REVIEW ARTICLE

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Early bisphosphonate therapy post proximal femoral fracture fixation does not impact fracture healing: a systematic review and meta-analysis

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Abstract

Background: There is conjecture on the optimal timing to administer bisphosphonate therapy following operative fixation of low-trauma hip fractures. Factors include recommendations for early opportunistic commencement of osteoporosis treatment, and clinician concern regarding the effect of bisphosphonates on fracture healing. We performed a systematic review and meta-analysis to determine if early administration of bisphosphonate therapy within the first month post-operatively following proximal femur fracture fixation is associated with delay in fracture healing or rates of delayed or non-union.
Methods: We included randomized controlled trials examining fracture healing and union rates in adults with proximal femoral fractures undergoing osteosynthesis fixation methods and administered bisphosphonates within 1 month of operation with a control group. Data were pooled in meta-analyses where possible. The Cochrane Risk of Bias Tool and the GRADE approach were used to assess validity.
Results: For the outcome of time to fracture union, meta-analysis of three studies ($n = 233$) found evidence for earlier average time to union for patients receiving early bisphosphonate intervention (MD $= -1.06$ weeks, 95% CI -2.01–-0.12, $I^2 = 8\%$). There was no evidence from two included studies comprising 718 patients of any difference in rates of delayed union (RR 0.61, 95% CI 0.25–1.46). Meta-analyses did not demonstrate a difference in outcomes of mortality, function or pain.
Conclusions: We provide low-level evidence that there is no reduction in time to healing or delay in bony union for patients receiving bisphosphonates within 1 month of proximal femur fixation.

Introduction

Osteoporosis continues to be a major contributor to morbidity and mortality.[1] A silent disease, many people only become aware of their diagnosis when they suffer an initial low-trauma fracture. Hip fractures are the most common subset, making up ~32% of all low-trauma fractures in Australia.[1] Up to 40% of patients with low-trauma fracture will be readmitted with subsequent fractures.[2] Timely diagnosis and treatment of osteoporosis can prevent future fractures by up to 50% in patients presenting with hip fractures.[3,4] Current Australian clinical care standards on the management of hip fractures[5,6] hence advocate for patients to receive secondary prevention in the form of antiresorptive therapy following initial hip fracture prior to discharge. This echoes an international trend supporting prompt initiation of antiresorptive therapy in high-risk individuals, such as people who have recently suffered a low-trauma fragility fracture.[7,8]

Bisphosphonates such as zoledronic acid, risedronate and alendronate are commonly used for secondary prevention of osteoporosis. Bisphosphonates work by inhibiting osteoclasts' bone

resorptive function. However, there is concern regarding the theoretical risk of bisphosphonates on fracture healing because osteoclasts are implicated in both primary, direct bone healing and the remodelling of bony callus present in secondary bone healing. Early studies in both animal[9–13] and human[14–19] models reported mixed outcomes ranging from delayed to enhanced fracture healing. Several of these reports are on 'atypical' bisphosphonate-related fractures, a cohort whose healing is now known to be significantly slower[20–22] and not reflective of 'normal' milieu.[20] Past systematic reviews[23,24] concluded that early initiation of bisphosphonates did not appear to impact fracture healing, however these reviews were not specific to hip fractures, had methodological flaws (e.g. combining data for hip fractures with spinal and other types of fractures in meta-analysis, bias due to inclusion of non-RCTs and retrospective studies). Additionally, these reviews defined 'early' bisphosphonate use as within 3 months post-operatively, by which time most patients would have been discharged home, limiting their real-world applicability. Publication of recent studies now allows specific analysis of the proximal femoral fracture cohort within a tighter and more practically meaningful timeframe.

The uncertainty in the literature has resulted in many surgeons choosing to delay initiation of antiresorptives during the inpatient period, deferring treatment to start in the community, months after fracture union. However, there is evidence that community follow-up and initiation of osteoporosis treatment is poor following discharge from hospital.[25,26] Recent data from the Australia New Zealand Hip Fracture Registry indicates that of 14 816 patients presenting with hip fracture in 2020 only 29% were discharged on antiresorptive treatment, compared with 10% on admission, citing this figure as indicative of a 'significant missed opportunity' to prevent future fractures.[5] It is possible that surgeon concern for impact on fracture healing is attributable for some of these 'missed opportunities'.

To elucidate the effect of early inpatient bisphosphonate treatment on proximal femur fracture healing, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) administering bisphosphonate therapy within the first month following proximal femoral fracture fixation.

