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REVIEW

Timing of the initiation of bisphosphonates after surgery for fracture healing: a systematic review and meta-analysis of randomized controlled trials

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Abstract
Summary We performed a systematic review and meta-analysis of randomized clinical trials. Early administration of bisphosphonates (BPs) after surgery did not appear to delay fracture healing time either radiologically or clinically. Furthermore, the anti-resorptive efficacy of BPs given immediately after surgical repair should positively affect the rate of subsequent fractures.
Introduction Bisphosphonates (BPs) are widely used in the prophylaxis and treatment of osteoporosis. However, early administration of BPs after surgical repair of a fracture may limit the reserve capacity of bone to heal. The aim of this review and meta-analysis was to analyze the benefits and adverse effects of early administration of BPs and give recommendations regarding when BPs should be utilized.
Methods We identified randomized controlled trials comparing the early administration of BPs to placebo, delayed BP treatment, or no therapy in adult patients after surgery. The search was performed in PubMed, the Cochrane Library, and Embase.
Results Ten studies with 2888 patients were included. Four trials used alendronate, three trials used zoledronic, two trials used risedronate, and one trial used etidronate. Early administration of BPs was considered less than 3 months after surgery. Patients treated with BP therapy had no significant differences in radiological fracture healing times compared with patients in the control group (mean difference [MD] 0.47, 95 % confidence interval [CI] −2.75 to 3.69). There were also no significant differences in the rate of delay or nonunion of fracture healing (odds ratio [OR] 0.98, 95 % CI 0.64 to 1.50). However, the bone mineral density (BMD) of total hips did significantly improve after 12 months of treatment with BPs. And most bone turnover markers of patients in the study group were significantly decreased.
Conclusions Early administration of BPs after surgery did not appear to delay fracture healing time either radiologically or clinically. Furthermore, according to the changes in BMD and bone turnover markers, the anti-resorptive efficacy of BPs given immediately after surgical repair should positively affect the rate of subsequent fractures.

Keywords Bisphosphonates · Early administration · Fracture healing · Meta-analysis · Systematic review

Introduction

Osteoporosis is a major public health concern. Bisphosphonate (BP) therapy has become the most widely used method for the treatment of osteoporosis [1–4]. BP therapy inhibits osteoclast-mediated bone resorption to prevent bone loss and to improve bone strength [5–8]. However, because osteoclasts are important for remodeling the callus into cortical bone, concerns remain regarding BPs' possible adverse effects on the healing process of fractures [9, 10].

It has long been debated whether BPs are helpful or harmful in acute fracture healing. Animal studies have reported controversial results, with some articles reporting delays in fracture healing [11–13], no effect [14, 15], or even enhanced fracture healing [16–21]. Some case reports suggest that a potential complication of long-term BP therapy may be a delay in fracture healing in humans [22–24]. A case control study reported that BP use in the post-fracture period was associated with an increased probability of nonunion (odds ratio [OR] 2.37, 95 % confidence interval [CI] 1.13 to 4.96) [25].

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Because it has been postulated that BPs may affect fracture healing, clinicians may consider waiting for several months following a fracture before introducing BP therapy into a patient's regimen. Recent randomized clinical trials of BPs are focused on whether the early use of BPs after surgery (less than 3 months) have any adverse or beneficial effects on fracture healing. Data from the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) Recurrent Fracture Trial showed that no clinically significant effects on fracture healing could be found after zoledronic acid treatment [26]. Lyles et al. [27] reported that treatment with zoledronic acid after a hip fracture is associated with a 35 % reduced risk of new clinical fractures and 28 % reduced risk of death from all causes. A systematic review [28] on BP used in the upper limb fractures concluded that differences in union time between BP users and non-BP users were not clinically significant.

To formulate recommendations on when BPs should be used, we conducted a systematic literature review and meta-analysis of randomized controlled trials (RCTs) to determine whether the timing of BP infusion affected the fracture healing.

Method

Search strategy

We searched PubMed, the Cochrane Library, and Embase in March 2014 for studies published between 1966 and February 2014 using the following combination of terms: "bisphosphonates," "bone remodeling," "bone healing," "delayed union," "nonunion," "fracture healing," and "fracture". No language restrictions were applied. Two investigators (YTLi and HFCai) independently completed the search and assessed the identified titles for relevance. Abstracts were screened for all potentially relevant titles, and full papers were obtained for all abstracts of potential relevance. In addition, for trials with several treatment groups, the eligibility of each individual group was assessed and only those relevant were included. The reference lists of the selected papers were also screened for articles that may have been overlooked in the initial search, and references cited in the identified articles were searched manually.

