Effect of local administration of bisphosphonate on orthodontic anchorage – A systematic review of animal studies

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Abstract:

BACKGROUND: Pharmacological means of anchorage control can improve patient compliance. Bisphosphonates could be helpful in orthodontic anchorage control if their actions could be localized to limit (or control) unwanted tooth movement while not interfering with the desired tooth movement.

OBJECTIVE: This systematic review aimed to examine and evaluate the quality of all animal studies that reported the effect of locally administered bisphosphonate on limiting orthodontic tooth movement.

DATA SOURCES: An electronic search was conducted in the PubMed-Medline, Scopus, Google Scholar, and Cochrane databases till May 2022, using the keywords anchorage, anchorage loss, molar movement, posterior tooth movement, incisor movement, incisor retraction, anterior retraction, unwanted tooth movement, tooth displacement, tooth movement forward, bisphosphonate, local bisphosphonate administration, bisphosphonate injection, and bisphosphonate vestibular induction. Only studies involving localized bisphosphonate administration for anchorage purposes were taken into account.

DATA SELECTION: Animal studies that simulated orthodontic tooth movement after localized injection of bisphosphonate and evaluated the rate of tooth movement were included in the review.

DATA EXTRACTION AND ANALYSIS: The quality of the studies was assessed by using ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments). Bias in the studies was analyzed by SYRCLE’s tool (Systematic Review Centre for Laboratory Animal Experimentation) for risk of bias.

RESULTS: The search strategy yielded 925 titles. After screening, 908 articles were discarded because they did not fulfill the inclusion/exclusion criteria based on the title and abstract. The remaining 16 articles were read entirely, of which nine were excluded as they involved systemic administration of bisphosphonates. Finally, after careful consideration, seven papers that met our inclusion criteria were included in the qualitative analysis. The majority of studies were assessed to have an uncertain risk of bias, with just one deemed low risk of bias.

CONCLUSION: This systematic review found that bisphosphonates limit orthodontic tooth movement around the application site without affecting adjacent sites. More potent bisphosphonates in smaller doses or less potent bisphosphonates in higher frequencies have been proposed to improve outcomes. However, the data quality is insufficient to recommend a protocol for bisphosphonate administration for anchoring control. Long-term studies evaluating various types, frequencies, and dosages of bisphosphonates are required to clarify the effects on orthodontic tooth movement.

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Keywords:
Animals, orthodontic anchorage procedures, orthodontics, pharmaceutical preparations

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Introduction

Orthodontics subjects teeth to a variety of forces. These operational forces generate a corresponding reciprocal force, generating tooth movement. Thus, “anchorage” refers to the opposition to such undesirable tooth movement. Good treatment outcomes require anchorage control. Newton’s Third Law of Motion states that every action has a counter-reaction. The “action” is indeed the movement of the targeted teeth, whereas the “counter-reaction” is the displacement of the anchoring unit. Extensive research has been done on improving anchoring control using various techniques such as headgears, transpalatal arch, Nance palatal arch, lingual stabilizing arch, interpalpillary elastics, miniscrews, mini-plates, mini implants, pharmacological agents, etc.[2-6]

Pharmacological management of the anchorage unit has the potential to alter the underlying biological mechanisms that occur all through orthodontic tooth movement, resulting in equivalent results while enhancing patient compliance. Bisphosphonate is a critical pharmacological substance that has been extensively researched in the literature for orthodontic anchoring. Several skeletal metabolic conditions can be addressed with bisphosphonates. This drug class was first developed in the middle of the nineteenth century and is now routinely used to treat osteoporosis, Paget’s disease, malignant bone metastasis, and osteogenesis imperfecta. Bisphosphonates are inorganic pyrophosphate analogs. Two phosphonates (PO3) linked to an oxygen molecule make up pyrophosphates found in body fluids such as saliva. Bisphosphonates are classified into two groups: non-nitrogenous (clodronate, etidronate, and tiludronate) and nitrogenous (alendronate, pamidronate, risedronate, ibandronate, zoledronate, etc.). The presence of the nitrogen atom enhances the drug’s potency. Both kinds of bisphosphonates have anti-osteoclastic properties. However, they work through different methods. Non-nitrogenous bisphosphonates bind to non-hydrolyzable analogs of adenosine triphosphate (ATP), interfering with ATP-dependent pathways and causing osteoclast apoptosis, whereas nitrogenous bisphosphonates inhibit the mevalonate pathway enzyme farnesyl pyrophosphate synthase, which inhibits the enzymatic modification of small guanosine triphosphate-binding proteins in osteoclast.[7-11]