Methods

Study selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. A prespecified protocol was registered prospectively with PROSPERO (https://www.crd.york.ac.uk/prospero/, response pending at time of publication).

Only prospective RCTs were considered for this review. The intervention was any form of bisphosphonate therapy initiated within 1 month post-operatively. Given national recommendations[27] for initiation of antiresorptive therapies following low-trauma fracture, we accepted patients receiving bisphosphonate therapy after the first month post-operatively in the control group, along with 'true' controls. Inclusion criteria for the population of interest included: adults with minimal-trauma fragility proximal femur fractures, no prior treatment with anti-resorptives, fixation with osteosynthesis methods (e.g. nailing, plating, screws).

Exclusion criteria were as follows: (i) Non-RCTs, (ii) joint replacement and excision (arthroplasty) rather than fracture fixation, (iii) paediatric populations, and (iv) studies examining pathological fractures (e.g. osteogenesis imperfecta), fractures associated with a mass/lesion, or 'atypical' fractures associated with bisphosphonate use, as the underpinning pathological processes would affect healing, rendering them non-comparable.

Outcomes

Primary outcomes of interest comprised time to fracture healing (radiological or clinical), and rates of delayed union, non-union and revision surgery. Secondary outcomes included mortality and patient-reported outcome measures (PROMs), such as function, pain and quality of life measures.

Literature searching

A literature search was performed on the following databases: PubMed, Embase, Medline and the Cochrane Library. Search strategies using relevant MeSH terms were developed in consultation with the entire research team, and with feedback from academic researchers; these have been included in Data S1. Grey literature searches were also performed, and the reference lists of previous systematic reviews and included papers were examined for relevant papers. No restrictions were made on publication language, status or year. This search was last performed 28th December 2021.

Data extraction

One study investigator ran the database searches and performed the initial title-screening process. Two investigators independently completed abstract screening to identify potentially relevant studies for full text review, which was also completed independently in duplicate. At each stage, disagreements were resolved via mediation in the first instance; a third independent reviewer was available to resolve any outstanding discrepancies. Data extraction of key study and outcome variables was again performed in duplicate into predesigned spreadsheets; discrepancies were resolved with mediation.

Validity assessment

Risk of bias was assessed for each study using the Cochrane Risk of Bias tool by two reviewers independently, with disagreements resolved via mediation. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to assess the overall quality of evidence.

Quantitative data synthesis

Data were analysed using Review Manager Software (RevMan version 5.4).[28] Where possible, data from several studies on the same outcome measure was combined in meta-analysis for quantitative

synthesis. Summary estimates of effect were expressed in mean difference (MD) and 95% confidence intervals (95% CI) for continuous outcomes, and relative risk (RR) and 95% CI for dichotomous outcomes. *A priori* subgroup analyses were planned for studies where bisphosphonate therapy was initiated after the first month versus the placebo or 'true' control groups.

Statistical heterogeneity was assessed via I^2 and chi-squared statistics, as well as by examination of the forest plot. A *P*-value cut-off less than 0.1 was used to interpret the significance of the chi-squared statistic, to account for the test's low power in the context of few studies and small sample sizes. To assess inconsistency of effect, the I^2 statistic was used; an I^2 value of 0–40% was considered possibly trivial heterogeneity, between 30% and 60% was considered moderate heterogeneity, 50–90% was considered to have substantial heterogeneity, and I^2 greater than 75% was considered highly heterogenous.[25] Where moderate-high heterogeneity was evident (chi-squared *P*-value <0.1, or I^2>50%), a subgroup analyses would be considered, and if this failed to account for the inconsistency, then random effects modelling would be used.

Results

Trial flow

The search results yielded 2514 results, of which six RCTs met inclusion criteria. The study selection process is illustrated in Figure S1.

Study characteristics

A total of six studies[18,29–33] comprising 1200 patients were included in this systematic review. Approximately 64.7% of participants were female, with an average age of 74.9 years old (two studies did not provide complete data for age[18] and sex[33]). All studies were RCTs exclusively examining proximal femur fractures. Four studies[29–32] reported values for bone mineral density (BMD) at the hip, but used such heterogenous measures that we are unable to derive average values. The mean BMI of patients at the outset of the three studies[30,31,33] which provided data for BMI was 23.0. One trial[18] did not disclose the type of surgery performed (other than stipulating that arthroplasties were excluded), and of the other five studies, four[29–31,33] utilized internal fixation via intramedullary nailing devices or compression screws, and one study[32] examined external fixator devices. Most studies[18,29,31,33] used a yearly 5 mg dose of intravenous (IV) zoledronic acid; two examined the use of weekly oral agents (35 mg risedronate[30] and 70 mg alendronate,[32] respectively). Most studies[18,30,31,33] treated both treatment and control arms with additional supplementation of calcium and vitamin D. We considered this acceptable so long as both groups received the same dose. Five[18,29–31,33] studies followed patients up to at least the 12-month timepoint, one study[32] followed patients to 3 months, where they considered all fractures healed. A summary of the characteristics of each included RCT is provided in Table 1.

