Beni-Suef University Journal of Basic and Applied Sciences

RESEARCH

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Effect of bisphosphonates on bone giant cell tumor recurrence: a meta-analysis

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Abstract

Background: We examined the impact of bisphosphonates as adjuvant therapy on the recurrence of giant cell bone tumors and the impact of various tumor stages and surgical techniques on this effect. Following a thorough examination of the literature up to January 2022, 10 studies including 601 adults with giant cell tumors of the bone were reported; 295 of these subjects received bisphosphonates as adjuvant therapy following surgery, and 306 served as the control group. To examine the possibility of lowering the recurrence of giant cell bone tumors, a comparison between bisphosphonates and a control group was made. In order to evaluate the impact of bisphosphonates as adjuvant therapy on the recurrence of the giant cell bone tumor, odds ratios (OR) with 95% confidence intervals (CIs) were determined. Additionally, the dichotomous technique with a random or fixed-effect model was used to examine the effects of various tumor stages and pertinent surgical procedures.

Results: Patients with giant cell tumors of the bone who received bisphosphonates as adjuvant therapy had significantly lower postoperative recurrence rates outcomes in all subjects with giant cell tumor of bone (OR 0.19; 95% CI 0.12–0.31, $p=0.001$), patients with stage I–II giant cell tumors of the bone (OR 0.29; 95% CI 0.11–0.76, $p=0.01$), patients with stage III giant cell tumors of the bone (OR 0.17; 95% CI 0.07–0.42, $p<0.001$); and post-intralesional curettage (OR 0.18; 95% CI 0.06–0.49, $p<0.001$) compared to control. Bisphosphonates were used in participants with giant cell tumors of the bone after broad excision, but there was no discernible difference between the two groups in terms of postoperative recurrence outcomes (OR 0.66; 95% CI 0.11–3.91, $p=0.65$).

Conclusions: In patients with giant cell tumors of the bone after intralesional curettage, the use of bisphosphonates as adjuvant therapy may lower the incidence of postoperative recurrence outcomes, but no appreciable difference was identified after extensive resection. According to the observed relationship, using bisphosphonates is advised to lower the likelihood of postoperative recurrence that can happen in patients with giant cell tumors of the bone.

Keywords: Giant cell tumor of bone, Bisphosphonates, Recurrence, Intralesional curettage, Wide resection

1 Background

A bone tumor called a giant cell tumor is aggressive and typically targets the ends of long bones. One-fifth of all benign and possibly malignant bone tumors are this type, which is most frequently observed in East and Southeast Asian individuals [1]. The disease is more prevalent in adults than in children in general [1]. Men and young people were more likely to develop giant cell tumors of the bone surrounding the knee. Additionally, it was discovered that patients who underwent intralesional curettage and were between the ages of 20 and 39 were more likely to experience local recurrence [2]. Having had intralesional curettage and having tumors in the proximal fibula enhanced the likelihood of local recurrence in patients with primary giant cell tumors of the bone surrounding the knee. These characteristics were independent risk factors for local recurrence. Given that it is encircled by the peroneal artery and the anterior tibial artery and vein, the proximal fibula's anatomical position

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may be a factor in this elevated risk of local recurrence. Thus, in order to lower the risk of local recurrence and preserve knee function, especially for young patients with high-risk tumor locations, it is essential to choose the optimal surgical treatment technique by taking the tumor location into consideration [2]. Surgery remains the best treatment option for giant cell tumors of the bone. A high recurrence rate, however, limits its use. Bone giant cell tumors are divided into three stages depending on their radiological appearance: latent (stage I), active (stage II), and aggressive (stage III) [3]. Patients with stage III cancer who undergo extensive resection may have very little movement afterward [4]. For cancers categorized as stage I or II, intralesional curettage is often carried out first. In the first two years following surgery, it has been demonstrated that the recurrence rates can reach 50% [5]. It has also been demonstrated that chemical cauterization, such as that using hypertonic saline, phenol, alcohol, or liquid nitrogen, as well as various physical managements following intralesional curettage, may lower the chance of recurrence [6, 7]. These procedures may lead to a variety of consequences, including infections, pathologic fractures, and soft tissue injuries. Recent research has demonstrated the potential benefits of using medications that affect bone metabolism, such as bisphosphonates, as an adjuvant therapy for giant cell tumors of the bone [8, 9]. The farnesyl pyrophosphate synthase enzyme is inhibited by bisphosphonates, which also increase bone mineralization [10]. Numerous studies showed that the use of bisphosphonates could reduce the risk of recurrence after surgery for giant cell tumors of the bone by inducing apoptosis in the stromal cell component [11, 12]. The use of bisphosphonates in giant cell bone tumors, however, is not well agreed upon. In addition to examining the effects of various tumor stages and surgical techniques, the goal of this meta-analysis was to ascertain the impact of bisphosphonates as adjuvant therapy on the recurrence of giant cell tumors of the bone.