Several studies have investigated the effect of systemically administered bisphosphonates in osteoporotic animals on orthodontic tooth movement. These studies revealed that orthodontic tooth movement was hampered in subjects receiving systemic bisphosphonate administration.[12-15] Bisphosphonate’s adverse effects could be used to advantage in orthodontics on a local level to limit (or) prevent unwanted movement while not interfering with beneficial tooth movement.

Objective

This systematic review aimed to examine and evaluate the quality of all animal studies that reported on the effect of locally administered bisphosphonate on limiting orthodontic tooth movement.

Materials and Method

Protocol and registration

The International Prospective Register of Systematic Reviews (PROSPERO) was used to register the protocol (CRD42021224033). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the formulation of the protocol, as well as during its execution and reporting.[16-18]

PICO analysis

P- Experimental animals with orthodontic appliances for simulating tooth movement
I – Local administration of bisphosphonate
C- Local administration of other pharmacological agents/Placebo
O- Orthodontic Tooth movement

Eligibility criteria

Inclusion criteria

• Experiments on healthy animals using the orthodontic appliance
• Administration of bisphosphonate injection before force application
• Studies reporting rate of tooth movement following administration of bisphosphonate locally compared with a saline injection or any other control group
• Qualitative data on the rate of molar displacement

Exclusion criteria

• No control group
• Systemic administration of bisphosphonate
• Review articles, systematic reviews, and meta-analysis

Search strategy

An electronic search was conducted in the PubMed-Medline, Scopus, Google Scholar, and Cochrane databases till May 2022, using the keywords anchorage, anchorage loss, molar movement, posterior tooth movement, incisor movement, incisor retraction, anterior retraction, unwanted tooth movement, tooth displacement, tooth movement forward, bisphosphonate, local bisphosphonate administration, bisphosphonate injection, and bisphosphonate vestibular induction.
Only studies involving localized bisphosphonate administration for anchorage purposes were taken into account. Two calibrated reviewers conducted the search, independently applying the inclusion and exclusion criteria to each article with adequate concordance. To broaden the search for relevant articles, selected article references were reviewed. The following factors were considered: sample size, dose, frequency, route, administration, the validity of measurement-taking techniques, suitable statistics, method error analysis, and measurement blinding.

**Result**

The flow of records through the reviewing process is shown in Figure 1. The search strategy yielded 925 titles. After screening, 908 articles were discarded because they did not fulfill the inclusion/exclusion criteria based on the title and abstract. The remaining 16 articles were read entirely, of which nine were excluded as they involved systemic administration of bisphosphonates.[13,14,19-25]

Table 1. Finally, after careful consideration, seven papers that met our inclusion criteria were included in the qualitative analysis.[26-32]

Table 2 summarizes the research’s general features. Coil springs were frequently used to promote orthodontic tooth movement by putting them between the incisors and molars. Likewise, springs that provided expansion stresses to the incisors or molars were utilized. The appliances applied forces ranging from 10 to 100 g, and the duration between applications varied from 2 weeks to 24 days.