Selection criteria

This systematic review and meta-analysis followed a detailed, prespecified protocol that set out the objectives, inclusion criteria for trials, data to be collected, and analyses to be completed.

Studies were considered for inclusion if they met the following criteria: (1) the type of study design was a RCT, (2) participants were adults with acute fractures and were accepting BP therapy following surgical repair of the fracture, and (3) the intervention was the initiation of BPs earlier than 3 months compared with the initiation of placebo at the same time, BPs begun later than 3 months after surgery, or no therapy.

Studies were considered for exclusion if they met the following criteria: (1) participants previously used BPs or parathyroid hormone, unless patients had undergone a washout period; (2) participants had breast cancer, prostate cancer, lung cancer, multiple myeloma, or other diseases that may affect bone healing; (3) the articles were not available or were published in languages other than English; and (4) the fracture treatment was nonsurgical or the surgery involved inserting prostheses, such as total hip arthroplasty (THA).

Data collection and endpoints

Up-to-date information on the data randomization and follow-up was sought, as well as the details of group allocation, age, gender, type of fracture and treatment, time of BP initiation, the medication used, and the body mass index (BMI) and bone mineral density (BMD). All data were thoroughly checked for consistency, plausibility, and integrity of randomization and follow-up. The two responsible trial investigators resolved any queries and verified the final database entries. The primary outcome was the time of fracture healing, as determined by radiography, which was defined as the time of fracture bridging by the trabecular or osseous bone in at least one cortex as seen on either anteroposterior or lateral radiographs.

Statistical analysis

Data were analyzed using Review Manager Software (RevMan version 5.2; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The results were expressed in terms of OR and a 95 % CI for dichotomous outcomes and in terms of mean difference (MD) and 95 % CI for continuous outcomes. The number of patients enrolled or randomized was used in the calculation of study and patient demographics.

Comparison groups included those patients in whom BP initiation was earlier than 3 months versus the parallel initiation of placebo, the initiation of BPs later than 3 months, or no therapy. The I^2 test and associated P values were used to assess the heterogeneity of the studies. We measured inconsistency across trials using the I^2 statistics; results ranged between 0 % (i.e., no observed heterogeneity) and 100 %, with high values reflecting increasing heterogeneity. P values <0.10 were considered statistically significant. An I^2 value less than 25 % was considered to be homogeneous; an I^2 value between 25 % and 50 % was considered to have low heterogeneity; an I^2 value between 50 % and 75 % to have moderate heterogeneity; and an I^2 value above 75 % to have high heterogeneity. A fixed effects model was applied when the studies were homogeneous or the statistical heterogeneity was low. However, when the statistical heterogeneity was moderate or high, we used the random effects

model. Two independent reviewers evaluated the studies' eligibility, assessed the quality, and assessed the extracted data, aiming for achieving a high level of correlation in the quality and validity of the findings. Disagreements were resolved by consensus.

Results

The literature search identified 1717 trials until February 2014, of which 41 were considered potentially relevant. Additional trials were identified by searching the reference lists of trials included in the study. Figure 1 illustrates the process of study selection. Ten trials [25–27, 29–46] were finally designed to evaluate the effect of the timing of BP initiation after surgery for fracture healing and fulfilled the inclusion criteria for published studies (including safety reports), including a large-scale multicultural RCT with a large number of reports written about it [26, 27, 38–46].

Patient characteristics

A total of 2888 patients were randomly assigned in the 10 trials included in this meta-analysis. Regarding sex, 22.4 % (n=646)

