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ORIGINAL ARTICLE

The use of bisphosphonate in the treatment of osteonecrosis of the femoral head: a meta-analysis of randomized control trials

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Abstract
Summary This meta-analysis revealed that bisphosphonates could not provide a better clinical outcome in the treatment of osteonecrosis of the femoral head (ONFH) when compared with placebo.
Introduction Bisphosphonates have been recommended to treat ONFH. However, the exact clinical outcomes after treatment are still controversial.
Methods A comprehensive search of PubMed, Embase, and Web of Science databases was undertaken, and only randomized control trials were included. The clinical outcomes consisted of progression to collapse, total hip arthroplasty (THA) incidence, and improvement of Harris hip score (HHS). The heterogeneities between the trials were assessed with the I^2 statistic, and random effects models were used for the meta-analysis.
Results Five eligible trials were identified involving 329 subjects with 920.9 patient-years of follow-up. The clinical outcomes of patients with ONFH was not significantly improved by bisphosphonate therapy (progression to collapse: risk ratio=0.71 (0.41, 1.24), p=0.23; THA incidence: risk ratio=0.61 (0.33, 1.15), p=0.13; HHS improvement: mean difference=3.26 (−5.12, 11.64), p=0.45). The I^2 statistic showed the existence of considerable heterogeneity (all $I^2 \geq 50$ %), which was explained by one trial where bisphosphonate alone was used with no additional therapy. However, when this trial was excluded, the clinical outcomes after bisphosphonate therapy were still not significantly improved compared with placebo.
Conclusions The current analysis does not support the use of bisphosphonates for ONFH. As potential serious adverse effects are associated with these drugs, only limited use can be recommended.

Keywords Bisphosphonates · Femoral head · Meta-analysis · Osteonecrosis

Introduction

Osteonecrosis of the femoral head (ONFH) is a debilitating and painful disease which mainly affects the young and middle-aged adults [1, 2]. The pathogenesis of ONFH is still unclear, but one critical factor could be explained by the imbalance of bone metabolism [3]. Once the ONFH happens, both the osteoclasts and osteoblasts would participate in the reparative process. And if the osteoclast activity exceeds the osteoblast activity, it could result in a decrease of mechanical strength in the repaired region and the following collapse of the femoral head [4]. For this reason, if the bone resorption associated with ONFH can be inhibited or delayed until an adequate new bone has been formed, it would seem to delay or avoid the joint failure.

Bisphosphonates are widely used in the treatment of osteoporosis diseases characterized by osteoclasts-mediated bone resorption [5–7]. To date, many animal experiments have reported the promising effects of these drugs on the prevention of collapse [8–10]. Unfortunately, the clinical outcomes are still controversial. Agarwala et al. continuously reported the encouraging clinical outcomes of bisphosphonates treatment after 1, 8, and 10 years follow-up, respectively [11–13]. However, other trials showed that bisphosphonates have no

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obvious effect on reducing disease progression, preventing the necessity for total hip arthroplasty (THA), or improving life quality [14, 15]. In addition, Hong et al. found that alendronate could not prevent the collapse of femoral head [16].

To make clear whether bisphosphonates should be recommended to the ONFH patients is a very realistic and pivotal question in the hospital. But, the small samples in the reported clinical trials of bisphosphonate therapy and low statistical power gave rise to the inconsistent clinical outcomes. Therefore, in this study, we conducted a meta-analysis of all randomized placebo-controlled trials of bisphosphonate therapy in the treatment of ONFH.

Methods

Search strategy

This meta-analysis was performed according to the PRISMA guidelines [17]. A systematic literature search has been conducted on PubMed, Embase, and Web of Science databases up to July 2015. The combination of terms "bisphosphonate," "osteonecrosis" or "avascular necrosis," and "femoral head" or "femur" was used without a publication date. The language was restricted to English. Relevant studies were retrieved accordingly. Meanwhile, we checked their references to find other relevant publications.

Selection criteria

Two authors (Yuan and Guo) independently reviewed the titles and abstracts of potentially eligible publications. The inclusion criteria included: (i) the allocation to treatments was randomized; (ii) one of the intervention arms was bisphosphonate therapy; (iii) it must have a placebo or control group; and (iv) it must at least have one of the clinical outcomes: progression to collapse, THA incidence, and Harris hip score (HHS).