Primary outcomes

See Table S1 for a summary of findings from included studies.

Time to fracture healing

Three studies[29–31] comprising 233 patients were eligible for inclusion in meta-analysis for this outcome (Fig. 1). Fracture healing was assessed using a combination of radiological and clinical methods (Table 1). Mean time to fracture healing was on average 1.06 weeks shorter in patients treated with early bisphosphonates (mean time to fracture healing 13.05 weeks in treatment group, compared with 14.11 weeks in control group), with test statistics indicating significance (95% CI −2.01–−0.12 weeks, $I^2 = 8\%$).

Delayed union

Five studies[18,29–32] comprising 718 patients reported on rates of delayed union (Fig. 2). Three[29,31,32] of these reported no instances of delayed union in either control or treatment groups. No statistically significant difference with low heterogeneity was found between groups for this outcome in meta-analysis (RR 0.61, 95% CI 0.25–1.46; chi-squared (1) = 0.00, $P = 0.95$, $I^2 = 0\%$).

Non-union and revision surgery

Five studies[18,29–32] commented on rates of non-union and revision surgery (Table S1). Two studies[31,32] reported zero revisions in either treatment or control groups. Colón-Emeric *et al.*[18] qualitatively reported no significant differences in rates of non-union when bisphosphonates were given early (within 2 weeks of fixation). Jalan *et al.*[29] reported one patient in each group who suffered symptomatic non-union, necessitating revision surgery (one for screw cut-out and one for screw penetration into articular surface). Kim *et al.*[30] reported two patients in the early bisphosphonates group and four patients in the delayed groups who required revision surgery for loss of fixation ($P = 0.55$ indicating non-significance), however it unclear if non-union was the cause of failure (as opposed to surgical technique or decision-making).

Secondary outcomes

Mortality

Two studies[29,30] reported on mortality, comprising 173 patients (Fig. S2). There was no significant difference in mortality between patients receiving early bisphosphonate therapy and those who did not (RR 0.7, 95% CI 0.26–1.88). Heterogeneity measures were moderate (chi-squared (1)= 1.92, $P = 0.17$, $I^2 = 48\%$).

Patient-reported outcome measures

Function

Two studies[29,31] comprising 143 patients reported on function using the Harris Hip Score (HHS) and the Modified Harris Hip Score (MHHS), validated patient-reported outcome measures[34] (Fig. S2). When combined in meta-analysis using standardized mean differences, there was no significant difference between patients receiving early bisphosphonate therapy and those who did not (MD −0.07 points, 95% CI −0.40–0.26). Heterogeneity measures were low (chi-squared (1) = 0.00, $P = 0.98$, $I^2 = 0\%$).

Table 1 Characteristics of included studies

Author	Year	Country	Study design	Number (Rx/control)	Mean age (*SD*)	Sex M/F	Surgical fixation type	Mean hip BMD (*SD*)	BMI (kg/m^2)	Time between operation and bisphosphonate administration	Outcomes examined
Colón-Emeric *et al.*[†]	2011	USA	RCT	247/222	N/A	n/r	Not disclosed, arthroplasties excluded	Not disclosed	Not disclosed	<4 weeks	Incidence of delayed union (clinical (pain, inability to weight bear, gait disturbance) and radiographic (unchanged fracture appearance, displacement inconsistent with fixation type, absence of callus formation across at least two cortices) criteria)
Jalan *et al.*	2021	India	RCT	41/42	Cases 71.8 (8.1) controls 72.3 (10.6)	38/45	IMN or DHS	Cases T = −2.58 (0.5) Controls T = −2.58 (0.6)	Not disclosed	2 days	Fracture healing (RUSH score), time to union, delayed and non-union, Function (MHHS)
Kim *et al.*	2012	Korea	RCT	30/60	Cases 75.0 (10.2) controls: Group B 75.3(9.5) Group C 78.1(9.9)	27/50	Compression screw or IMN	Cases 3.2 g/cm^2 (0.6) Controls: Group B 2.8 g/cm^2 (0.9) Group C 3.3 g/cm^2 (0.8)	Cases 20.8 (2) Controls: Group B 20.1 (0.5) Group C 21.5 (2.5)	<1 week	Fracture healing (radiographic continuity in at least two cortices), time to union, delayed and non-union Function (Koval score) Complication rates (displacement, revision surgery)