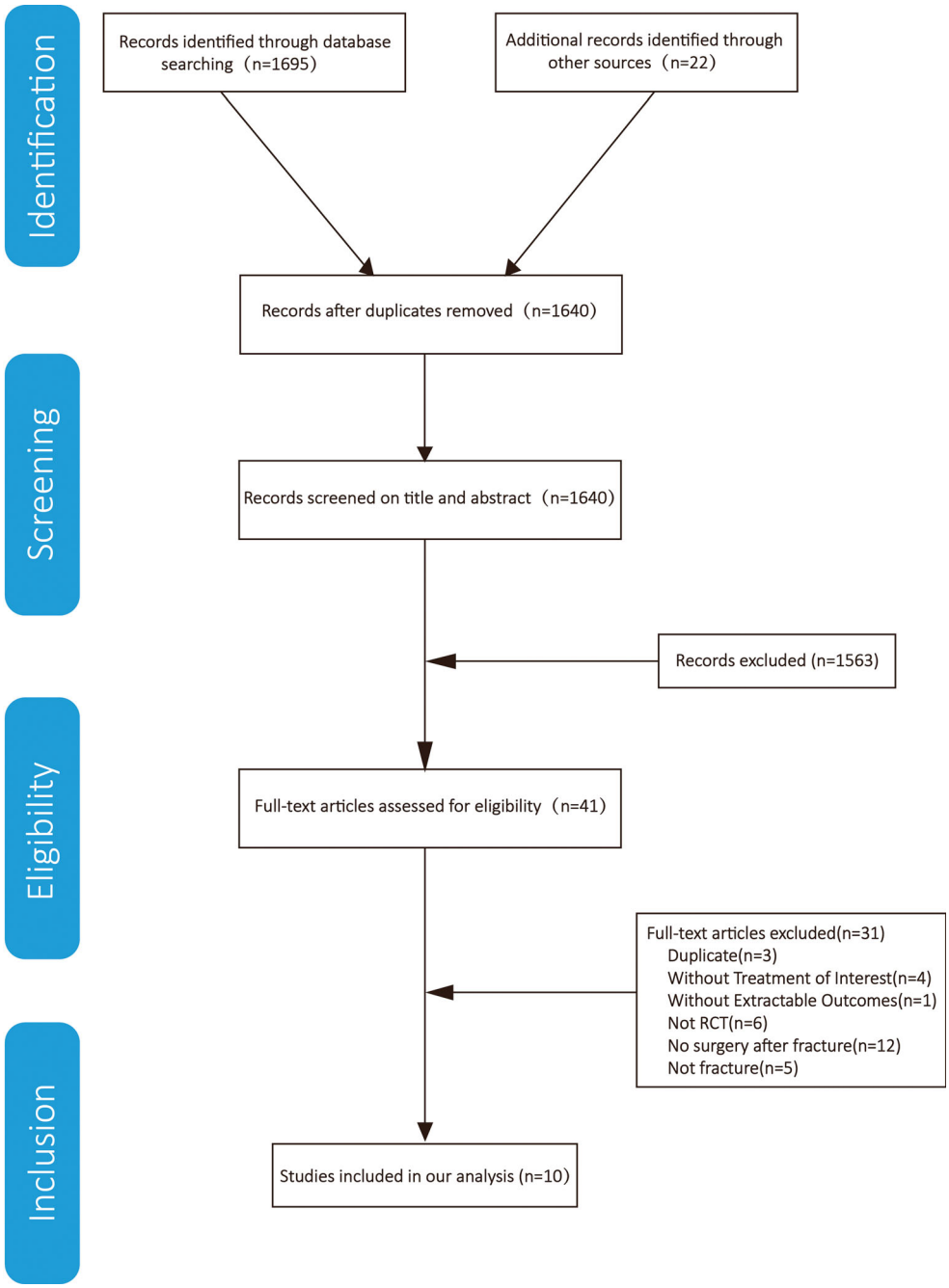

Fig. 1 Flow diagram of selection of studies

Table 1 Characteristics of included studies

Studies	Age		Sex		BMI(kg/cm^2)		Baseline T-score		Type of fracture	Type of surgery	Follow-up time
	Mean	SD	Female	Male	Mean	SD	Range	*N*			
Utchiyama et al. [29]	70		76	4			≤−2.5 −2.5 to −1 >−1.0	11 15 14	Distal radius fracture	Open reduction and internal fixation (ORIF)	6 months
Li et al. [25]	64	6	53	29	22.9	3.5	≤−2.5 −2.5 to −1 >−1.5	20 14 7	Transforaminal lumbar interbody fusion (TLIF) surgery	Open reduction and internal fixation	12 months
Kim et al. [30]	75.1	10	50	24	20.8	2.1			Intertrochanteric fracture	Internal fixation	≥12 months
Hyun et al. [31]	≥50						≤2.5	All	Distal radial fracture	Volar locking plate fixation	6 months
Harding et al. [32]	49	6	60		27.1	3.2	≤−2.5 −2.5 to−1 >−1.0	0 9 37	Knee osteoarthritis high tibial osteotomy	The hemicallotasis technique (HCO)	≥18 months
Cecilia et al. [34]	81	7	191	48	25.3	3.7	2.62±1.07		Intracapsular hip fracture (44 %) Intertrochanteric hip fracture (56 %)	Surgery	12 months
Altintas et al. [35]	75	6	59	0					Intertrochanteric fracture Femoral neck fractures	External fixation Pertrochanteric fixator and pins	3 months
Sato et al. [36]	75		80	0					Femoral neck fracture (48.8 %) Trochanteric fracture (51.3 %)	Operative reduction	≥3 months
Poest et al. [37]	46	13	18	23	25.2	–			Tibial and fibular shaft fracture (10) Distal tibial fractures (5) Ankle fracture (26) Bimalleolar (15) Trimalleolar (11)	Open reduction and internal or external fixation	12 months
Colon et al. [46]	75	10	1619	508	24.7	4.4	≤−2.5 −2.5 to −1 >−1.5	885 734 234	Femoral neck 1164 (54.8 %) Intertrochanteric 702 (33.0 %) Subtrochanteric 106 (5.2 %) Other/unknown 153 (7.1 %)	Surgery	36 months

