.6
Vandermeer JS 2011 (IB Treated Vs Normal)	557	646	5	303.4	30.1	6	0.32	253.6	-380.0	887.2
Vandermeer JS 2011 (IB Treated Vs Saline)	557	646	5	799.9	348.9	5	0.25	-242.9	-962.4	476.6
Vandermeer JS 2011 (IB Treated vs IB+BMP-2 Treated)	557	646	5	269.8	25.2	6	0.32	287.2	-346.3	920.7
Heterogeneity ( $\tau^2 = 7374.1, I^2 = 99.99\%$ , Test for overall effect $z = 2.22, p = 0.026$ )							Overall	-41.53	-78.20	-4.85

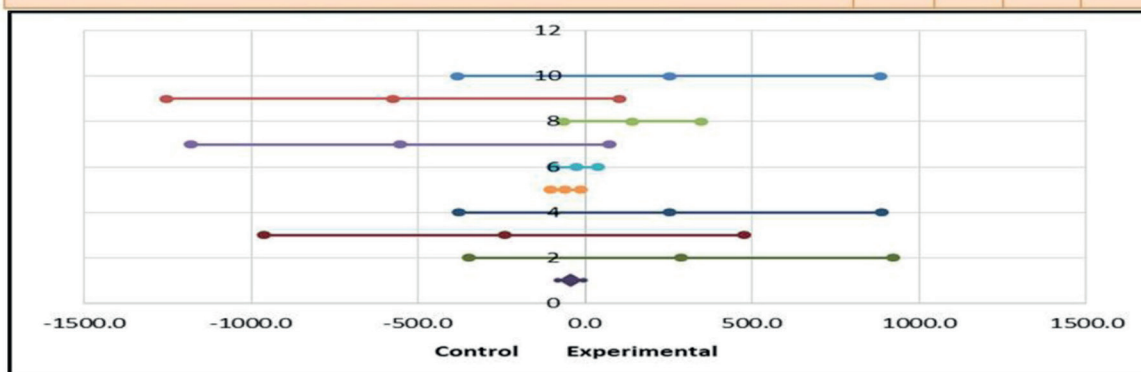


Figure 10. Forest plot of Trabecular Separation.

statistically significant improvement in all the three groups whereas BV and TN showing statistically insignificant improvement in group A and significant in group B and C. There was a statistically significant improvement of TT in group A and C but insignificant in group B. The TS data analysis did not reveal any difference in outcomes compared to that obtained in the previously pooled dataset. This difference in the outcome while analysing animal studies when moving from a heterogenous to a more homogenous dataset signifies the importance of bias limitation. Thus, interpreting the results without having a homogenous dataset would not be wise. Extrapolating the results of animal data to the human population further poses a significant limitation.

The results of animal trials and clinical trials were somewhat discordant. The above findings could be attributed to no measures taken for bias limitation in animal studies. The improvement in healing of osteonecrosis as depicted by

the chosen parameters in animal models cannot be extrapolated to the adult population. The healing response may be limited or different due to differences in drug administration routes. One another important point to consider is that animals and human beings show different sensitivity to bisphosphonates. Although there were significant improvements in most of the parameters chosen for analysis in an animal model but based on outcomes alone, the decision to use bisphosphonates to treat ONFH in humans is still a complex judgement to make.

Meta-analysis in the literature says that surgical treatment is a modality associated with superior head sphericity than nonoperative treatment in children older than six years of age<sup>24</sup>. However, surgery has its own set of complications and compliance issues on the part of the patient. A promising pharmacotherapy can help tide over these problems. In pharmacotherapy, just as there are no long-term data on clinical

outcomes, there are no long-term data on the safety profile of the use of bisphosphonates too. Therefore, long-term complications with these agents cannot be excluded. Much of the literature is available on surgical management of these cases; however, since comparative studies (with surgery) are lacking, it is impossible to draw a definitive conclusion at this stage. So, RCTs using bisphosphonates with the standard surgical procedure must also be undertaken, considering the side effects and associated complications to establish refuting the use of bisphosphonates. A data pooling with a similar study design and the comparison group was not possible either because of the different scales used. Complications were also overlooked since some studies reported a short term follow up<sup>11,15,16,17,20</sup>, while others did not report complications at all<sup>11,13,15</sup>. Finally, none of the included studies reported data about the paediatric population, which is undoubtedly the most important

in this review. Studies using standardised clinical trial models with a decent study sample and a reasonable follow up with a good record of adverse effects would have enabled us to draw realistic conclusions in this meta-analysis. We could not find any study in literature satisfying our requirements. Further, animal models using standardised experimental subjects and procedural techniques or study design may help eliminate differences in animal and human studies, helping us draw comparative conclusions.

