

Efficacy of Intramuscular Infusion of Clodronate in Patients With Erosive Osteoarthritis: A Systematic Review

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Abstract Introduction: Erosive osteoarthritis (EOA) is a rarer form of osteoarthritis (OA) and more aggressive, damaging cartilage and bone and leading to joint deformities. A nitrogen-free bisphosphonate, clodronate, may have a positive impact on treating EOA. Anti-inflammatory, osteoclast-inhibiting, chondrogenesis, bone resorption inhibition, and pain control make clodronate a promising EOA treatment. Aims and objectives: This study aims to evaluate the efficacy of intramuscular administration of clodronate infusion in the treatment of EOA. **Method:** A systematic review was performed to evaluate the therapeutic efficacy of clodronate in the treatment of EOA. To find relevant material about the efficacy of injectable clodronate in the treatment of EOA, a systematic search was undertaken on PubMed and Google Scholar with Boolean operators and specific keywords, including "clodronate, erosive osteoarthritis, and osteoarthritis.". **Result:** The studies on clodronate for EOA reveal promising clinical analgesic properties, increased hand strength, and radiological outcomes that eventually lead to pain relief and improved physical and mental health. Some studies found clodronate to be effective in preventing bone marrow lesions and reducing cartilage degradation. The studies show a generally low risk of bias across key domains. Selection bias is well-controlled, with only a few exceptions. Performance bias is effectively managed in all studies. Detection bias is mostly low-risk, with a few exceptions. Attrition bias is well-addressed, though a couple of studies raise concerns. Other biases vary. Recruitment bias, baseline imbalance, and loss of clusters are rare. Incorrect analysis is seldom seen. Overall, the studies demonstrate high methodological rigor, instilling confidence in their findings' validity and reliability. **Conclusion:** The study has concluded that clodronate can effectively alleviate pain, reduce the release of pro-inflammatory mediators, and prevent articular degradation.

Key Words osteoarthritis, clodronate, pain, erosive osteoarthritis, joint pain

1. Introduction

Osteoarthritis (OA) is a developing disease worldwide, causing significant pain and disability for many people. It is more common in older women, and the prevalence increases with age [1]. Erosive osteoarthritis (EOA) is a rare kind of OA that causes severe cartilage destruction as well as bone erosion, resulting in abnormalities and reduced hand function, mostly due to inflammatory alterations in synovial fluid and subchondral bone [2]. EOA's initial symptoms include swelling, stiffness, and pain in the affected joints, and X-rays frequently reveal central bone erosions, subchondral cysts, bone fusion, and joint space narrowing [3]. Gender and advanced age are significant risk factors for the development of EOA, with genetics also being a contributing role [4]. The lack of knowledge about the early pathophysiology of EOA precludes the development of medications that can stop its

progression (Figure 1) [5], [6]. However, initiatives are being undertaken by healthcare professionals to adopt a treatment process that controls pain and enhances physical activity as well as improves the quality of life of the patients [4]. Acetaminophen and nonsteroidal anti-inflammatory medicines (NSAIDs) are the first lines of treatment for EOA, while clodronate, a "nitrogen-free bisphosphonate" typically prescribed for "osteo-metabolic disorders," has also been considered for this condition [7]. Bisphosphonates are the non-hydrolyzable, synthetic analogs of pyrophosphates containing R1 and R2 side chains binding to central carbon and a P-C-P core [6]. Both bisphosphonate's chains are noted to inhibit the resorptive actions of osteoclast bone [8], [9]. Incorporation of clodronate within cells inhibits "farnesyl diphosphonate synthase" within osteoclasts thereby preventing isoprenoid lipids formation necessary for prenylation of

GTPase like Ras, Rac, and Rho [10]. Furthermore, apart from its demonstrated anti-resorptive effectiveness in several disorders associated with bone resorption, particularly when used over an extended period, it also exhibited the ability to inhibit the production of pro-inflammatory mediators of nitric oxide from macrophages [11]–[15]. Hence, owing to its diverse impact on many pathways implicated in the progression of OA, its anti-inflammatory and anti-resorptive characteristics, along with a satisfactory safety record, makes it a very promising candidate for novel therapeutic interventions targeting this condition. Clodronate is a particularly appropriate option for the treatment of EOA [16]–[24].