2 Method

2.1 Study design

The epidemiological statement was the subject of the current meta-analysis, which comprised studies that followed a predetermined study procedure [13].

2.2 Data pooling

Data were collected from randomized controlled trials (RCTs) and retrospective studies investigating the effect of bisphosphonates as adjuvant therapy on the giant cell bone tumor recurrence and studying the impact of various surgical techniques and tumor stages on this outcome. All studies were conducted on people and were in any language. Study size had no bearing on inclusion. Review articles, comments, and research that failed to provide a measure of an association were all eliminated from the list of publications. Figure 1 depicts the entire course of the study. The publications in the meta-analysis were only included if the next inclusion criteria were met:

1. The study was either a retrospective study or an RCT.
2. The target population had bone cancers with large cells.
3. The intervention program was built around the use of bisphosphonates as an adjuvant therapy after surgery.
4. Results from the study comprised both the bisphosphonates and control groups.

2.3 Identification

The PICOS idea was used to create a protocol of search tactics [14], and we defined it as follows: P (population): subjects had giant cell tumor of bone; I (intervention/exposure): bisphosphonates treatment as an adjuvant therapy post-surgery; C (comparison): bisphosphonates group compared to control group; O (outcome): giant cell bone tumor recurrence; and S (study design): no restriction [15].

Using a combination of keywords and related terms, we first carried out a thorough search of the databases OVID, Embase, Cochrane Library, PubMed, and Google Scholar up until May 2022 for giant cell tumor of bone, bisphosphonates, recurrence, intralesional curettage, and wide resection as shown in Table 1. In order to exclude studies that did not find a connection between bisphosphonate therapy and the recurrence of giant cell bone tumors, duplicate studies were removed, titles and abstracts were checked for accuracy, and all the selected studies were entered into an EndNote file.

2.4 Screening

The primary author's last name, study period, publication year, country, region, population type, clinical and treatment characteristics, categories, qualitative and quantitative method of evaluation, information source, outcome evaluation, and statistical analysis were all used as bases for data abbreviation. Additionally, characteristics related to the study and the subjects were also included on a standard form [16]. When different data were available from a single study based on the evaluation of the impact of bisphosphonates as adjuvant therapy on the recurrence of giant cell bone tumors or the analysis of the impact of various tumor stages and surgical approaches on this effect, we extracted them independently. The two authors separately examined the methodological quality of the chosen research in order to