Clodronate was administered over a 7-day and 21-day period by Nakaš *et al.* (2017) and Liu *et al.* (2004), respectively, at increasing concentrations of 10 μmol per day and 50 μl per day. On average, Nakaš *et al.* (2017) found a 0.88 mm decrease in tooth movement on the third day and a 2.31 mm decrease on the seventh day, whereas Liu *et al.* (2004) found a 0.02 mm decrease in tooth movement on the tenth day, 0.10 mm decrease on the fifteenth day, and 0.17 mm decrease on the twenty-first day. Both these studies demonstrated that increasing concentrations of clodronate inhibited tooth movement. Relatively small doses of clodronate administered more frequently produced better outcomes. In Adachi *et al.* (1994) study, risedronate was used at increasing concentrations of 50 μl for 21 days. On the 10th, 15th, and 21st days, tooth movement was reduced by an average of 0.07 mm, 0.1 mm, and 0.2 mm. This research confirms that inhibition of tooth movement is more concentration-dependent. Venkataramana, Kumar *et al.* (2014) administered 1.2 mg of ibandronate as a single dose. The results of this study indicated a 0.2 mm reduction in tooth movement. In Fernández-González *et al.* (2016) and Ortega *et al.* (2012) studies, 16 μg of zoledronate was administered as a single dose preparation. The result indicated that tooth movement was inhibited by an average of 0.69 mm and 0.55 mm. Table 3 displays the results obtained from the listed research. All the studies showed a decrease in tooth movement irrespective of the type and dosage of the locally administered bisphosphonate used.

The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE’s) risk of bias tool was used to assess the risk of bias in individual studies.[33] Results of risk-of-bias assessments are summarized in Table 4. The majority of studies were assessed to have an uncertain risk of bias, with just one deemed to have a low risk of bias.[29] In general, the majority of studies assessed had an uncertain risk of bias in the areas of random sequence generation, allocation concealment, and outcome assessor blinding due to insufficient evidence to construct a strong judgment on the risk of bias. Nonetheless, the majority of studies used groups that were similar in terms of gender, age, and weight of the participants at baseline, and so were deemed to have a low risk of bias in the relevant domain. There was no information on whether animals were housed randomly or whether caregivers and investigators were blinded to the intervention each animal received, leaving the majority of trials at risk of bias.[29] Due to a lack of data, it was impossible to determine if the trials were free of publication bias, and subgroup analyses were not performed. Table 5 summarizes the Animal Research Reporting of In Vivo Experiments (ARRIVE) quality of evidence assessment.[34] Overall, the quality of available evidence on the impact of various types of bisphosphonates on orthodontic tooth movement was rated as low at best.

**Discussion**

Various studies retrieved for qualitative analysis in this systematic review used different types of bisphosphonates at various doses. All trials, on the other hand, consistently showed that local administration
of all types of bisphosphonates impeded orthodontic tooth mobility. The amount of tooth movement varied according to the potency and dosage of the bisphosphonate type. The evidence was deemed to be of poor quality, compelling the clinician to proceed with caution when making relevant recommendations. There were no adverse reactions reported in any of the studies. However, conclusive evidence is still lacking in the majority of cases. Our final qualitative analysis included seven studies, which evaluated the effect of locally administered bisphosphonate on anchorage control. The various types of bisphosphonate used in the study are Clodronate, Zoledronate, Risedronate, and Ibandronate. The type of bisphosphonate used was not mentioned in Fujimura et al. (2009) study. The method of Tooth movement evaluation varied among the studies.

Naka et al. (2017) evaluated the role of localized clodronate administration in the incisor area (Rat) by placing separators between the upper incisors. He proved that localized clodronate treatment significantly inhibits tooth movement and that the period between applications should be shortened to reduce dosage concentration. Fernández-González et al. compared the effect of locally administered zoledronate and osteoprotegerin near the first molar area (Rat) in limiting its movement when retracted with a mini implant. He demonstrated that a single, locally applied dosage of zoledronate or a high, twice-weekly dose of Osteoprotegerin allowed for maximum anchoring when orthodontic force was applied. Ibandronate was examined for its effect on molar movement during retraction (Rabbit) by Venkataramana, Kumar et al. (2014). They demonstrated that ibandronate is an
Table 2: Study characteristics of included studies