**Strengths and Limitations of This Study**

This meta-analysis is done on the less explored possible alternative of medical management for Perthes disease.

Literature available on animal studies (experimental studies) and adult osteonecrosis of the femoral head (ONFH) have been extensively studied, thus providing us insight into the possibility of future use of bisphosphonate in Perthes disease.

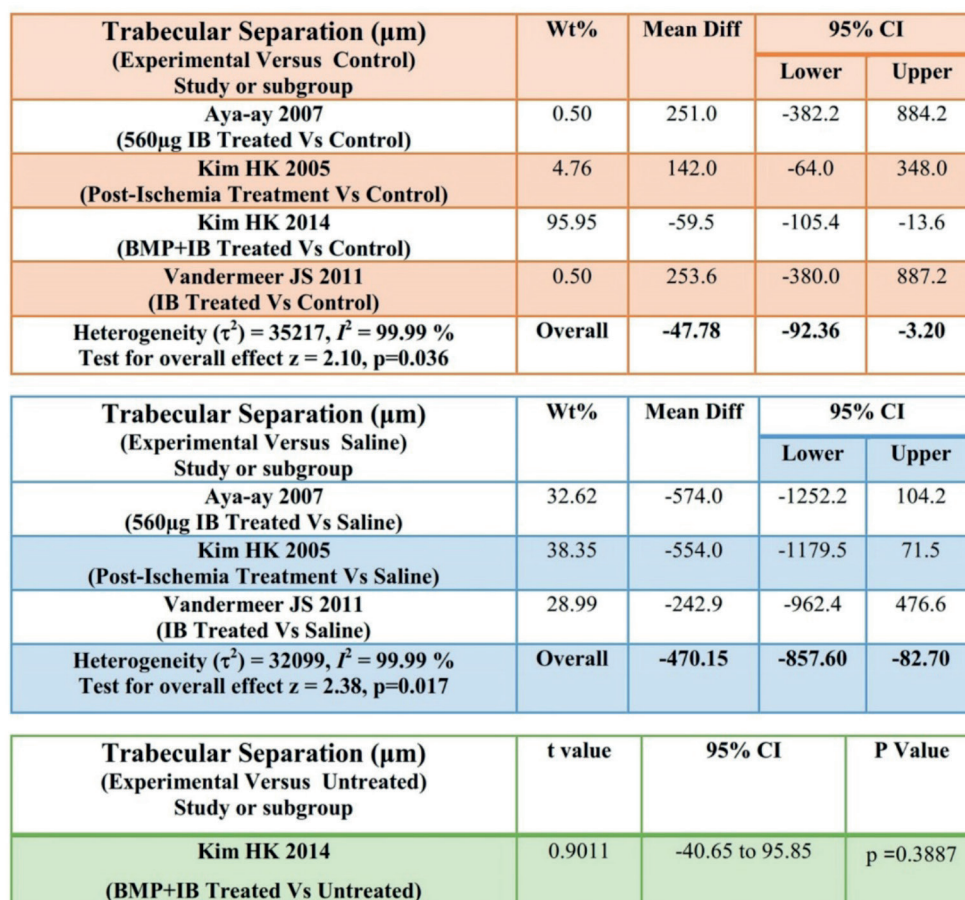
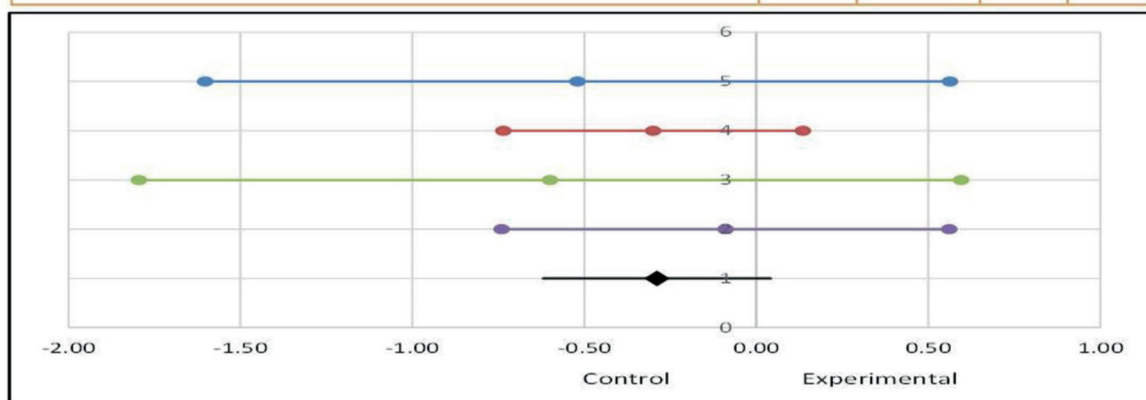