2. Methods

This is a systematic review being conducted by the authors at Qassim University between January, 2023 and September, 2023.

A. Search Strategy

The search strategy is a crucial procedure for obtaining valuable and insightful information regarding the content. In context with the current study based on analyzing the efficacy of intramuscular infusions of clodronate among patients suffering from erosive osteoarthritis, online libraries like PubMed, Google Scholar, Researchgate, and Web of Science were used for retrieving relevant journals and articles. The Boolean method has been used for refining the search process and obtaining journals and articles that highlight the efficacy of clodronate in the treatment of OA. Terms like "clodronate and osteoarthritis," "erosive osteoarthritis and clodronate therapy," "intramuscular clodronate and osteoarthritis treatment," and "intra-articular clodronate administration and osteoarthritis treatment" were used for obtaining relevant journals and articles. The study found 102 documents initially. Some documents were excluded due to their duplicacy or ineligibility for various reasons. Out of 22 articles, 5 were removed because the relevant findings could not be obtained. Lastly, five articles were removed that were published before 2012; the results may be inconsistent. Finally, this review considered 12 studies for evaluation.

PICOS stands for Population, Intervention, Comparison, Outcome, and Study design. It's a framework used in evidence-based medicine to formulate a clinical question. For this review, while including studies, PICOS was assumed to be:

- Population: Patients diagnosed with erosive osteoarthritis.
- Intervention: clodronate regimen.
- Comparison (if applicable, this depends on the study design): This could be a placebo group or another treatment option.
- Outcome: The specific outcomes measured for evaluation of the outcomes. These are pain reduction, joint function improvement, radiographic changes, etc.
- Study Design: This could be a randomized controlled trial (RCT), Clinical Trial and Case Series.

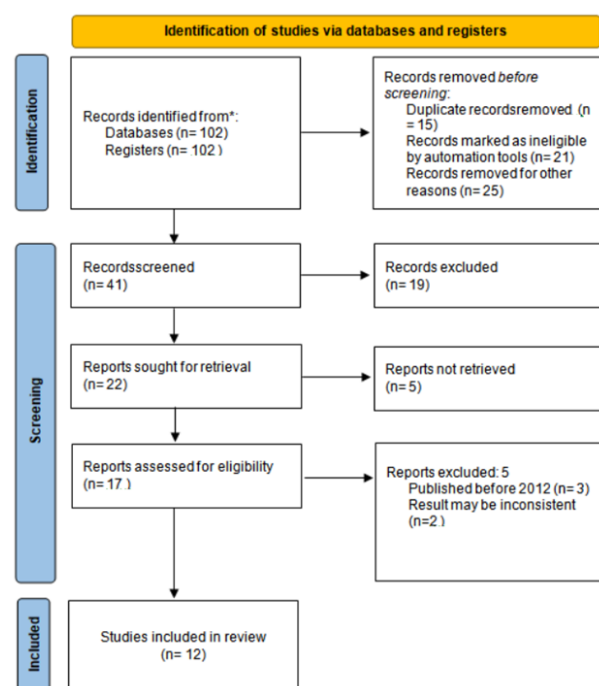


Figure 1: PRISMA flow chart for research study selection

B. Quality Assessment

The Cochrane Collaboration's Quality Assessment Tool, known as the "Risk of Bias" tool, is a cornerstone in evaluating the rigor of systematic reviews, particularly focused on randomized controlled trials (RCTs). This tool scrutinizes crucial aspects of study design and execution. It assesses random sequence generation, allocation concealment, blinding of participants and outcome assessors, management of incomplete outcome data, selective reporting, and potential sources of bias. Each domain is rated as 'Low risk', 'High risk', or 'Unclear risk' of bias. This systematic approach ensures a meticulous examination of study quality, offering a reliable foundation for evidence-based healthcare decisions [12], [14], [19].