Date extraction and quality assessment

For each trial, we extracted the following items: (i) the surname of the first author and the year of publication, (ii) the characteristics of the study population, (iii) the detailed information of bisphosphonate therapy, and (iv) the clinical outcomes. The progression to collapse indicated that the radiologic evaluation was defined as more severe findings at follow-up as compared with baseline. However, if this data could not be obtained, we would use the number of collapsed hips instead. If the above items cannot be obtained from the publication, we would try to contact the original authors by e-mail.

Quality assessments were also conducted by two authors independently (Yuan and Yan), and any disagreements between authors were resolved by discussion. Also, the evidence level of each trial was distinguished according to the Cochrane handbook for systematic reviews of interventions [18].

Statistical analysis

Analyses were calculated with the software STATA package v.11.0 (Stata Corporation, College Station, TX, USA) and Review Manager, version 5.0 (RevMan, The Cochrane Collaboration, Oxford, UK). The overall differences were expressed in terms of pooled risk ratio or mean difference with 95 % confidence interval. The random effects model was used for analysis. The heterogeneity was estimated by I^2 statistic method, and the $I^2 \geq 50$ % was considered a significant heterogeneity. Publication bias was checked by the funnel plot using Begg's regression model. Sensitivity analyses was performed according to the "1-study removed" analyses. p value <0.05 was considered statistically significant.

Results

Trials included in the meta-analysis

A total of 3122 articles were retrieved from PubMed, Embase, and Web of Science, of which 8 trials that potentially met our expectation were identified. After that, two trials were excluded because they were not randomized trials [19, 20]; one trial that was excluded for the efficacy of bisphosphonate was combined with other therapies [21]. The flow of the literature search was summarized in Fig. 1.

The details of five trials in our study [14, 15, 22–24] were displayed in Table 1. All these trials were with level I

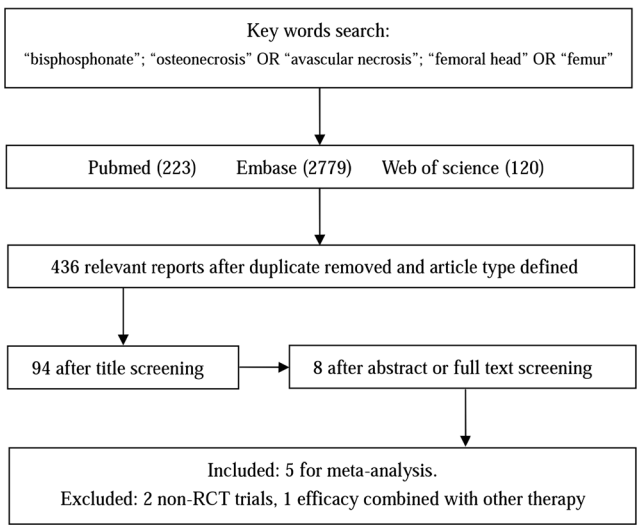

Fig. 1 Flowchart of selecting process for meta-analysis

Table 1 Characteristics of the included trials

Study	Year	Treatment	Supplement	Number/hips	Age (year)	Duration (month)
Lai et al. [23]	2005	Alendronate	None	20/29	42.6	24
		Placebo	None	20/25	42.4	24
Wang et al. [14]	2008	Alendronate	ESWT	23/30	35.7	24.87
		Placebo	ESWT	25/30	38.6	26.14
Chen et al. [15]	2012	Alendronate	Ca+vit D	26/32	48.4	24
		Placebo	Ca+vit D	26/33	44.2	24
Kang et al. [22]	2012	Alendronate	MD+Ca+vit D	39/55	43.8	63
		Placebo	MD+Ca+vit D	40/52	45.3	63
Lee et al. [24]	2015	Zoledronate	Ca+vit D	55/55	44	24
		Placebo	Ca+vit D	55/55	45	24

ESWT extracorporeal shockwave therapy, *Ca* calcium, *MD* multiple drilling

evidence. In total, they included 329 patients with 920.9 patient-years of follow-up. Four trials [14, 15, 22, 23] used oral alendronate (70 mg per week) and one trial [24] used intravenous zoledronate (5 mg per year) as the bisphosphonate therapy, and all patients were nontraumatic osteonecrosis. One trial compared bisphosphonate alone with placebo [23] and the other four with extracorporeal shockwave therapy (ESWT) [14] or oral calcium and vitamin D [15, 24] or multiple drilling core decompression plus calcium and vitamin D [22] to the recruited patients as a supplement. All the study durations were at least 2 years.