Figure 11. Forest plot of Trabecular Separation in stratified groups.

Pain Score	Bisphosphonate			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
Chen CH 2012	5.81	2.04	26	6.33	1.86	26	9.29	-0.52	-1.60	0.56
Gao yan 2011	0.90	1.20	32	1.20	0.30	32	57.38	-0.30	-0.74	0.14
Lee YK 2015	3.30	2.80	55	3.90	3.50	55	7.61	-0.60	-1.80	0.60
Wang CJ 2008	0.60	1.06	23	0.69	1.19	25	25.73	-0.09	-0.74	0.56
Heterogeneity ( $\tau^2$ ) = 0.0, $I^2$ = 0.0 %; Test for overall effect $z = 1.72$ , $p=0.086$							Overall	-0.29	-0.62	0.04

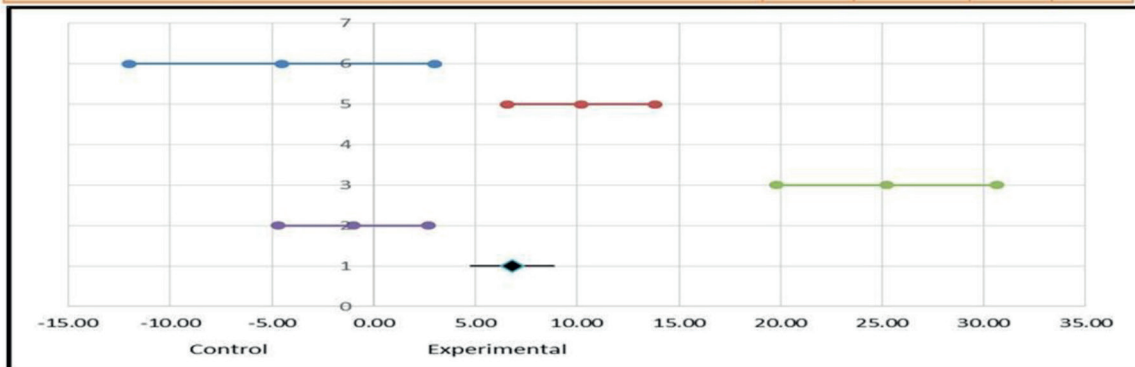


Pain Score	Wt%	Mean Diff	95% CI	
			Lower	Upper
Chen CH 2012	12.51	-0.52	-1.60	0.56
Wang CJ 2008	77.25	-0.09	-0.74	0.14
Lee YK 2015	10.25	-0.60	-1.80	0.60
Heterogeneity ( $\tau^2$ ) = 0.0, $I^2$ = 0.0 % Test for overall effect $z = 1.83$ , $p=0.067$	Overall	-0.36	-0.74	0.02

A

Figure 12. Forest plot of Pain Score. A, Forest plot of Pain Score in stratified groups.