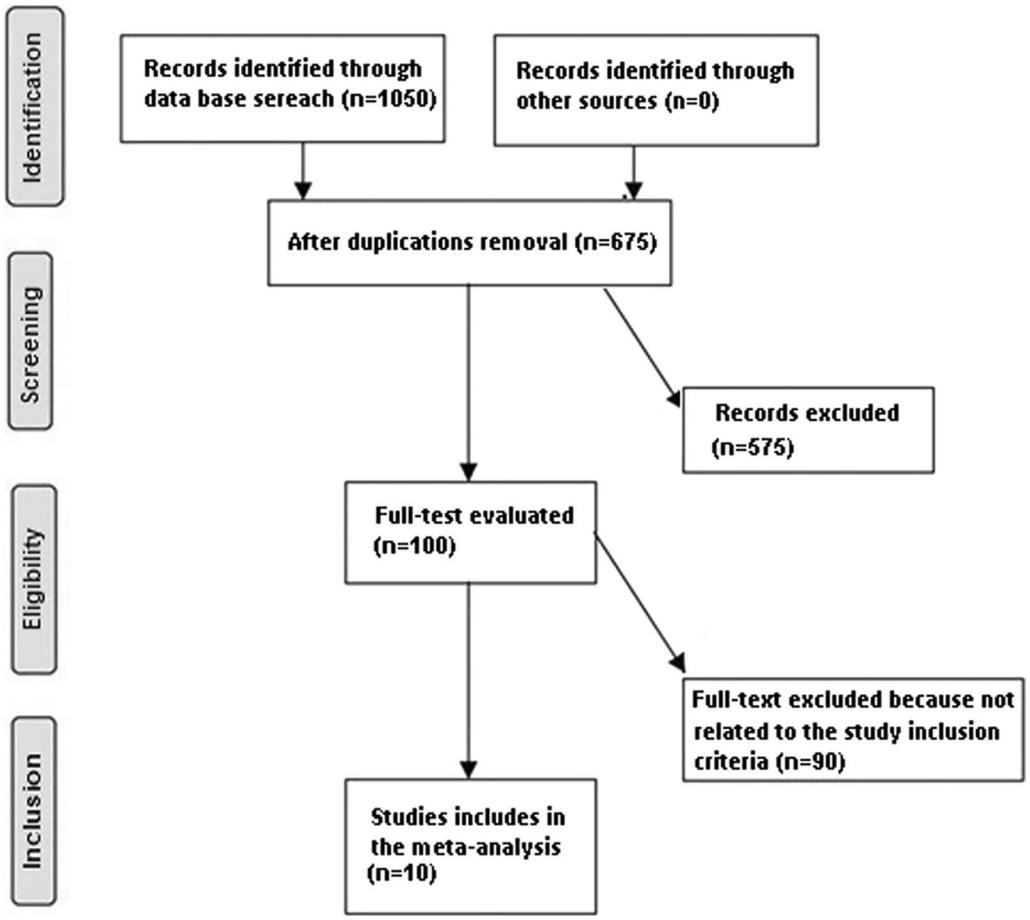

Fig. 1 Schematic representation of the research process

Table 1 Search strategy for each database

Database	Search strategy
Pubmed	#1 "giant cell tumor of bone"[MeSH Terms] OR "Bisphosphonates"[All Fields] OR "recurrence"[All Fields] OR "Intralesional curettage"[All Fields] #2 "efficacy"[MeSH Terms] OR "giant cell tumor of bone"[All Fields] OR "wide resection"[All Fields] #3 #1 AND #2
Embase	'giant cell tumor of bone'/exp OR 'Bisphosphonates'/exp OR ' recurrence'/exp OR Intralesional curettage #2 'efficacy'/exp OR 'ICBG'/exp OR wide resection #3 #1 AND #2
Cochrane library	(giant cell tumor of bone):ti,ab,kw (Bisphosphonates):ti,ab,kw OR (recurrence):ti,ab,kw (Word variations have been searched) #2 (Intralesional curettage):ti,ab,kw OR (efficacy):ti,ab,kw OR (wide resection):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

determine the likelihood bias in the specific studies. The "risk of bias tool" from the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 was used to assess the methodological quality [17]. Each study was graded according to the evaluation criteria and given one of the three risks of bias listed below: Uncertainty: In the event that one or more of the quality requirements were not met, or were only partially met, the study was deemed to have a significant risk of bias. High: If any one or more of the criteria weren't met or weren't included, the study was assessed to have a high risk of bias. Low: If all quality criteria were satisfied, the study was assessed to have a low risk of bias. The original article was revised to remove any inconsistencies.

2.5 Eligibility

The primary conclusion examined the impact of bisphosphonates as adjuvant therapy on the recurrence of giant cell bone tumors and synthesized the contributions of various tumor stages and surgical techniques.

2.6 Inclusion

Sensitivity analyses were only performed on studies that examined the impact of bisphosphonates as an adjuvant therapy on the recurrence of giant cell bone tumors or examined the impact of various tumor stages and surgical techniques on this effect in comparison with controls. For subclass and sensitivity analyses, comparisons between bisphosphonate adjuvant therapy and control regimens were made.

2.7 Statistical analysis

The odds ratio (OR) and 95% confidence interval were calculated in the current meta-analysis using the dichotomous method and a random- or fixed-effect model (CI). It was determined to have an I2 index that ranged from 0 to 100 percent. No, low, moderate, and high heterogeneities were indicated by values around 0%, 25%, 50%, and 75%, respectively [18]. When I2 was larger than 50%, the random effect model was selected, and when it was lower than 50%, the fixed-effect model was selected. By stratifying the initial evaluation based on the previously mentioned outcome categories, a subcategory analysis was finished. For the current analysis, statistical significance for differences between subcategories was defined as a p value < 0.05. Using the Egger regression test and funnel plots showing the logarithm of ORs versus their standard errors, publication bias was evaluated both intuitively and quantitatively (publication bias was considered present if $p \geq 0.05$ [14]. Two-tailed tests were used to calculate all p values. Version 5.3 of Reviewer Manager was used to provide the statistical analyses and graphs (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

3 Results

Ten papers between the years of 2008 and 2020 that matched the inclusion criteria and were included in the meta-analysis were chosen from a total of 1050 relevant studies that were evaluated [19–28]. Table 2 displays the results of this research.