Table 2 Detail of intervention

Study	BP	Schedule	Control	Ne/Nc	Mean time between fracture and treatment start	
					Study	Contral
Uchiyama et al. [29]	PO.alendronate	35 mg/week	Delay	40/40	A few days postoperatively	4 months postoperatively
Li et al. [25]	IV.zoledronic	5 mg/year	Placebo	41/41	3 days postoperatively	3 days postoperatively
Kim et al. [30]	PO.risedronate	35 mg/week	Delay	60/30	From 7 days postoperatively	3 months postoperatively
Gong et al. [31]	PO.alendronate	70 mg/week	Delay	30/30	14 days postoperatively	3 months postoperatively
Harding et al. [32]	IV.zoledronic	4 mg/year	Placebo	25/21	28 days postoperatively	28 days postoperatively
Cecilia et al. [34]	PO.alendronate	70 mg/week	No therapy	125/114	2 to 4 days postoperatively	2 to 4 days postoperatively
Altintas et al. [35]	PO.risedronate	5 mg/day	No therapy	26/20	5 days postoperatively	5 days postoperatively
Sato et al. [36]	PO.etidronate	200 mg/day	Placebo	40/40	1 day postoperatively	1 day postoperatively
Poest et al. [37]	PO.alendronate	10 mg/day	Placebo	21/20	A few days after surgery	–
Colon et al. [46]	IV.zoledronic	5 mg/year	Placebo	1054/1057	≤90 days postoperatively	≤90 days postoperatively

BP bisphosphonate, *PO* oral, *IV* intravenous, *Ne* number of experiment group, *Nc* number of control group

of patients were men and 77.6 % (n=2242) were women (Table 1). As for fracture type, three trials included fractures of the distal radius [29, 31, 37], five trials were hip fracture [27, 30, 34, 35, 37, 47], and one trial included spinal fractures [25]. The overall mean age was 74.2 years. The average BMI of the 16,944 patients at baseline was 24.6. The baseline T-score was different; one study included all of the patients whose T-scores were ≤2.5 [31]. There was also variability in the type of fracture. Two of the studies included patients who had distal radius fractures [29, 31], six involved hip fractures [27, 30, 34, 35, 37, 47], one included spinal surgery [25], and one included keen surgery [32, 33]. The more detailed characteristics of the included studies are listed in Table 1.

Trial design

In four trials [29, 31, 34, 37], patients were randomly assigned to alendronate in addition to standard-of-care therapy. Four trials used alendronate [29, 31, 34, 37], three trials used zoledronic [25, 32, 33, 46], two trials used risedronate [30, 35], and one trial used etidronate [36]; the schedule varied as reflected in Table 2. The control group included the delayed use of BPs or use placebo instead of BPs or no therapy. The time of the first administration of BPs after surgery varied from 1 to 90 days in the experimental group compared with 3 to 4 months in the delayed group.

Quality of trials

Allocation concealment was reported as adequate in five trials [25, 31–34, 46] and as high risk in three trials [29, 32, 33, 35]. Few of the trials have been open label. The quality assessment of the included trials has been performed according to the Cochrane risk of bias tool, as described in detail in Fig. 2. We appraised the rate of patients lost to follow-up, and in the majority of the studies, the rate was lower than 20 %. However, there was one trial in which the dropout rate was high (39 %) [34].

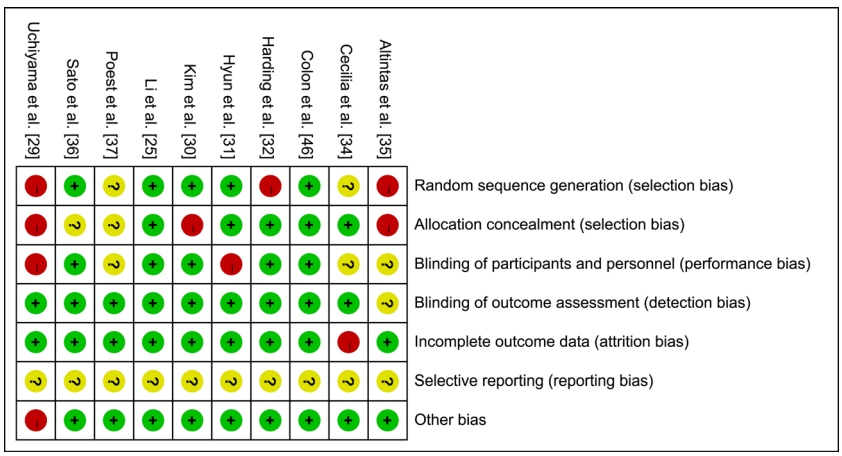

Fig. 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study. The *red with a minus* means high risk of bias; the *yellow with a question mark* means unclear; the *green with a plus* means low risk of bias