Table 1 Continued

Author	Year	Country	Study design	Number (Rx/control)	Mean age (*SD*)	Sex M/F	Surgical fixation type	Mean hip BMD (*SD*)	BMI (kg/m^2)	Time between operation and bisphosphonate administration	Outcomes examined
Li *et al.*	2016	China	RCT	30/30	Cases 75.0 (4.8) controls 74.0 (5.8)	24/36	PFNA	Cases 0.7 g/cm^3 (0.1) Controls 0.7 g/cm^3 (0.1)	Cases 25.4 (2.8) controls 25.2 (2.6)	3 days	Fracture healing (clinical (pain-free weight-bearing and palpation/ percussion) and radiographic (trabecular bridging)), time to union Function (HHS) Pain (VAS) Quality of Life (OQOLS) BMD Adverse effects
Moroni *et al.*	2007	Italy	RCT	8/8	Cases 83 (7) Controls 86 (4)	0/16	External fixator	Cases 0.5 g/cm^3 (0.2) controls 0.5 g/cm^3 (0.1)	Not disclosed	<1 week	Fracture healing (radiographic callus or trabecular bridging fracture site), time to union, delayed and non-union Pin site infections Mean pin extraction torque
Liu *et al.*	2019	China	RCT	353/129	Cases 75.4 (12.5) control 73.3 (13.8)	n/r	IMN	Not disclosed	Cases 23.5 (8.2) controls 22.3 (9.6)	<1 week	Bone metabolic markers Pain (VAS) Refracture rate Quality of life (SF-36)

[†]Data from Lyles *et al.* 2007 Horizon-Recurrent Fracture Trial.[3]

BMD, bone mineral density; BMI, body mass index; DHS, dynamic hip screw; HHS, Harris hip score (score/100); IMN, intramedullary nail; MHHS, Modified Harris hip score (score/100); n/r, proportion not reported; OQOLS, osteoporosis quality of life scale; PFNA, Proximal femoral nail antirotation; RUSH, radiographic union score for hip[8–30]; SF-36, short form-36 (0–100); VAS, visual analog scale.

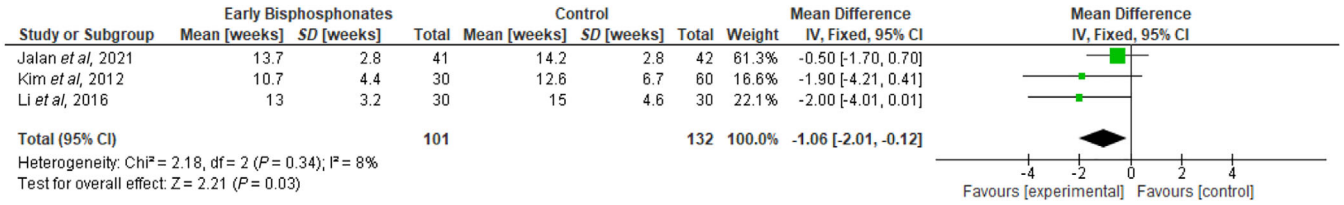

Fig. 1. Time to fracture healing (weeks).

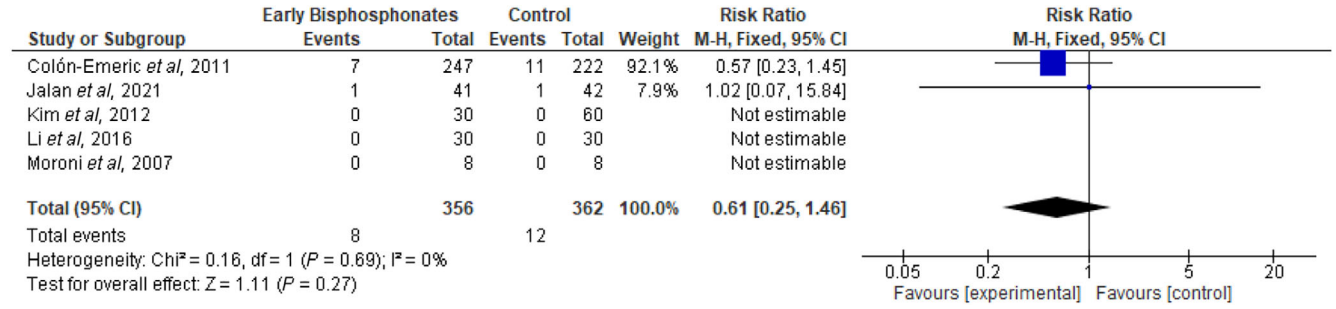

Fig. 2. Delayed union.