C. Inclusion and Exclusion Criteria

The study based on determining the efficacy of clodronate in the treatment of OA comprised of consideration of 12 articles that highlighted the effectiveness of clodronate in erosive osteoarthritis.

- 1) Inclusion criteria:
 - 1) articles published on and after 2012.
 - 2) articles that emphasized only the effectiveness of clodronate in the treatment of EOA and OA.
 - 3) articles published in English.
 - 4) articles that are Randomized Control Trial or Clinical trial, meta-analysis and systematic review.
- 2) Exclusion Criteria:
 - 1) If results are inconsistent.

- 2) If proper findings of clinical and radiological outcomes were not done.
- 3) If supporting documents were not provided.

3. Results

Table 1 summarizes studies from 2000 to 2023 in a systematic review on Clodronate’s effects. These studies involve varying participant sizes and groups, with the majority being randomized controlled trials (RCTs). The dosage and regimen of Clodronate differ across studies, administered either intramuscularly or intravenously. Clinical and radiological outcomes are evaluated. Frediani et al. (2020) and Saviola et al. (2012) demonstrate significant pain reduction with Clodronate. Saviola et al. (2017) highlight increased hand functionality and pain reduction. Valenti et al. (2017) report reduced osteoarticular pain and improved health. Aitken et al. (2018) note increased mesenchymal stem cells and reduced pain. Frediani et al. (2020) show Clodronate’s pain reduction and impact on bone marrow lesions. Beniamino P et al. (2013) observe pain reduction and prevention of cartilage degradation. Zheng et al. (2022) find Clodronate reduces fracture risk. Hilding M. et al. (2007) report significant pain reduction in the Clodronate group, despite some side effects. Saviola et al. (2023) focus on pain reduction, inflammation, and cartilage regeneration. Rossini et al. (2019) assess pain relief through visual analogue scores. Overall, these studies demonstrate Clodronate’s potential in reducing pain, improving functionality, preventing bone loss, and reducing fracture risk in various musculoskeletal conditions.

Figure 2 presents a summary of included studies categorized by different types of bias. In terms of selection bias, which relates to how participants are assigned to groups, most studies demonstrate a low risk, except for a few that have some concerns. Similarly, performance bias, involving blinding of participants and personnel, is generally well-controlled across all studies, with only a couple showing some concerns. Detection bias, associated with blinding of outcome assessment, is mostly low risk, with a few exceptions. Attrition bias, pertaining to incomplete outcome data, is well-addressed in most studies, although a couple of them raise some concerns. Other biases not fitting into specific categories are noted in varying degrees. Recruitment bias, baseline imbalance, loss of clusters, and incorrect analysis are rare occurrences. Overall, most studies exhibit a commendable level of methodological rigor, with low risk of bias in critical domains, suggesting a high degree of confidence in the validity and reliability of their findings. Details are given in Figure 2.

Figure 3 provides an evaluation of included studies based on their risk of bias in various domains. In terms of selection bias, which pertains to how participants are allocated to groups, most studies exhibit a low risk. Random sequence generation and allocation concealment, critical aspects of this bias, are generally well-controlled with 11 and 10 studies respectively demonstrating low risk. Only one study each raises some concerns in these areas. Regarding performance



Figure 2: The quality summary of each study included in this review

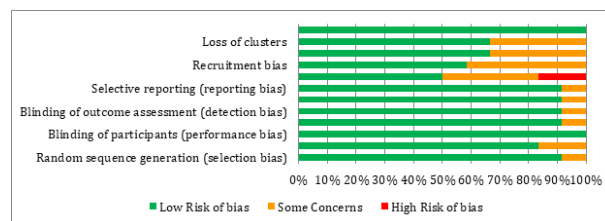


Figure 3: Risk of bias graph showing each risk of bias item

bias, which involves blinding of participants and personnel to prevent their knowledge of group assignment from influencing outcomes, most studies perform well. Blinding of participants and personnel is implemented effectively in 12 out of 12 studies. Detection bias, associated with blinding of outcome assessment, is also well-addressed. Eleven studies have a low risk in this category, while one has some concerns. Attrition bias, pertaining to incomplete outcome data, is controlled in most studies, with 11 demonstrating low risk and only one indicating some concerns. Other biases, not falling into specific categories, are identified in varying degrees across studies. Six studies show low risk, four have some concerns, and two are rated as having a high risk of bias. Recruitment bias, baseline imbalance, and loss of clusters are infrequent, with most studies exhibiting low risk in these domains. Finally, incorrect analysis is rarely observed, with 12 studies conducting appropriate analyses, resulting in a low risk of bias. Overall, the included studies demonstrate a commendable level of methodological rigor, as the majority exhibit low risk of bias across various critical domains. This suggests a high degree of confidence in the validity and reliability of their findings.