Clinical outcomes with bisphosphonate therapy

The proportion of patients who experienced the progression to collapse was not significantly reduced by bisphosphonate therapy under a random effects model, risk ratio 0.71 (0.41–1.24), p=0.23, with a significant heterogeneity between the trials (I^2=75 %) (Fig. 2a). Likewise, the THA incidence was not reduced as well under a random effects model, risk ratio 0.61 (0.33–1.15), p=0.13, with a significant heterogeneity as well (I^2=50 %) (Fig. 2b). The two heterogeneities were largely explained by the Lai et al. trial [23] in which placebo-treated patients showed extremely bad clinical outcomes. When this trial was excluded, bisphosphonates still had no significant effect on delaying the progression or reducing the THA incidence under random effects models with no heterogeneity (progression to collapse: risk ratio 1.04 (0.81–1.32), p=0.78, I^2=0 %; THA incidence: risk ratio 0.78 (0.53–1.13), p=0.18, I^2=0 %).

As to HHS, we successfully obtained the necessary data from Kang et al. [22] by e-mail but failed from Lai et al. [23]. The pooled results showed that there is no significant improvement of HHS under a random effects model, mean difference 3.26 (−5.12–11.64), p=0.45, with I^2=82 % (Fig. 2c). We failed to find the cause of heterogeneity, but the small sample size could be an important factor.

Publication bias and sensitivity analysis

No significant publication bias was found in any of the pooled studies (p>0.05; Fig. 3 for the detection of THA incidence comparison). In addition, sensitivity analysis showed no changes of the clinical outcomes when any study was excluded.

Discussion

Bisphosphonates are used by some physicians for the therapy of ONFH in routine clinical practice, but the evidences for the clinical outcomes are very limited. The rationale of using this drug for the treatment of ONFH was based on that the activity of osteoclasts could be inhibited and the collapse of femoral head would be prevented or delayed [25, 26]. However, the clinical outcomes from the previous reports were rather inconclusive.

Although the pathogenesis of ONFH is very complicated, the randomized placebo-controlled trials could provide the strongest evidence. In our meta-analysis, all the included trials were with the evidence of Level I. We found that bisphosphonate therapy could not bring a better clinical outcome compared with placebo. This medicine could not delay the progression to collapse, reduce the incidence of THA requirement, nor improve the quality life for patients with ONFH.

From our included studies, we found that one trial influenced the heterogeneity of the pooled results, which reported the promising clinical outcomes of bisphosphonate therapy when compared with placebo [23]. Further analysis revealed that only bisphosphonates or placebo was used for patients in that trial while the rest of the included trials were all with additional therapy (such as ESWT, calcium, vitamin D, et al.) as a supplement. However, we can at least conclude that