Harris Score	Bisphosphonate			Control			Wt%	Mean Diff	95% CI	
	Mean	SD	Total	Mean	SD	Total			Lower	Upper
Chen CH 2012	79.30	14.20	26	83.80	12.80	26	7.39	-4.50	-11.99	2.99
Kang PD 2012	91.50	8.70	39	81.30	7.40	40	31.80	10.20	6.59	13.81
Lai KA 2005	74.40	7.80	20	49.20	9.20	20	14.10	25.20	19.78	30.62
Lee YK 2015	87.50	10.80	55	85.30	15.30	55	16.63	2.20	-2.80	7.20
Wang CJ 2008	94.30	4.50	23	95.30	8.00	25	30.11	-1.00	-4.71	2.71
Heterogeneity ( $\tau^2$ ) = 104.0, $I^2$ = 99.95 %; Test for overall effect z = 6.57, p<0.001							Overall	6.83	4.79	8.87

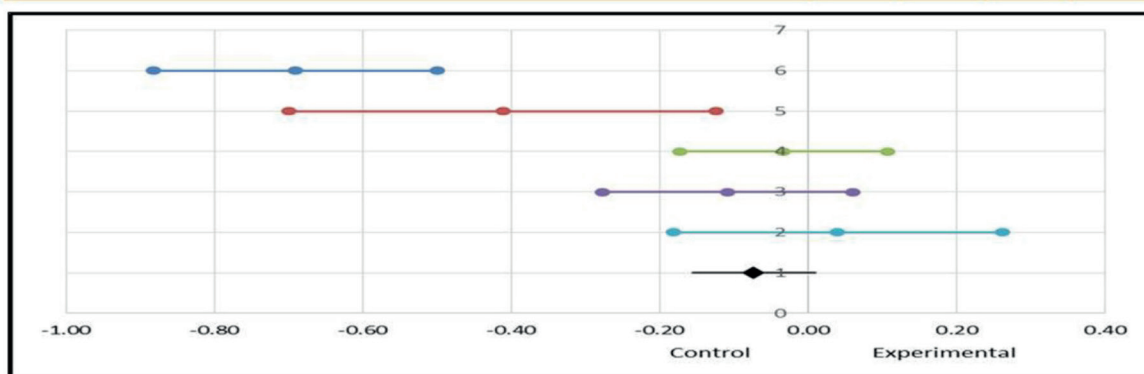


A

Harris score	Wt%	Mean Diff	95% CI	
			Lower	Upper
Chen CH 2012	19.38	-4.50	-11.99	2.99
Lai KA 2005	37.00	25.20	19.78	30.62
Lee YK 2015	43.62	2.20	-2.80	7.20
Heterogeneity ( $\tau^2$ ) = 239.9, $I^2$ = 99.99 % Test for overall effect z = 5.59, p<0.001		Overall	6.11	12.71

Figure 13. Forest plot of Harris Score. A, Forest plot of Harris Score in stratified groups.

Collapse of the femoral head	Bisphosphonate			Control			Wt%	Prop Diff	95% CI	
	Events	Total	Outcome	Events	Total	Outcome			Lower	Upper
Lai KA 2005	2	29	0.069	19	25	0.760	18.65	-0.69	-0.88	-0.50
Nishii 2006	1	20	0.050	6	13	0.462	8.25	-0.41	-0.70	-0.12
Wang CJ 2008	2	30	0.067	3	30	0.100	34.96	-0.03	-0.17	0.11
Kang PD 2012	12	55	0.218	17	52	0.327	24.19	-0.11	-0.28	0.06
Chen CH 2012	10	32	0.313	9	33	0.273	13.94	0.04	-0.18	0.26
<b>Heterogeneity (<math>\tau^2 = 0.08, I^2 = 60.30\%</math>; Test for overall effect <math>z = 1.76, p=0.079</math>)</b>							<b>Overall</b>	<b>-0.07</b>	<b>-0.16</b>	<b>0.01</b>



Collapse of the femoral head	Wt%	Prop Diff	95% CI	
			Lower	Upper
Lai KA 2005	45.66	-0.69	-0.88	-0.50
Nishii 2006	20.21	-0.41	-0.70	-0.12
Chen CH 2012	34.13	0.04	-0.18	0.26
<b>Heterogeneity (<math>\tau^2 = 0.354, I^2 = 91.82\%</math> Test for overall effect <math>z = 1.32, p=0.186</math>)</b>	<b>Overall</b>	<b>-0.09</b>	<b>-0.22</b>	<b>0.04</b>

A

Figure 14. Forest plot of Collapse of the Femoral Head. A, Forest plot of Collapse of the Femoral Head in stratified groups.