In the chosen studies, 601 participants with giant cell bone tumors were enrolled; 295 of them received postoperative bisphosphonates as an adjuvant therapy, while 306 served as the control group.

At the beginning of the investigation, there were between 14 and 153 individuals. Ten studies examined the effects of bisphosphonates as adjuvant therapy and a control on postoperative recurrence in subjects with giant cell tumors of the bone. Five of the studies examined subjects with stage I–II giant cell tumors, six examined subjects with stage III giant cell tumors, four examined subjects with intralesional curettage, and three examined subjects with wide resection.

Table 2 Characteristics of the selected studies for the meta-analysis

Study	Country	Total	Bisphosphonates
Tse et al. [19]	China	44	24
Zheng et al. [20]	China	39	19
Xu et al. [21]	China	102	37
Fan et al. [22]	China	55	29
Xu et al. [23]	China	85	32
Ding et al. [24]	China	37	22
Xu et al. [25]	China	35	19
Kundu et al. [26]	India	37	18
Lipplaa et al. [27]	Netherlands	14	8
Xu et al. [28]	China	153	87
Total		601	295

In all populations evaluated, the incidence of the postoperative recurrence was significantly lower in the bisphosphonate group than in the control group in patients with giant cell tumor of the bone and post-intralesional curettage.

Patients with giant cell tumor of the bone who received bisphosphonates as adjuvant therapy had significantly lower postoperative recurrence rates outcomes in all subjects with giant cell tumor of bone (OR 0.19; 95% CI 0.12–0.31, $p = 0.001$), patients with stage I-II giant cell tumor of the bone (OR 0.29; 95% CI 0.11–0.76, $p = 0.01$), patients with stage III giant cell tumor of the bone (OR 0.17; 95% CI 0.07–0.42, $p = 0.001$), and post-intralesional curettage (OR 0.18; 95% CI 0.06–0.49, $p < 0.001$) all had postoperative recurrence outcomes that were significantly with no heterogeneity (I2 = 0%) compared to controls as shown in Figs. 2, 3, 4 and 5, bisphosphonates did not significantly affect postoperative recurrence outcomes in individuals with giant cell tumor of the bone following broad resection (OR 0.66; 95% CI 0.11–3.91, $p = 0.65$) with no heterogeneity (I2 = 0%) compared to control as shown in Fig. 6.

Age, ethnicity, and gender could not be adjusted for in stratified models to examine the effects they had on comparative results because there have been no reported data regarding these variables. However, most subjects in the selected studies were adults since the disease prevalence is more common in adults. There

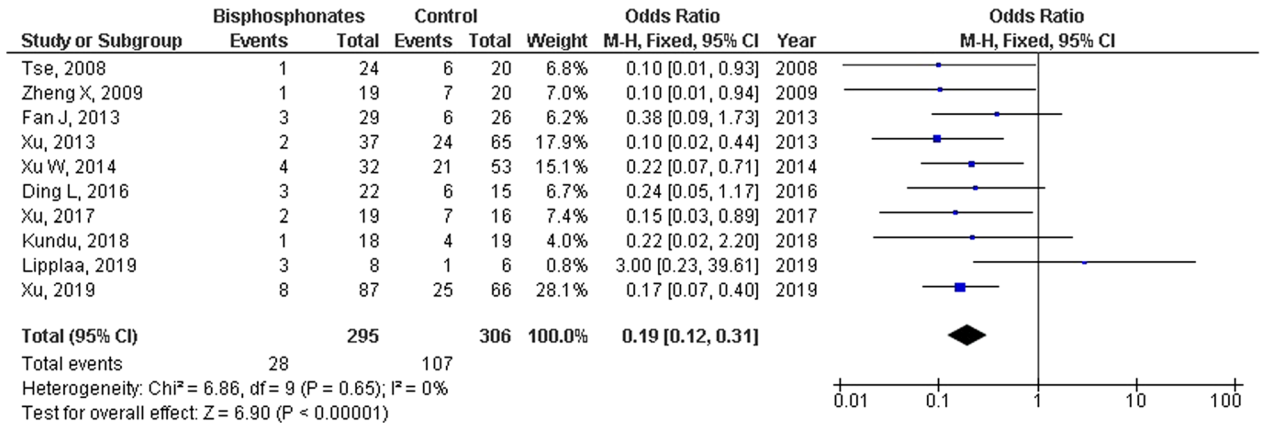

Fig. 2 The forest plot showing the influence of bisphosphonates in comparison to controls on postoperative recurrence outcomes in patients with giant cell tumors of the bone in all stages