| Study (Name of the first author and year of study) | Subject characteristics (Species, sex, age, weight, total number) | Tooth movement model | Group characteristics (number, injecting agent, dosage, frequency, route, administration) | Assessment of tooth movement |
|--------------------------------------------------|---------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------|-------------------------------|
| Nakaš et al. (2017) [31]                          | Adult winter Rat, 14 Males, 46 Females, 8-6 weeks, 343-233g, 60 | Elastic band - Between the incisors 3 days 7 days | The experimental group (E1)- 15, application of 10 mMol of clodronate in 3-day intervals. E2-15, application of 2.5 mMol of clodronate in 3-day intervals E3-15, application of 10 mMol of clodronate in 7-day intervals E4-15, application of 2.5 mMol of clodronate in 7-day intervals | Impression -Plaster model - scanned Digital measurements of incisor movements (3D3M software package) The maxillary incisor movements were evaluated according to the fixed position of the molars. Teeth movements were calculated by measuring the distance between incisors and molars on the treated and control sides: Point 1 - The middle of the distal proximal surface of incisors on the right side 2 mm from the gingiva Point 1' - The middle of the mesial proximal ridge of the first molar on the right side Point 2 - The middle of the distoproximal surface of incisors on the left side 2 mm from the gingiva Point 2' - The middle of the mesial proximal ridge of the first molar on the left side. Distance between points 1 and 1’ and 2 and 2’ was used to represent tooth movement in millimeters. |
| Fernandez-Gonzalez et al. (2016) [30]            | Sprague-Dawley Rat, Male, 420-460 g, 36 | Niti coil Spring between Maxillary molar and 6-mm-length mini-screw between the roots of the upper incisors. 50 g force, 7, 14, and 21 days | Experimental group 1-12,16 ug of zoledronate, Experimental group 2-12, 5 mg/kg of human OPG-Fc, Control group 3-12, untreated Site of injection Sample size calculation is done. | PVS Impressions- diastema distal to the right maxillary first molar -Models were scanned with a 100 mm ruler and then magnified 100, and diastema was measured using imaging software (Adobe Photoshop) |
| Venkataramana, Kumar SS, et al. (2014) [32]      | New Zealand rabbits, 16 weeks, 3.5-4 kg, 20 | NiTi closed coil springs between the mandibular molar and incisors. 100 g force. 21 days. | Group-1 (control)-10, 1 ml Saline. Group-2 (experimental)- 10, Ibandronate 0.3 mg/kg Site of injection: mesial aspect of mandibular 1st molar mucoperiosteum Sample size calculation: nil | Lateral cephalogram- 1st and 21st days. The magnitude of molar tooth movement in the mesial direction was measured manually using a standard metric scale based on two reference points that are, a mesio-occlusal tip of the second molar (M1) to the disto-occlusal tip of the first molar (M2) |
| Ortega et al. (2012) [29]                         | Retired breeder Sprague-Dawley rats, Male, 30 | NiTi closed coil spring between incisor and second molar. 1st molar extracted. 10g force. 21 days | Group-1 (control)-15, 50 ul Saline Group-2 (experimental)- 15,16 ug of zoledronate Site of injection: 1/3rd injection e mesiopalatal and distopalatal aspects of the maxillary left second molar and the vestibule above the first molar. Sample size calculation: 30 | Lateral cephalogram at 1st, 7th, and 21st day. The lines N-Po and occlusal plane were drawn, and a perpendicular line was constructed from N to intersect the occlusal plane (N0). A line perpendicular to N-Po was constructed through the most distal point of the wire (W) until it intersected the occlusal plane (W0). Measurement A was the distance N to a perpendicular from N-Po through W, measurement B was the distance N0-W0, and |

Contd...
antiresorptive drug that, when applied locally, reduces molar tooth movement in rabbits and can be used to improve pharmacological anchorage. Ortega et al. (2012) [29] evaluated the influence of zoledronate on molar displacement during retraction (Rat). Local use in preventing molar movement during retraction. They demonstrated that a single, small, locally administered dosage of zoledronate was sufficient for maximal anchoring in extraction space closure. Zoledronate reduced periodontal bone loss around the second and third molars as well as at the extraction site without causing any side effects. Fujimura et al. (2009) [28] studied the effect of locally administered bisphosphonate on maxillary molar anchorage and observed that bisphosphonates administered rats had less tooth movement, osteoclasts, and root resorption than nondrug administered animals. The sort of bisphosphonate utilized, however, was not disclosed in the article. Liu et al. (2004) [27] and Adachi et al. (1994) [26] studied the effect of locally administered clodronate and residronate in similar study settings. The bisphosphonate was injected near the upper first molar with the contralateral molar functioning as a control, tooth movement was stimulated using a standard expansion spring with the right and left molar movement buccally. Both investigations discovered significantly less molar tooth movement in the local bisphosphonate-administered side during expansion, as well as reduced relapse when the expansion force was released, confirming the pharmacologically produced anchoring and retention phenomenon.