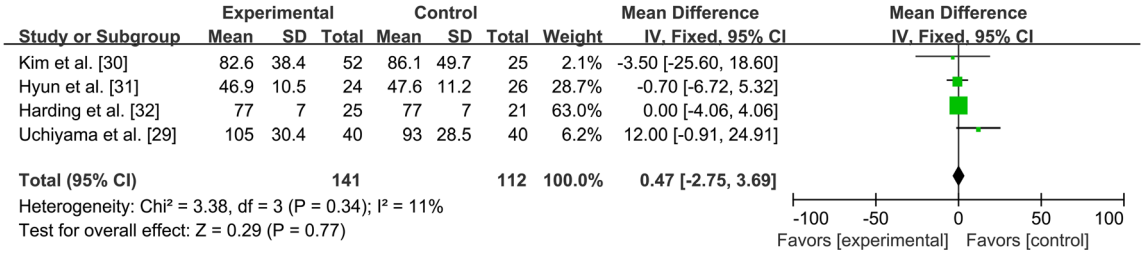

Fig. 3 Forest plot for radiological fracture healing time

Radiological fracture healing time

Time of radiographic fracture healing was defined as the time to fracture bridging by trabecular or osseous bone in at least one cortex as seen on either anteroposterior or lateral radiographs. Four trials (253 patients) were eligible for the meta-analysis of radiological fracture healing times [29–33]. All patients in these studies underwent internal fixation. According to the results, patients who were treated with early BP therapy had no statistically significant difference in radiological fracture healing times compared with patients in the control group (MD 0.47, 95 % CI −2.75 to 3.69; I^2 of heterogeneity 11 %, P=0.34; fixed effects model) (Fig. 3).

Delay or nonunion of fracture healing

The delay and nonunion rates were two of the most serious complications of fracture healing. Four trials (2365 patients) were eligible for the meta-analysis of risk of delay or nonunion of fracture healing. Patients who were treated with early BP therapy did not have a significantly higher risk of delay or nonunion of fracture healing than patients in the control group (OR 0.98, 95 % CI 0.64 to 1.50; I^2 of heterogeneity 18 %, P=0.30; fixed effects model) (Fig. 4).

Clinical assessment

The clinical outcome was evaluated using a variety of assessments, which are all listed in Table 3. Different types of assessment could not be compared with each other, so we created a systematic review rather than a meta-analysis. No significant differences were observed between the mean DASH scores, ODI scores, KOOS scores, Quick DASH, Koval classifications, and Rankin scales of the two groups. As for health-related quality of life (HRQoL), benefits were noted at 24 months of follow-up in the experimental group. The end-of-study time point also showed a treatment benefit, while the 36-month time point did not.

Change in bone mineral density

The change in bone mineral density is one part of the influence the BPs had on bone. We compared two groups to decide whether early use of BPs had any negative influence on this change. BPs significantly improved total hip bone mineral density after 12 months of treatment compared with the control group, as reported by Cecilia D van der Poest Clement (except contralateral hip) and Cathleen S [27, 34, 37]. When it comes to the femoral neck [27, 37], two studies reported that there was a statistical difference between the two groups [27, 34, 37], while the results from Cecilia. D [34] and van der Poest Clement (for contralateral femoral neck bone) [27, 34, 37] suggested there was no difference. Additionally, as reported by two studies, the BP group also had better lumbar spine bone mineral density [27, 37]. More detail is shown in Table 4.