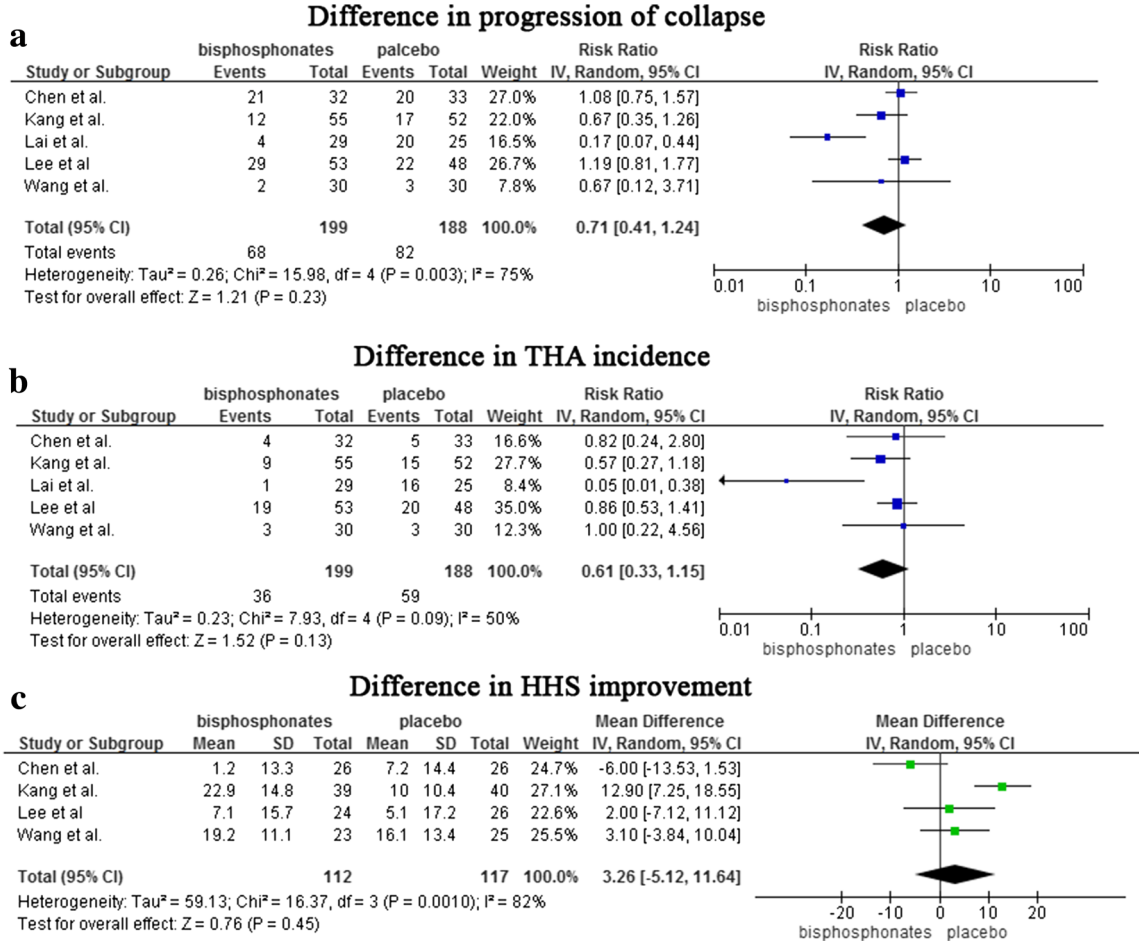

Fig. 2 Clinical outcomes of progression to collapse (**a**), THA incidence (**b**), and HHS improvement (**c**) with bisphosphonate therapy when compared with placebo

bisphosphonate could not provide an additional efficacy in the treatment of ONFH.

Nevertheless, the limitations of this study should not be ignored. Firstly, we limited our meta-analysis to trials in English. Although the effect of excluding non-English studies on the results of a meta-analysis is unclear, exclusion of such trials may have little effect on the summary effects of bisphosphonates and may actually give a more conservative

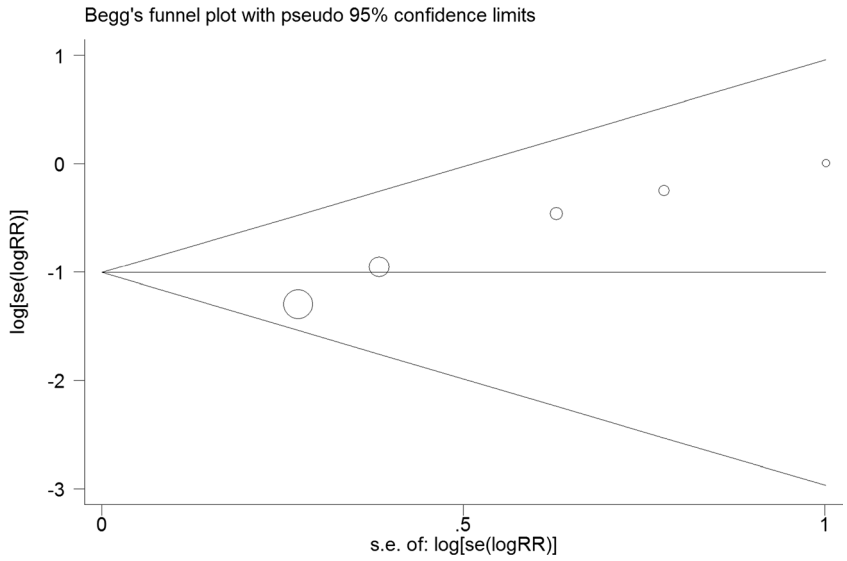

Fig. 3 Funnel plot for the detection of publication bias

estimate. Secondly, the number of patients included in this meta-analysis was relatively small due to the long-time treatment period (at least 2 years). Lastly, considering that ONFH is a condition that could last for many years, it is uncertain whether the delayed collapse would happen over a period of time.

In general, our current meta-analysis has shown limited evidence to support the use of bisphosphonates for ONFH, and larger sample size of randomized controlled trials is needed to confirm these results. Until such evidence becomes available, patients with ONFH and physicians should be aware of the very limited evidence to support better clinical outcomes with bisphosphonate therapy. Moreover, they should also note that patients on a long-term bisphosphonate treatment are at an increased risk of serious adverse effects [27] such as osteonecrosis of the jaw and atypical subtrochanteric fractures.

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Conflicts of interest None.

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