The method of evaluating tooth movement also differed between studies. Pre and post-plaster models magnified with a profile projector were used by Liu et al. (2004) [27] and Adachi et al. (1994) [26] Fernández-González et al. (2016) [33] used imaging software to make measurements of models. Nakas et al. (2017) [31] performed measurements on scanned digital models. Fujimura et al. (2009) [28] evaluated the model using a stereoscopic microscope. Pre and post-lateral cephalograms were superimposed by Venkataramana, Kumar et al. (2014) [32] and Ortega et al. (2012) [29]. However, the results of all the studies are

| Study (Name of the first author and year of study) | Subject characteristics (Species, sex, age, weight, total number) | Tooth movement model | Group characteristics (number, injecting agent, dosage, frequency, route, administration) | Assessment of tooth movement |
|---------------------------------------------------|---------------------------------------------------------------|----------------------|---------------------------------------------------------------------------------|-------------------------------|
| Fujimura et al. (2009) [28]                        | C57BL mice, male, 8 weeks, 12                                 | NiTi closed coil spring between the anterior alveolar bone and first molar, 10 g force, 12 days | Group-1 (control) - 2, 1 ml Saline daily Group-2 (experimental) - 2 uL/20 ml daily Site of injection: adjacent to upper molar. Sample size calculation: Nil | Silicon Impression-plaster model upper jaw was magnified×10 with a profile projector and traced. The contours of the palatal cusps of the second and third molars of the tracings were then superimposed on those of the second and third molars on tracings from a pre-treatment plaster model. The distance between the crests of the mesiopalatal cusps of the first molars before and after tooth movement was measured using sliding calipers. |
| Liu et al. (2004) [27]                             | Adult winter Rat, 8-9 weeks old, 180 g, 26                     | Standard expansion Spring right and left molar moved buccally, force- 120 mN, 3 weeks              | Split mouth Group-1 (control) - 26, 1 ml Saline Group-2 (experimental) - 13,50 ul of clodronate Site of injection: sub-periosteum adjacent to upper 1st molar Sample size calculation: Nil | The animal sacrificed-12 days-maxilla removed-injection type PVS Impression of maxilla - Distance between the 1st and second molar measured in impression on a stereoscopic microscope |
| Adachi et al. (1994) [26]                          | Male Wistar rats, 9 to 10 weeks old, 227 g, 126               | Standard expansion Spring right and left molar moved buccally, force- 165 mN, 3 weeks             | Split mouth Group-1 (control) - 41, 1 ml Saline Group-2 (experimental) - 41, 50 ul of Residonate Site of injection: sub-periosteum adjacent to upper 1st molar Sample size calculation: Nil | Silicon Impression-plaster model upper jaw was magnified×10 with a profile projector and traced. The contours of the palatal cusps of the second and third molars of the tracings were then superimposed on those of the second and third molars on tracings from a pre-treatment plaster model. The distance between the crests of the mesiopalatal cusps of the first molars before and after tooth movement was measured with sliding calipers. |
Table 3: Summation of results of the included studies