Kim *et al.*[30] used the Koval classification to measure recovery of functional mobility, which classifies ambulation into seven levels. He found that there was no difference at 1 year post-operatively between groups receiving early bisphosphonate therapy and those who received delayed therapy (early bisphosphonates group mean 2.4 ± 1.7, versus delayed bisphosphonate groups 2.4 ± 2.1 and 2.2 ± 1.5; $P = 0.948$, Table S1).

Pain

Data from two studies[31,33] comprising 542 patients reported on pain using the Visual Analog Scale (VAS) were combined in meta-analysis. There was no significant difference in pain between patients receiving early bisphosphonate therapy and those who did not (MD −0.44 points on a VAS, 95% CI -1.57-0.70, Fig. 2). Heterogeneity measures were moderate-high (chi-squared (1) = 2.57, $P = 0.11$, $I^2 = 61\%$), and therefore a random effects model was utilized.

Quality of life

One study[31] examined quality of life using the Osteoporosis Quality of Life Scale (OQOLS), a tool comprising 75 items across five domains (disease, physical, social, psychological and satisfaction).[35] Li *et al.*[31] reported that the early intervention group had higher mean OQOLS ratings compared with the control group at 12 months post-operatively (83.30 ± 9.4 vs. 78.26 ± 9.8, $P = 0.04$).

Liu *et al.*[33] used the Short Form Survey (SF-36) to quantify quality of life, reporting significant improvements in the body pain and physiological function dimensions of the score at 24 months, compared with control group counterparts (see Table S1).

Quality of trials

The overall quality of the evidence was assessed using the GRADE framework.[36] Studies were appraised via the Cochrane Risk of Bias tool, and their results summarized in Fig. S3. All studies performed well in their description of attrition and in reporting their stated outcomes. Over 50% of studies either had unclear or high risk of bias from lack of allocation concealment and blinding. Inconsistency was generally very low across all outcomes except for the outcome of pain for which random effects modelling was chosen. Imprecision is likely, owing to the small number of studies included for each meta-analysis, which resulted in downgrading of the evidence. Publication bias was not assessed given the small numbers of trials. The GRADE of the overall quality of evidence provided by this review and meta-analysis was hence judged to be low.

Although subgroup analysis to examine the difference between early and late bisphosphonate administration was initially planned *a priori*, small study numbers precluded this.

Discussion

Concerns with regards to fracture healing in the setting of bisphosphonate are based on the role of osteoclast-mediated resorption in bone remodelling of callus. Studies on existing bisphosphonate users who suffer a fracture have concluded that there is some delay in radiographic union, however this does not seem to translate into issues with symptoms or clinical healing.[37] This effect is not replicated with bisphosphonate-naïve patients commenced on treatment post-fracture.[37] Early animal models seemed to indicate that bisphosphonate initiation following fractures resulted in delays of conversion from woven bone to mature lamellar bone and increased fracture bridging and callus size, but no delays to callus formation itself[13,20,38–40] however there was some discrepancies between

studies.[31] A systematic review and meta-analysis in 2015 on early bisphosphonate therapy in all types of fractures in adult humans found no delays in radiological or clinical union time or rates of delayed or non-union.[23] A criticism of this review is that pooled analysis of data from trials looking at different bone fracture sites were utilized; assuming similar healing rates and mechanisms is specious given the differences in structure and function between, for example, weight bearing long bones and cancellous vertebrae.