Total Hip Arthroplasty	Bisphosphonate			Control			Wt%	Prop Diff	95% CI	
	Events	Total	Outcome	Events	Total	Outcome			Lower	Upper
Chen CH 2012	4	32	0.125	5	33	0.152	20.19	-0.03	-0.19	0.14
Kang PD 2012	9	55	0.164	15	52	0.288	22.95	-0.12	-0.28	0.03
Lai KA 2005	1	29	0.034	16	25	0.640	14.25	-0.61	-0.81	-0.41
Lee YK 2015	19	55	0.345	20	55	0.364	17.75	-0.02	-0.20	0.16
Nishii T 2006	0	20	0.000	2	11	0.182	10.92	-0.18	-0.41	0.05
Wang CJ 2008	23	30	0.767	25	30	0.833	13.94	-0.07	-0.27	0.14
Heterogeneity ( $\tau^2$ ) = 0.0, $I^2$ = 0.0 %; Test for overall effect $z = 3.11$ , $p=0.002$							Overall	-0.12	-0.19	-0.04

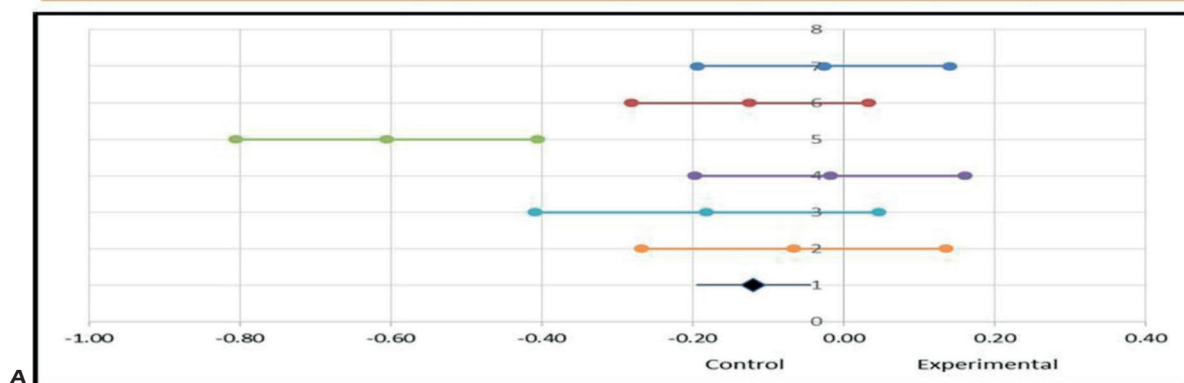


Figure 15. Forest plot of Total Hip Arthroplasty. A, Forest plot of Total Hip Arthroplasty in stratified groups.

Lack of sufficient available literature on the use of bisphosphonates in Perthes disease.

We could not find any RCT available in the literature comparing surgical and medical management of Perthes disease.

## Conclusions

Having robust data on human clinical trials is mandatory, as translating the results of experimental studies on animal models into clinical trials on humans is a complicated procedure, owing to discordant findings. RCT's, with the use of bisphosphonates with the standard surgical procedure, is suggested, taking into consideration the side effects and associated complications to establish or refute the use of bisphosphonates.

## Contributors

AS was involved with the study design, data collection, analysis, and write-up. He is the guarantor. VK, SA and VV

assisted with the study design, data collection, analysis and revisions. AS, VK and SA contributed to the study design, proofread and revisions in the article.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## Funding

This study was supported by Research Cell, King George's Medical University, Lucknow, vide Intramural Seed Grant (SRAMA), Letter No. 492/R-Cell-19, Dated- 25/06/2019.

## Data Sharing Statement

Prepublication history and additional material have been provided in the **Supplementary Materials**. For any query, please contact [ajaiapedortho62@gmail.com](mailto:ajaiapedortho62@gmail.com).

## Acknowledgments

Registration of Meta-analysis: PROSPERO-CRD42020165701.

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