Effect of Bisphosphonates on Periprosthetic Bone Mineral Density Loss After Hip Arthroplasty: An Indirect Treatment Comparison of Randomized Controlled Trials

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INTRODUCTION

- Total hip arthroplasty (THA) has become a popular and successful surgical option for patients with hip osteoarthritis or hip fracture[1]
- Some studies revealed that more than 75% of the revision arthroplasties were performed due to prosthesis loosening and peri-prosthetic fracture, which were accompanied by severe periprosthetic bone loss[2]
- Currently, bisphosphonates are anti-resorptive agents which promote bone mineralization and inhibit the biological effect of osteoclasts[3,4]
- Previous published meta-analysis have confirmed a protective effect of bisphosphonates on periprosthetic bone mineral density (PBMD) after hip arthroplasty (HA)[5] but no direct comparison on the effect of different bisphosphonates has been conducted
- Therefore, we conducted an indirect treatment comparison (ITC) to evaluate the effects of different bisphosphonates on PBMD after HA

METHODOLOGY

- A systematic literature search in Embase, Medline, and Cochrane CENTRAL through Ovid was conducted to identify randomized controlled trials (RCTs) comparing bisphosphonates versus placebo/no-treatment/others in PBMD loss after HA
- Studies were included in which: 1) patients undergoing total hip arthroplasty, 2) any bisphosphonates, 3) femoral periprosthetic BMD measured with dual-energy X-ray absorptiometry as an outcome, 4) follow up equal to or more than 12 months, 5) the trial was a RCT
- Indirect estimates of alendronate and zoledronic acid versus other bisphosphonates were calculated according to the results of their direct comparisons with a common control from the random effect meta-analysis
- Extracted data were converted to weighted mean difference (WMD) and analyzed in Review Manager 5.3.5 software using DerSimonion Laird (random effect) method
- ITC was performed using the Canadian Agency for Drugs and Technologies in Health (CADTH) ITC tool

RESULTS

- A total of 418 studies (Medline = 76, Embase = 255, CENTRAL= 87) were screened through the initial search.
- Among these included studies, 361 studies were excluded on the basis of duplicates, titles and abstracts, and the remaining full text of 57 studies were read. Finally, after full text screening a total of 17 studies met the inclusion criteria
- Included studies were conducted in Germany (2), UK (1), Finland (2), Italy (1), Sweden (2), Slovenia (1), USA (1), Japan (6), Taiwan (1), and involved 807 participants aged between 54-75 years.
- Type of fixation was uncemented in 15 trials and cemented in 2 trials, and duration of follow up was 12 months to 12 years
- All studies measured the periprosthetic femoral BMD by the dual energy x-ray absorptiometry (DEXA)

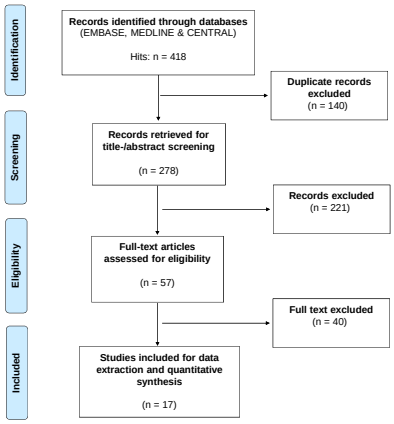

Figure 1. PRISMA flow diagram for the study selection

- Pooled results from the meta-analysis of included RCTs reported a significant improvement in PBMD with alendronate (WMD: 0.11, 95%CI: 0.05-0.17, p=0.0004, I^2=55%; and WMD: 0.11, 95%CI: 0.02-0.20, p=0.01, I^2=0%) and zoledronic acid (0.18, 95%CI: 0.08-0.28, p=0.0003, I^2=31%; WMD: 0.16, 95%CI: 0.06-0.26, p=0.001, I^2=52%) after HA versus control group at 12 months and 2-4 years, respectively
- No association was found with risedronate, etidronate, pamidronate, and clodronate versus control group at 12 months and 2-4 years
- However, results from ITC showed no significant improvement in PBMD with alendronate and zoledronic acid vs. other bisphosphonates at 12 months and 2-4 years though zoledronic acid showed numerically higher mean difference in terms of PBMD improvement at both time points (Table 1)

RESULTS (contd.)