The findings of our systematic review, specific to both adult, low-trauma proximal femur fractures treated with osteosynthesis fixation and commencement of bisphosphonates in the first month following operation, are in line with the existing literature. Our meta-analysis provides low-quality evidence that early administration of bisphosphonates within the first month post-operatively is not associated with a delay in fracture healing time, and in fact may be associated with a statistically (but likely not clinically) significant faster healing time by an average of 1 week. We hypothesise that the reduced time to union may be due to studies utilizing radiological measures of union – findings of increased fracture callus bridging and size with bisphosphonates in animal models may account for the appearance of early union radiographically.[9–11,20] Our meta-analyses found no evidence that early administration of bisphosphonates results in delayed union, mortality or PROMs like pain and function, and descriptive review of studies does not support a significant difference for rates of non-union or return to theatre. These findings are in line with current literature.[23,24,37]

Strengths

A strength of our review is that we had a highly specific question with tight timeframe, increasing the validity and applicability of our findings, in comparison to previous reviews which combined differing types of fractures with a protracted definition of early bisphosphonate administration. We specifically chose the 1-month cut-off to reflect real-world pressures, and as most studies reported radiological union by 4 weeks on average, administration after this point may be biased towards no effect. Another strength is in our strict inclusion of only RCTs, decreasing the potential for selection bias. We think that the design of our study results in better quality evidence to guide practical clinical decision-making.

Limitations

The chief limitation of our review is the small numbers included in meta-analysis. We included RCTs exclusively, strengthening the quality of the evidence but excluding data from well-made cohort studies and non-randomized controlled trials. It is, however, worth noting that their findings on fracture healing and function aligned with the conclusions of our review and meta-analyses. Khan *et al.*[41] performed a quasi-randomized controlled trial in patients treated with zoledronic acid infusions post-operative day 3, and found significantly reduced mean time to radiological union in the treatment group (12.77 ± 1.89 weeks vs. 15.86 ± 0.94 weeks, $P = 0.04$). Another quasi-randomized trial[42] reported significantly better mean hip function (HHS) scores in patients receiving early bisphosphonate treatment 12 months post-operatively (81.93/100 vs. 72.9/100, $P < 0.05$). Another excluded study[43] comprising 90 patients reported no significant difference in RUSH scores or fracture union rate at 6 months, nor function (HHS) at 1 year.

Some included studies were methodologically imperfect, with a lack of blinding and allocation concealment. Given the paucity of studies included in this study, we have downgraded the level of evidence. Another shortcoming is that we did not collect data on adverse effects, however we felt that the safety profile of these commonly used drugs are widely available and beyond the scope of this review. One study[32] used external fixators rather than internal fixation; we chose to include this paper as we felt that underlying bone healing mechanisms would respond similarly to bisphosphonates, however we were mindful that the higher morbidity and mortality of this infrequently-chosen method of proximal femur fixation introduced some element of heterogeneity. However, this would be more pronounced had there been a marked difference in mortality or pin site infection, which was reported as zero incidences.

Implications for practice and future research

The findings of this review suggest that there is no significant delay to fracture healing in patients who are initiated opportunistically on bisphosphonate therapy shortly after proximal femoral fracture fixation, nor is there a difference in delayed or non-union rates, mortality and patient related outcomes. This finding is in line with non-RCT studies and previous reviews, and may serve to alleviate the fears of some clinicians who are presently deferring treatment initiation until after fracture union; this is important to not miss opportunities for secondary prevention of osteoporosis-related fractures.

More high quality RCTs are called for regarding the early administration of bisphosphonate therapy in the population. We recommend greater transparency with regards to the randomisation process and blinding of outcome assessors. There is a 300-patient RCT registered in progress presently[44]; its results should be combined in future updates. While out of the scope of the current review, future directions of research could consider longer-term follow up regarding the attrition rate and efficacy of secondary prevention with opportunistic post-operative bisphosphonates, as well as the impact of different dosing regimens (e.g. annual infusions vs. weekly tablets). This is particularly given there is evidence of poor retention to treatment.[45] However, Reid *et al.*[46] suggested a preventative effect with a single dose of zoledronic acid persisting up to 3 years, elevating the significance of opportunistic administration. Other barriers to inpatient administration of early bisphosphonates should also be explored.[5] Future reviews could also consider the addition of high-quality observational studies, with the understanding that there is a risk of introducing bias.

Conclusions

This systematic review and meta-analysis provides low-level evidence that there is no reduction in time to healing or delay in bony union for patients receiving bisphosphonates within 1 month of proximal femur fixation. Further high quality RCTs are needed to strengthen the findings of this review.

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Author contributions

Yui Yee Felice Tong: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing. **Samuel Holmes:** Data curation; formal analysis; investigation; validation; writing – review and editing. **Andrew Sefton:** Conceptualization; project administration; supervision; visualization; writing – review and editing.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplementary Figure 1 – PRISMA flowchart
Supplementary Figure 2 – Meta-analyses for secondary outcomes: Mortality, Function and Pain
Supplementary Figure 3 – Risk of bias bar chart and summary
Supplementary Table 1 – Summary of Findings
Supplementary Material 1 – Search strategies