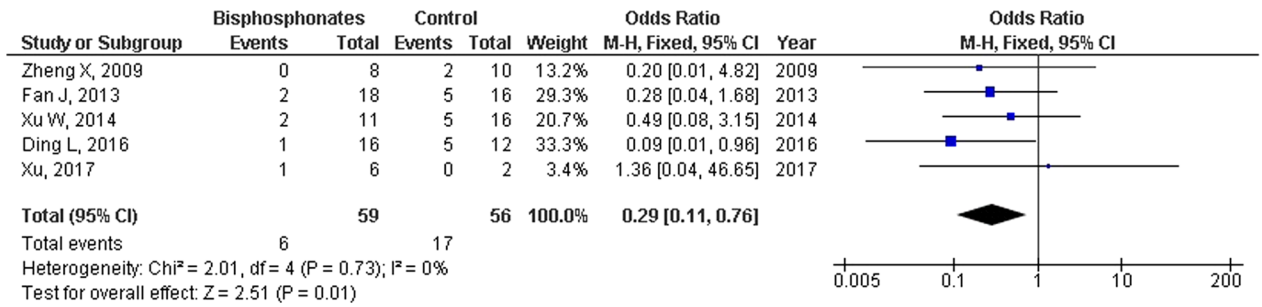

Fig. 3 The forest plot of how bisphosphonates affect postoperative recurrence outcomes in patients with stage I–II giant cell bone tumors as compared to controls

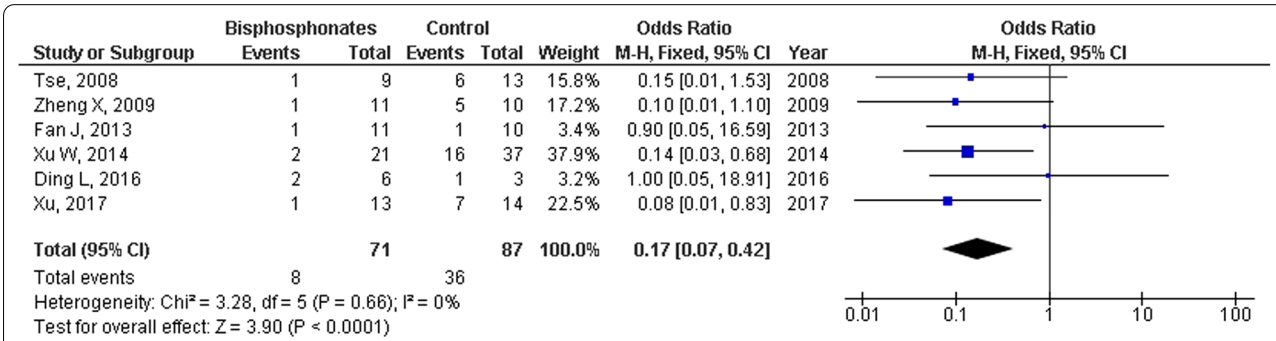

Fig. 4 The forest plot showing how bisphosphonates affect postoperative recurrence outcomes in patients with stage III giant cell bone tumors when compared to controls

was no indication of publication bias ($p = 0.87$) according to the quantitative analyses utilizing the Egger regression test and funnel plot visual analysis. However, the majority of the included RCT were discovered to have poor methodological quality, no selective reporting bias, and relatively scant outcome data.

4 Discussion

In the current meta-analysis, 10 trials recruited 601 participants with giant cell bone tumors at the start of the study; 295 of them received adjuvant bisphosphonate medication after surgery, and 306 served as the control group [19–28].