Bone turnover markers assessment

Bone turnover markers fulfill an essential role in bone metabolism; a decrease in these markers may have an important clinical impact on the assessment of bone mineral density. Data from

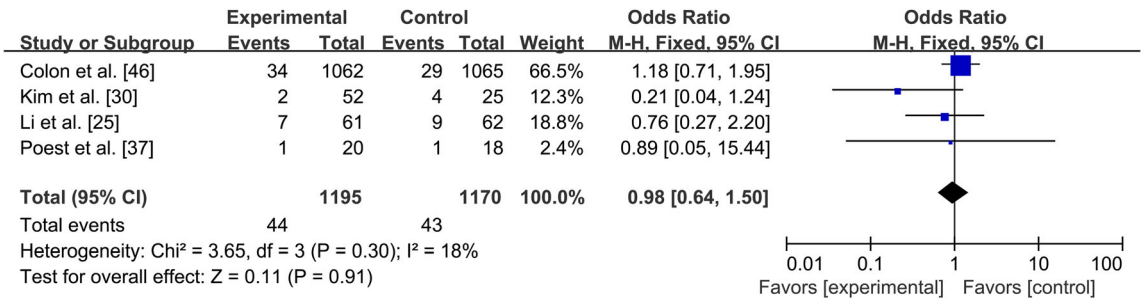

Fig. 4 Forest plot for delay or nonunion of fracture healing

Table 3 Clinical healing

Study ID	Definition of endpoint	Time	Ne	Result of BP group	Nc	Result of control group	*P* value
Uchiyama et al. [29]	Quick DASH score	6 months	40	9.6	40	8.6	No difference
Li et al. [25]	Oswestry Disability Index	Baseline	41	23.6	41	23	No difference
		3 months	41	12.9	41	13.7	No difference
		6 months	41	11.1	41	14.2	No difference
		9 months	41	9.3	41	14.3	No difference
		12 months	41	10.3	41	14.7	No difference
Kim et al. [30]	Koval classification	12 months	52	2.4±1.87	25	2.2±1.54	0.948
Gong et al. [31]	DASH score	6 months	24	17±14	26	15±14	0.61
Harding et al. [32]	KOOS	First day after fixator removed	25		21		No difference
Sato et al. [36]	Rankin scale	3 months	36	1.3±0.1	37	1.1±0.1	0.59
Colon et al. [46]	HRQoL (Change from baseline)	6 months	886	5.43±0.51	895	5.73±0.51	0.6573
	LSM±SE	12 months	813	7.96±0.57	821	7.03±0.56	0.2285
		24 months	496	9.26±0.76	490	6.17±0.77	0.0024
		36 months	114	7.12±2.05	110	4.06±2.04	0.1457
		End of study	923	7.67±0.56	942	5.42±0.56	0.0034

Ne: number in experimental group, *Nc* number in control group

these studies suggested that early BP therapy decreased the N-telopeptide of type I collagen (NTX), the amino-terminal propeptides of type I collagen (PINP), the C-telopeptide of type I collagen (CTX), β-crosslets (BCLs), and ionized calcium significantly compared with the control group [25, 29, 34–37]. However, significant increases were observed in intact parathyroid hormone (PTH) and 1, 25-$(OH)_2$D [34, 36]. There was no statistically significant difference in 25-OHD [34, 36, 37] between the two groups. When it comes to osteocalcin (BGP or OC), Sato Y reported a significant increase after 3 months in the study group, although this finding was inconsistent with the result reported by Cecilia D and van der Poest Clement after 12 months. As for bone alkaline phosphatase (BALP), Uchiyama S and van der Poest Clement reported decreases after 6 and 12 months in the study group, respectively, but Cecilia D reported that there was no difference between the two groups after 12 months. When it comes to deoxypyridinoline (DPD), Sato Y reported a decrease after 3 months, while van der Poest Clement reported that there was no difference after 12 months. All data are listed in Table 5.

Table 4 Bone mineral density

Study ID	Definition of endpoint	Time	Ne	Result of BP group	Nc	Result of control group	*P* value
Uchiyama et al. [29]	Lumbar spine	6 months	40	6.5 (−3 to 29)%	40	−0.2 (−36.5 to 13.4)%	0.002
Harding et al. [32]	Proximal femur (the osteotomy gap)	6 months	25	1.14±0.27 g/cm^2	21	1.01±0.18 g/cm^2	0.1
Cecilia et al. [34]	Total hip	12 months	125	0.79±7.05 %	114	−1.78±7.51 %	0.008
	Lumbar spine			0.32±7.45 %		−0.52±4.46 %	0.380
	Trochanteric			1.07±7.68 %		−2.63±9.53 %	0.01
	Intertrochanteric			−1.97±8.46 %		−1.26±7.40 %	0.021
	Femoral neck			1.21±6.91 %		−2.43±10.45 %	0.713
Poest et al. [37]	Total hip–fractured	12 months	20	−1.9±1.1 %	18	−5.9±1.0 %	0.009
	Total hip–contralateral			1.1±0.8 %		−0.4±0.6 %	No difference
	Femoral neck–fractured			0.6±1.3 %		−4.0±1.4 %	0.016
	Femoral neck–contralateral			1.4±1.1 %		−0.6±1.0 %	No difference
	Lumbar spine			2.8±1.2 %		−0.6±1.0 %	0.044
Colon et al. [46]	Total hip	12 months	1065	2.6 %	1062	−1.0 %	<0.001
	Femoral neck			0.8 %		−1.7 %	<0.001