4. Discussion

EOA is characterized by degenerative as well as inflammatory phenomena in proximal and distal interphalangeal joints. Our study found that clodronate can reduce osteoarticular pain and this experiment was conducted among 23 patient trials who use clodronate weekly to reduce osteoarticular pain and enhance physical and mental health. It also highlighted mesenchymal stem cell effects. Conventional radiographs

Sl no.	Author	Year (2011-2023)	No. of participants (patients and controls)	Grouping	Type of study	Treatment and Regimen of Clodronate	Clinical Outcomes	Radiological outcomes
1.	Pradhan et al [28]	2020	74	Group A with Clodronate and Placebo group	RCT	Intramuscular clodronate 200 mg daily for 15 days.	Pain reduction	A study of morphological (morphometric) and clinical (VAS) outcomes. Clodronate (200 mg daily) significantly reduced pain and improved functional status in patients with erosive osteoarthritis. Clodronate (200 mg daily) significantly reduced pain and improved functional status in patients with erosive osteoarthritis.
2.	Sankila et al [26]	2012	38	Group A consisted of 24 patients treated for 21 weeks with clodronate 200 mg iv for 15 days followed by intramuscular 200 mg iv for 15 days weekly for 11.5 months. Group B consisted of 14 patients treated with hydroxychloroquine 200 mg daily for 11.5 months.	RCT	200 mg clodronate (IV once for 7 days, followed by 100 mg clodronate (IM once for 14 days) once 1 month.	Clodronate presents an analgesic drug that can pain reduce. Increase of strength in both the hands	Significant reduction in number of painful joints
3.	Sankila et al [25]	2017	45	Group A: 24 patients treated for 21 weeks with intramuscular 200 mg iv for 15 days followed by intramuscular 200 mg iv for 15 days weekly for 11.5 months. Group B: 21 patients treated for 21 weeks with intramuscular 200 mg iv for 15 days followed by intramuscular 200 mg iv for 15 days weekly for 11.5 months.	RCT	Clodronate (ClO) infused through the intraosseous route as a dosage of 200 mg daily for 10 days. Maintenance dosage was given at 200 mg daily (IM) after 1 month and 6 months.	Improving the functionality of the hand and pain reduction	By X-ray, it shows that radiolucency of the drug reduces the amount of erosion of the hand
4.	Nahata et al [29]	2017	26	Group A: 13 patients treated for 21 weeks with intramuscular 200 mg iv for 15 days followed by intramuscular 200 mg iv for 15 days weekly for 11.5 months. Group B: 13 patients treated for 21 weeks with intramuscular 200 mg iv for 15 days followed by intramuscular 200 mg iv for 15 days weekly for 11.5 months.	RCT	200 mg clodronate weekly	By consuming this drug, it can reduce osteoclastic pain and enhance physical and mental health	The morphological (morphometric) and clinical (VAS) outcomes. Clodronate (200 mg daily) significantly reduced pain and improved functional status in patients with erosive osteoarthritis.
5.	Adnan et al [28]	2018	44	Group A with Clodronate and Placebo group	RCT	200 mg clodronate weekly	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI
6.	Flakoll et al [31]	2020	74	Group 1 (intramuscular clodronate 200 mg daily for 15 days and then once weekly for 11.5 months). Group 2 (intramuscular clodronate 200 mg daily for 15 days and then once weekly for 11.5 months).	RCT	Intramuscular clodronate 200 mg	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI
7.	Pradhan et al [28]	2020	74	Group A with Clodronate and Placebo group	RCT	Intramuscular clodronate 200 mg	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI
8.	Pradhan et al [28]	2020	74	Group A with Clodronate and Placebo group	RCT	Intramuscular clodronate 200 mg	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI
9.	Pradhan et al [28]	2020	74	Group A with Clodronate and Placebo group	RCT	Intramuscular clodronate 200 mg	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI
10.	Zhang et al [31]	2022	2000 participants	2001 in control group (NSAID) and 999 patients in study group (Clodronate)	RCT	Clodronate 100 mg daily for 15 days and then once weekly for 11.5 months.	Reduce fracture risk in women	The latest therapy and further shows an impact for women fractures using combined therapies
11.	Sankila et al [25]	2017	45	Group A with Clodronate and Placebo group	Case Series	200 mg clodronate weekly	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI
12.	Sankila et al [25]	2017	45	Group A with Clodronate and Placebo group	Case Series	200 mg clodronate weekly	Clodronate reduces pain and BML	MRI signals: magnetic imaging demonstrates clodronate therapy before and after MRI