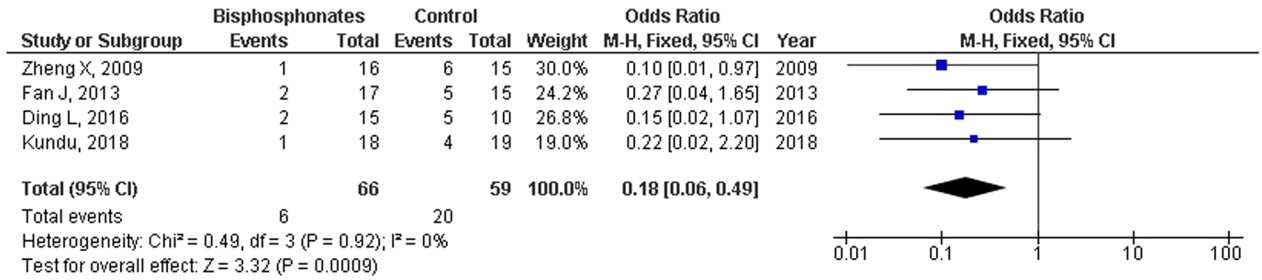

Fig. 5 The forest plot of the results of intralesional curettage in patients with giant cell tumors of the bone after the effects of bisphosphonates were compared to those of a control group

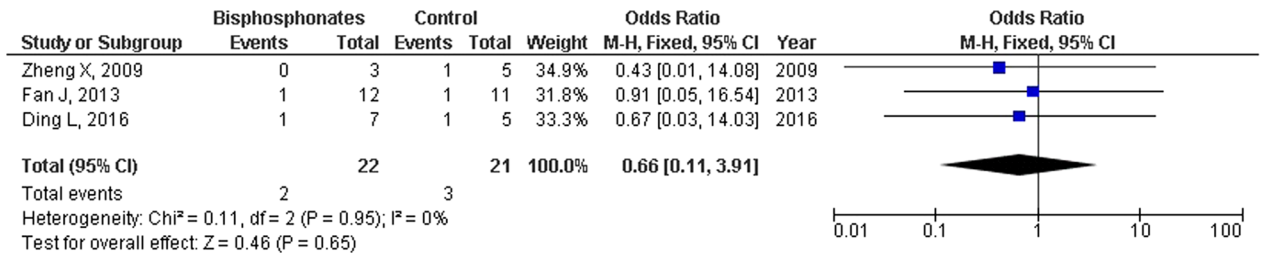

Fig. 6 The forest plot showing how bisphosphonates affect postoperative recurrence outcomes in patients with giant cell tumors of the bone after extensive excision as compared to a control group

The extent of the postoperative recurrence outcomes in subjects with giant cell tumor of bone and post-intralesional curettage was significantly lower in the bisphosphonates group than that in the control group in all studied populations [19–28]. The lack of a meaningful difference after extensive resection, which may have been caused by the few studies included (only 3), to be exact indicates the need for additional research to support these conclusions. However, the high p values after wide resection ($p = 0.65$) indicate that the insignificant difference discovered after wide resection will not change with the inclusion of further research.

According to this finding, patients with giant cell tumors of the bone may experience a lower chance of postoperative recurrence outcomes if bisphosphonates are used as adjuvant therapy after surgery. Since these results are different from the control, there are additional factors to be present [19–28]. However, due to the small sample sizes of the studies we picked, the small number of studies included in our meta-analysis, and the potential for bias, care should be used when analyzing the results.

Giant cell tumor of bone commonly does not stay latent and tends to progress to destroy the affected bone [29]. The disease is more prevalent in adults (> 18 years old) than in children in general [1]. As a result, surgical intervention should be considered as soon as possible. Since the tumor is completely removed, wide resection provides the advantage of decreased recurrence rates. Notably, it has been applied to tumors in the Campanacci stage III or to tiny bones like the fibula or ulna when there are no evident bone dysfunctions [30]. That could be why we could not find any significant difference between bisphosphonates and control groups in wide resection. Though, this surgical procedure may result in limited movement. Interestingly, the intralesional curettage combined with adjuvant techniques is considered the preferred management of giant cell tumor of bone. It showed better results in bone functions despite the higher risk of recurrence [31]. In addition to their ability to lower the rate of giant cell bone tumor recurrence postoperatively, multiple studies have recently demonstrated that bisphosphonates have a cytotoxic effect on the neoplastic stromal cells of giant cell tumors of the bone [19–28]. However, it is still unknown how bisphosphonates work to fight tumors. It has been demonstrated that by impeding the mevalonate pathway, bisphosphonates can cause neoplastic stromal cells to undergo apoptosis. Bisphosphonates have also been demonstrated to block the zinc-dependent proteolytic activity of matrix metalloproteinase, which is crucial for the degradation of extracellular matrix proteins, invasion, and migration. This activity is exhibited by the tumor cell-derived matrix metalloproteinases-2 and metalloproteinase-9 [32]. Wide excision