| Study                               | Nakas et al. (2017) | Fernández-González et al. (2016) | Venkataramana, Kumar et al. (2014) | Ortega et al. (2012) | Fujimura et al. (2009) | Liu et al. (2004) | Adachi et al. (1994) |
|-------------------------------------|---------------------|----------------------------------|-----------------------------------|----------------------|----------------------|-------------------|---------------------|
| Result                              | Day 14 Experimental | Day 14 Experimental              | Day21 Group-1 (control)           | Days 21 Measurement  |
|                                     | Experimental group 1: 97.37±2.74 mm | Experimental group 2: 98.25±1.82 mm | ‑0.25±0.01 mm                     | ‑0.24±0.21 mm        |
|                                     | 7 days After        | 7 days After                     | 21 Day 21 Experimental            | N-PO: Control group: | Control group: 0.27 mm |
|                                     | Experimental group 2: 98.29±2.7 mm | Experimental group 3: 100.8±0.03 mm | 0.17±0.01 mm                     | 0.15±0.39 mm         |
|                                     | 3 weeks             |                                 |                                   | mm Group-2 (experimental) | 0.18±0.46 mm       |
|                                     | 3 weeks             |                                 |                                   | ‑0.203±0.291 mm      | mm Measurement A:   |
|                                     | 3 weeks             |                                 |                                   |                       | Control group: ‑0.83±0.45 mm |
|                                     | 3 weeks             |                                 |                                   |                       | mm Experimental group: ‑0.118±0.23 mm |
|                                     | 3 weeks             |                                 |                                   |                       | mm Measurement B:   |
|                                     | 3 weeks             |                                 |                                   |                       | Control group: ‑0.81±0.45 mm |
|                                     | 3 weeks             |                                 |                                   |                       | mm Experimental group: ‑0.06±0.28 mm |
|                                     | 3 weeks             |                                 |                                   |                       | Measurement c:       |
|                                     | 3 weeks             |                                 |                                   |                       | Control group:       |
|                                     | 3 weeks             |                                 |                                   |                       | ‑0.94±0.45 mm       |
|                                     | 3 weeks             |                                 |                                   |                       | mm Experimental group: ‑0.24±0.21 mm |

Table 4: Summary of risk of bias assessment according to SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation)

| Study                               | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Summary |
|-------------------------------------|---|---|---|---|---|---|---|---|---|----|---------|
| Nakas et al. (2017) | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |
| Fernández-González et al. (2016) | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |
| Venkataramana, Kumar et al. (2014) | Unclear | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |
| Ortega et al. (2012) | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Fujimura et al. (2009) | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |
| Liu et al. (2004) | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |
| Adachi et al. (1994) | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |

1: Was the allocation sequence adequately generated and applied?; 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?; 3: Was the allocation to different groups adequately concealed during the study?; 4: Were the animals randomly housed during the assessment?; 5: Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?; 6: Were animals selected at random for outcome assessment?; 7: Was the outcome assessor-blinded?; 8: Were incomplete outcome data adequately addressed?; 9: Are reports of the study free of selective outcome reporting?; 10: Was the study free of other problems that could result in a high risk of bias? SYRCLE’s risk of bias tool.

incomparable due to the method’s heterogeneity and the wide range of bisphosphonates used. As shown, high-potency bisphosphonates such as zoledronate and ibandronate were able to inhibit tooth movement at low concentrations and single dosage, whereas low-potency bisphosphonates such as clodronate are effective at low concentrations but only when used at a higher frequency. Numerous authors have reported on the use of bisphosphonates at low doses to prevent adverse effects such as osteonecrosis (30–32).

The review’s well-established methodology is one of its most notable features. There were no preconceived limits on language, publication date, or status of publication for gathering data from electronic and manual sources through May 2022. In addition, screening, eligibility verification, information abstraction, bias risk assessment, and evidence quality evaluation were all carried out in duplicate to reduce bias. Disagreements were resolved through dialogue, and a final agreement was reached.