Table 1: Summary of the studies considered in this systematic review

done on hand showcase a combination of erosion and bony proliferation that highlight characteristics and patterns of joints commonly known as "saw-tooth" or "gull-wing" deformities [23]–[25]. Swelling and pain are commonly found among patients. Radiological characteristics of EOA involve the narrowing of joint space, marginal osteophytes, and subchondral sclerosis. Excessive osseous proliferation results in severe deformities and often results in interphalangeal ankylosis [26]. EOA is often confused with psoriatic arthritis and patients suffering from EOA often exhibit radiological and clinical features like that of PSA [25]. Furthermore, the formation of new bone and the destruction of interphalangeal joints are often confused in the case of both these diseases. Clodronate, "nitrogen-free bisphosphonate" is predominately used for treating other disorders [27]–[29]. In context study based on the efficacy of intramuscular Clodronate for long-term treatment of OA, was carried out on 74 patients. Patients were divided into two groups group 1 received Clodronate (intramuscularly) at 200mg regularly for 15 days followed by once in a week for 11.5 months [28]–[30]. Group 2 on the other hand received "intramuscular Clodronate" in the same proportions for 2.5 months. "Visual Analogue Scale" was recorded. Study results highlighted that in both groups, there was a significant reduction in VAS scores till 3 months. Group 1 experienced Vas reduction while the Vas score increased for Group 2 [30]. Furthermore, our study found that in the trial conducted among 60 patients, weekly injections of clodronate resulted in increased mesenchymal stem cells, decreased pain (VAS score), and enhanced cognitive and physical functioning. Moreover, MRI findings of fewer lesions in the bone marrow corroborated this effect. In addition, this study also found that daily injections of clodronate for 15 days, clodronate reduced discomfort and bone marrow lesions, according to magnetic resonance imaging.

Bisphosphonates proves to be effective in BME and Clodronate is popular for its analgesic as well as anti-inflammatory property. Intervenes Clodronate on the other hand proves to be effective in the treatment of BME when administered at 300 mg/day for near about 10 days and has proved to be effective for the treatment of painful episodes of EOA [29]. The role played by Clodronate in OA is a matter of debate however, it proves to be a promising therapy in the case of EOA and has proved to be superior to hydroxychloroquine in pain reduction. Furthermore, Clodronate also plays a significant role in chondrocyte differentiation also results in SOX9 upregulation [31], [32]. Bisphosphonates are known for their peripheral as well as central anti-inflammatory im-

pacts. The study found that Clodronate may prevent bone loss and fractures. Anti-inflammatory effects on vertebral fractures and discomfort were discussed. Vertebral fractures were evaluated using vertebral morphometry, and this study found that 800 mg of clodronate reduced fracture risk. Interestingly bisphosphonate application on an animal model of "collagen-induced arthrosis" indicates rational usage of antiresorptive drug emphasized upon role of osteoclastic activation in case of structural bone erosions by "pro-inflammatory cytokines" [33]–[36]. On the other hand, our study found that weekly 2 mg clodronate decreased pain and pro-inflammatory mediators, preserving cartilage. The influence on subchondral bone was shown by MRI. Clodronate intramuscularly for 15 days to lessen MRI-detected loss of subchondral bone and damage to cartilage. However, "amino-bisphosphonates exacerbated joint inflammation" irrespective of its positive impacts however, Clodronate resulted in a positive impact on inhibiting joint inflammation and structural damage [37], [38]. A therapeutic dosage of intramuscular Clodronate followed by a "maintenance dose" is effective for managing symptomatic knee OA thereby enhancing functional outcomes as well as diminishing pain and BML [39]–[41].