eliminates the marginal positive of bone during intralesional curettage and hence lowers recurrence rate, which could be one explanation for the observed difference in result. Another explanation is that soft tissue infiltration causes recurrence, and broad resection removes all the infiltrated soft tissue [33]. Bisphosphonates can help reduce tumor size preoperatively and prevent surgical dissemination, but their usage should be limited because late surgery may result in progressive tumor growth. The duration of postoperative use of bisphosphonates ranges from three months to two years. Long postoperative use of bisphosphonates was considered essential because recurrence occurs mostly in the first two years post-surgery [34]. The main adverse reactions of bisphosphonates are mild and nonfatal including fever and digestive upset. However, bisphosphonates should not be used in subjects with renal dysfunction or stress fractures. Also, some studies reported that long-term and large-dose of bisphosphonates may prompt osteonecrosis of the jaw and atypical fracture of long bones [35, 36]. This meta-analysis showed the influence of bisphosphonates on the giant cell bone tumor recurrence. However, more research is still required to demonstrate these potential connections and contrast the impact of bisphosphonates and denosumab therapy. In patients with giant cell tumors of the bone, denosumab was shown to be associated with respectable rates of tumor remission and decreased the need for morbid surgery [37]. Larger, more homogeneous samples are required for these researches. This was also suggested in an earlier meta-analysis study that revealed comparable encouraging results for bisphosphonates in lowering the recurrence of giant cell bone tumors [38]. Since our meta-analysis study was unable to determine if differences in age, ethnicity, and gender are related to the outcomes, well-conducted RCT are required to evaluate these parameters as well as the interaction of different ages, ethnicities, and other variations of participants.

In summary, the data suggest that using bisphosphonates as an adjuvant therapy may lower the risk of recurrence outcomes post-surgery in subjects with giant cell tumor of bone especially post-intralesional curettage. From the study presented here, we recommend the use of bisphosphonates as an adjuvant therapy to reduce the possibility of postoperative recurrence that could occur in subjects with giant cell tumor of bone.

4.1 Limitations

Since so many of the papers found in this study were not included in the meta-analysis, there may have been selection bias. The excluded papers, however, did not meet the requirements for inclusion in our meta-analysis. Additionally, we were unable to determine whether or not the results are influenced by gender, race, or age. However, most subjects in the selected studies were adults since the disease prevalence is more common in adults. The study's goal was to evaluate the effect of bisphosphonates as adjuvant therapy on the recurrence of giant cell bone tumors and analyze the impact of various tumor stages and surgical techniques on this effect. The study's data came from prior studies, which may have introduced bias due to missing details. In the current meta-analysis, ten RCTs were analyzed, eight of which had small sample sizes ($n \leq 100$). The age, sex, and nutritional status of the subjects were all potentially biased-inducing factors. Regrettably, some unpublished articles and incomplete data may bias the effect under study. The dose and he formulation of bisphosphonates were variable in the selected studies and this might induce bias. However, we could not study different formulation or dose effect separately since the number of studies related to each dose and formulation was limited.

5 Conclusions

Using bisphosphonates as an adjuvant therapy may lower the incidence of postoperative recurrence outcomes in adult subjects with giant cell tumor of bone. These findings were significant post-intralesional curettage; however, no significant difference was found post-wide resection. Based on this relationship, the use of bisphosphonates may be recommended as an adjuvant therapy to reduce the incidence of postoperative recurrence that could occur in subjects with giant cell tumor of bone.

Abbreviations

OR: Odds ratio; CIs: 95% Confidence intervals.

Acknowledgements

Not applicable.

Author contributions

(1) Conception and design: MA. (2) Administrative support: all authors. (3) Provision of study materials: all authors. (4) Collection and assembly of data: ME. (5) Data analysis and interpretation: ME. (6) Manuscript writing: ME. (7) Final approval of manuscript: all authors. All authors read and approved the manuscript.

Funding

There was no external funding for this study itself. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 17 July 2022 Accepted: 30 August 2022
Published online: 05 September 2022

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