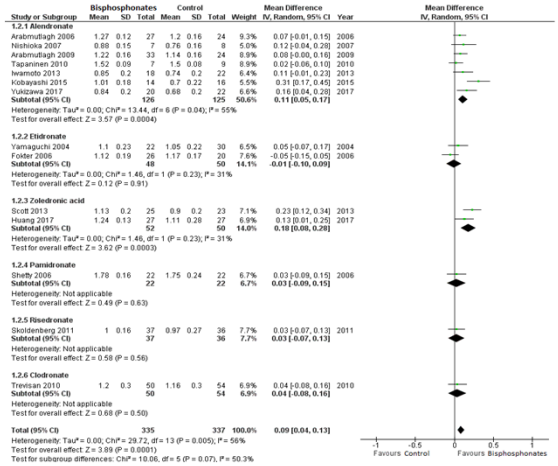

Figure 2. Forest plots for the effect of bisphosphonates on periprosthetic BMD at 12 months

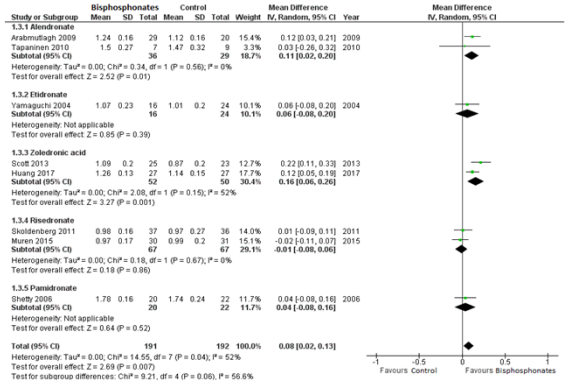

Figure 3. Forest plots for the effect of bisphosphonates on periprosthetic BMD at 2-4 years

Alendronate	12 months		2-4 years	
	MD (95% CI)	P value	MD (95% CI)	P value
Zoledronic acid	-0.07 (-0.19, 0.05)	0.99	-0.05 (-0.18, 0.08)	0.94
Risedronate	0.08 (-0.04, 0.19)	0.99	0.12 (0.01, 0.23)	0.06
Pamidronate	0.08 (-0.05, 0.21)	0.97	0.7 (-0.08, 0.22)	0.53
Etidronate	0.12 (0.01, 0.23)	0.99	0.05 (-0.12, 0.22)	0.67
Clodronate	0.07 (-0.06, 0.20)	0.99	-	-
Zoledronic acid	12 months		2-4 years	
	MD (95% CI)	P value	MD (95% CI)	P value
Risedronate	0.15 (0.01, 0.29)	0.83	0.12 (-0.04, 0.03)	0.88
Pamidronate	0.15 (-0.01, 0.31)	0.85	0.17 (0.05, 0.29)	0.90
Etidronate	0.19 (0.05, 0.33)	0.98	0.1 (-0.07, 0.27)	0.91
Clodronate	0.14 (-0.01, 0.29)	0.86	-	-

Table 1. Indirect treatment comparison of alendronate and zoledronic acid vs. other bisphosphonates on periprosthetic BMD at 12 months and 2-4 years

CONCLUSION

- Meta-analysis of RCTs found that alendronate and zoledronic acid showed significant improvement in PBMD in patients with HA versus control
- However, ITC results found no significant differences for PBMD among the bisphosphonates. Though the results showed that zoledronic acid had better outcomes compared to aledronic acid, these findings should be interpreted with caution owing to low sample size and heterogeneity in the included population
- Further direct head to head trials with long term follow up are needed to confirm findings

References:
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