Studies based on the efficacy of Clodronate further highlight that knee replacement surgery, performed globally becomes painful over time and thus highlights the requirement for analgesic treatment. In contrast, clodronate is described as an analgesic in our study, suggesting pain relief. However, it lacks patient data and clinical results. The trial included 40 people who received injectable clodronate for 10 days plus additional painkillers and anti-inflammatory drugs. Detailed clinical outcomes are unavailable. Bisphosphonates for instance Clodronate play a vital role in painful knee prostheses. Studies highlight that patients belonging to the age group 73 to 81 years were treated with "rehabilitation cycles" besides IM and IV clodronate [38]–[42]. "TegnerLysholm Score" and "Visual analogue scale" were utilized for assessing improvement in disease condition after clodronate treatment. Study results thereby indicated that clodronate along with rehabilitation exercise can diminish pain and improve the function of knee prostheses [43]–[45]. Furthermore, high dose clodronate administration after 3 months proves to be much more effective than weekly administration of the dose. Study results based on comparison of the treatment of OA with hyaluronic acid and clodronate highlighted the absence of statistically significant differences existing between groups [38]. In context to safety perspective, usage of bisphosphonates in the case of OA, prevalent adverse events associated

with bisphosphonate usage include gastrointestinal, specifically dyspepsia complications. Significant differences were absent in the case of bisphosphonates when compared to placebo [45]–[49].

Much information is required to be accumulated in the context of OA progression and pain experienced by OA patients. Thus, there is much requirement to conduct future studies based on bisphosphonates among OA patients coupled with radiographic analysis. Future studies should therefore focus on targeting at assessing bisphosphonate usage for EOA management would further be advantageous in selecting phenotypes of individuals for assessing the groups that would gain benefit from intervention [47]–[49]. The study should consider the inclusion of staging and severity assessed by not only joint space narrowing but also involve bone marrow lesions, "joint space narrowing". Since most of the outcome and pain data were recorded utilizing Vas and WOMAC, future trials should focus on the inclusion of measures for making a valid comparison with other existing studies [40]. The temporal sequence of the impact of bisphosphonate intervention is also required to be considered in future studies not only highlighting functional outcomes but also including the impact of structural modifications including synovitis, narrowing of joint space, and bone marrow lesions. Since EOA and OA is reported to be a chronic long-term disease and effective pharmacological intervention is required to be tolerated for a longer period, long-term "follow-up data" beyond 1 year would help identify the long-term impact of bisphosphonates on both EOA and OA.

5. Conclusion

The study has concluded that clodronate can effectively alleviate pain, reduces the release of pro-inflammatory mediators, and prevents articular degradation. The findings of the study suggest that using clodronate, at different dosages and by various routes, produces favourable outcomes in terms of pain reduction and enhanced functionality among people diagnosed with EOA. The treatment reduces painful joints and improves grip strength, range of motion, and dexterity. By lowering levels of pain, inflammation, and bone marrow lesions, it promotes cartilage regeneration and lessens the likelihood of fractures. Improvements in bone health and loss of subchondral bone are also shown on MRI scans. This current study is a systematic review which evaluated other trials, but do not present any statistical analysis. Further, a meta-analysis can be conducted in the future to statistically analyze the effect of clodronate and a dose-response relationship can be established. However, this current systematic review has brought forward the clinical efficacy of clodronate in osteoarthritis and it is expected to hold significant clinical importance in the future.

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Conflict of interest

Author declares no conflict of interests. Author read and approved final version of the paper.

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