Ne number in experimental group, *Nc* number in control group

Table 5 Change of bone maker in each study

Study ID	Marker	Time	Ne	Result of BP group	Nc	Result of control group	*P* value
Uchiyama et al. [29]	BALP	6 months	40	−35.4 (−71.2 to 54.1)%	40	−8.8 (−63.5 to 81.7)%	<0.001
	NTX	6 months	40	−48.6 (−84.4 to 24.7)%	40	−32.4 (−69.3 to 87.7)%	0.036
Li et al. [25]	PINP	10 days	41	−18.0 %	41	−19.1 %	No difference
		3 months	41	−29.7 %	41	7.1 %	<0.0001
		6 months	41	−34.1 %	41	–	<0.0001
	CTX	10 days	41	−62.5 %	41	24.6 %	<0.0001
		3 months	41	−70.8 %	41	33.3 %	<0.0001
		6 months	41	–	41	19.3 %	<0.0001
		12 months	41	−77.1 %	41	–	<0.0001
Cecilia et al. [34]	BCL	12 months	68	0.35	79	0.49	<0.001
	BALP	12 months	68	11.2	79	16.8	No difference
	BGP	12 months	68	7.5	79	10.5	<0.05
	25-OHD	12 months	68	36.7	79	41.2	No difference
	iPTH	12 months	68	64	79	56.8	<0.05
Altintas et al. [35]	Urine NTX	3 months	26	−49.70 %	20	5.80 %	<0.0001
Sato et al. [36]	Calcium	3 months	36	−7.2±4.0 %	37	−4.70±4.0 %	<0.0001
	Intact PTH	3 months	36	117.2±11.5 %	37	53.0±5.3 %	<0.0001
	Intact BGP	3 months	36	324.4±57.6 %	37	222.3±31.3 %	0.0436
	Urine DPD	3 months	36	−67.5±3.0 %	37	−43.7±1.8 %	<0.0001
	25-OHD	3 months	36	−13.9±2.1 %	37	−13.8±3.1 %	0.91
	1,25-OHD	3 months	36	67.1±4.4 %	37	30.1±5.0 %	<0.0001
Poest et al. [37]	Urine NTX	12 months	20	−48 %	18	−16 %	<0.001
	Urine DPD	12 months	20	−41 %	18	−33 %	No difference
	Serum BALP	12 months	20	Baseline	18	30 %	*P*<0.01
	Serum OC	12 months	20	Baseline	18	Baseline	No difference

Ne number in experimental group, *Nc* number in control group, *NTX* N-telopeptide of type I collagen, *PINP* amino terminal propeptides of type I collagen, *CTX* C-telopeptide of type I collagen, *BCL* β-crosslaps, *PTH* parathyroid hormone, *OC* osteocalcin, *BALP* bone alkaline phosphatase, *DPD* deoxypyridinoline

Adverse events

Significant differences were identified between the BP group and the control group with regard to myalgias, pyrexia, muscle pain, and influenza-like symptoms [27, 33]. As a review suggests that approximately 18 % of patients receiving the first doses of IV bisphosphonate experience an acute-phase reaction (fever, headache, myalgia, arthralgia, malaise), the incidence can be reduced by approximately 50 % by acetaminophen and dose decreases with subsequent infusions [48]. Additionally, treatment with zoledronic acid after a hip fracture is associated with reduced risks of death [27]. Relevant data mentioned above are reported in Table 6.

Discussion

This meta-analysis, which included 253 individuals with healing time measurements from four RCTs and 2365 participants with delayed or nonunion rates of fracture healing measurements from six RCTs, demonstrated that there were no differences between the two groups, despite BPs acting as a potent anti-resorptive agent. Moreover, early BP administration had no apparent adverse effects on radiological or clinical results. One possible explanation is that BPs do not directly affect osteoblasts or other cells participating in the inflammatory phase, soft callus formation or hard callus formation [49] but could delay remodeling of the hard callus involving osteoclasts [50]. Furthermore, fracture recovery was more greatly affected by fracture stability provided by internal or external fixation than by the pharmacological effects of BPs. Despite some case reports suggesting a potential complication of fracture healing of BP therapy after long-term use [22–24], our study only included the participants who had not accepted BP therapy before surgery of fracture or had undergone a washout period.

Early administration of BPs was associated with higher BMDs. Additionally, one of the HORIZON–RFTs reported that patients dosed between 6 weeks and 3 months after hip

Table 6 Adverse effects

Study ID	Adverse effects	Time	Rate of BP group *n*,%	Rate of control group n,%	*P* value
Uchiyama et al. [29]	No apparent adverse effects	6 months	–	–	–
Kim et al. [30]	Excessive displacement	–	2(3.8 %)	4(16 %)	0.159
	Revision surgery	–	5(9.6 %)	1(4 %)	0.684
Gong et al. [31]	Adhesive capsulitis of the shoulder	6 months	2(8.3 %)	1(3.8 %)	0.943
Harding et al. [32]	Deep vein thrombosis	–	0	1(4.8 %)	0.93
	Muscle pain and influenza-like symptoms	–	13(52 %)	2(9.5 %)	0.002
	Pneumonia	–	1(4 %)	0	1.000
Cecilia et al. [34]	Contralateral hip fracture	6 months	2(2.9 %)	2(2.5 %)	No difference
	Mild gastric symptoms	6 months	2(2.9 %)	0	No difference
Sato et al. [36]	Peptic ulcer	3 months	1(2.8 %)	0	0.989
Poest et al. [37]	No apparent adverse effects	–	–	–	–
Colon et al. [46]	Any adverse event	–	867(82.3 %)	852(80.6 %)	0.34
	Any serious adverse event	–	404(38.3 %)	436(41.2 %)	0.18
	Death	–	101(9.6 %)	141(13.3 %)	0.01
	Myalgia	–	33(3.1 %)	9(0.9 %)	<0.001
	Pyrexia	–	73(6.9 %)	9(0.9 %)	<0.001
	Stroke—serious adverse event	–	46(4.4 %)	38(3.6 %)	0.37
	Atrial fibrillation	–	29(2.8 %)	27(2.6 %)	0.79

fracture exhibited greater increases in total hip and femoral neck BMDs at month 12 compared with patients dosed earlier than 6 weeks [45]. Further detailed analysis is required and should be performed to determine when the administration benefits BMD the most.

Bone turnover markers play roles in bone metabolism, and decreases in these markers have important clinical value in the assessment of mineral density [51]. CTX, NTX, and DPD are bone resorption markers, while PINP and BALP are bone formation markers [52]. Most bone turnover markers in either the serum or the urine of patients in the study group were significantly decreased ($P<0.05$). Thus, we concluded that BPs inhibited bone metabolism and reduced markers of bone turnover.

This meta-analysis had several limitations. First, the sample sizes of most of the included studies and the study number included in the final analysis were small. Second, the study contained three types of control groups: receiving placebo in parallel, delayed BP treatment, or no therapy. We combined these three groups together because the use of placebo in the early 3 months, BPs after 3 months, or no therapy did not affect the bone healing process in the early stages. Third, the initial pooling of all distal radius, hip, spine, and other kinds of fractures is somewhat controversial. Although there is no definitive evidence that BPs have different effects on various bone types, inherent differences in the structure and function of different bones and variations in reported delay/nonunion rates (all fractures healed for the distal radius [29, 31], 2–16 % for hip [27, 30, 34, 35, 37, 47], and 12–14 % for spine [25]) may suggest that these types of fractures may undergo differential healing processes. In the analysis of fracture healing time, two studies of distal radius [29, 31], one of the hip [30], and one of knee [32, 33] were included, and the result was consistent with many studies [30, 32, 42]. While in the analysis of the delay or nonunion of fracture healing, three studies including the hip [27, 30, 37, 53] and one including the spine [25] were reviewed. Because of the limited number of studies, we did not sub-analyze the different bone types.

The studies included in this meta-analysis were quite variable in terms of patient age, gender, BMI, baseline BMD, type of fracture and surgery, BP type, dose, administration route, initial time, duration, and fracture healing definition. Most studies defined the time to cortical bridging as the fracture healing time, while one defined the consolidation of approximately two-thirds of the osteotomy gap [32, 33] and others did not give a definition. Although a multitude of other covariates of interest are known to exist, we were unable to analyze them all because of inconsistent reporting in the original studies. These sources of heterogeneity were appropriately treated through a random effects model.

In summary, our findings suggest that early administration of BPs after surgery will not delay fracture healing time, either radiologically or clinically. Furthermore, according to the changes in BMD and bone turnover markers, the anti-resorptive efficacy of BPs given immediately after surgical repair should positively affect the rate of subsequent fractures.

Thus, the possible complications of fracture healing in early BP therapy do not outweigh the benefits.

Conflicts of interest None.

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