It is also worth noting that the existing evidence is not only derived from animal studies but also entails administering bisphosphonate in a variety of forms and doses that are difficult to compare between species. The data’s universal application to human clinical conditions is restricted by the employment of specialized techniques to induce orthodontic tooth movement. Also included in this research is the distribution of the medication to healthy animals, which may have ramifications for tissue homeostasis. Although orthodontic tooth movement occurs in three dimensions, the majority of research examined the presence and extent of tooth movement using traditional, lateral cephalograms and two-dimensional measurement in models. It has been hypothesized that cone-beam computed tomography would be useful in this regard. Finally, the lack of
| Item                | Recommendation                                                                                             | Nakas et al. (2017)   | Fernandez-Gonzalez et al. (2016)   | Venkataramana, Kumar et al. (2014)   | Ortega et al. (2012)   | Fujimura et al. (2009)   | Liu et al. (2004)   | Adachi et al. (1994)   |
|---------------------|-------------------------------------------------------------------------------------------------------------|----------------------|------------------------------------|--------------------------------------|----------------------|-----------------------|----------------------|----------------------|
| Title               | 1 Provide as accurate and concise a description of the content of the article as possible                   | Yes                  | Yes                                | Yes                                  | Yes                  | Yes                   | Yes                  | Yes                  |
| Abstract            | 2 Provide an accurate summary of the background and research objectives, including details of the species or strain of animal used, key methods, principal findings, and conclusions of the study | Yes                  | Yes                                | Yes                                  | Yes                  | Yes                   | Yes                  | Yes                  |
| Background          | 3 a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology. | Yes                  | Yes                                | Yes                                  | Yes                  | Yes                   | Yes                  | Yes                  |
| Objectives          | 4 Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. | Yes                  | Yes                                | Yes                                  | Yes                  | Yes                   | No                   | Yes                  |
| Ethical statement   | 5 Indicate the nature of the ethical review permissions, relevant licenses (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research. | Yes                  | Yes                                | Yes                                  | Yes                  | Yes                   | Yes                  | Yes                  |
| Experimental animals| 6 For each experiment, give brief details of the study design, including a. The number of experimental and control groups. b. Any steps taken to minimize the effects of subjective bias when allocating animals to treatment (e.g. randomization procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group, or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out. | Yes                  | Yes                                | Yes                                  | Yes                  | No                    | No                   | Yes                  |
| Experimental animals| 7 For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example, a. How (e.g. drug formulation and dose, site and route of administration, anesthesia, and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier (s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for the choice of specific anesthetic, route of administration, drug dose used). | Yes                  | Yes                                | Yes                                  | Yes                  | Yes                   | Yes                  | Yes                  |
Table 5: Contd...

| Item                          | Recommendation                                                                 | Nakas et al. (2017) | Fernandez-Gonzalez et al. (2016) | Venkataramana, Kumar et al. (2014) | Ortega et al. (2012) | Fujimura et al. (2009) | Liu et al. (2004) | Adachi et al. (1994) |
|-------------------------------|---------------------------------------------------------------------------------|---------------------|----------------------------------|-----------------------------------|---------------------|----------------------|-----------------|---------------------|
| Housing and husbandry        | Provides details of a. Housing (type of facility, e.g., specific pathogen-free [SPF]; type of cage or housing; bedding material; some cage companions; tank shape and material, etc., for fish). b. Husbandry conditions (e.g. breeding program, light/dark cycle, temperature, quality of water, etc., for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out before, during, or after the experiment | Yes                 | Yes                              | Yes                               | Yes                 | Yes                  | Yes             | Yes                 |
| Sample size                  | a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group. b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used. c. Indicate the number of independent replications of each experiment, if relevant. | No                  | Yes                              | No                                | Yes                 | No                   | No              | No                  |
| Allocating animals to an experimental group | a. Give full details of how animals were allocated to experimental groups, including randomization or matching if done. b. Describe the order in which the animals in the different experimental groups were treated and assessed. | Yes                 | Yes                              | No                                | Yes                 | No                   | No              | No                  |
| Experimental outcomes        | Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioral changes). | Yes                 | Yes                              | Yes                               | Yes                 | Yes                  | Yes             | Yes                 |
| Statistical methods          | a. Provide details of the statistical methods used for each analysis. b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron). c. Describe any methods used to assess whether the data met the assumptions of the statistical approach. | Yes                 | Yes                              | Yes                               | Yes                 | Yes                  | Yes             | Yes                 |
| Baseline data                | For each experimental group, report relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) before treatment or testing. (This information can often be tabulated). | Yes                 | Yes                              | Yes                               | Yes                 | No                   | Yes             | Yes                 |
| Numbers analyzed             | a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%). b. If any animals or data were not included in the analysis, explain why. | Yes                 | Yes                              | Yes                               | Yes                 | Yes                  | Yes             | Yes                 |
| Outcomes and estimation      | Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval). | Yes                 | Yes                              | Yes                               | Yes                 | Yes                  | Yes             | Yes                 |
| Adverse events               | a. Give details of all important adverse events in each experimental group. b. Describe any | No                  | Yes                              | No                                | No                  | No                   | No              | No                  |
Table 5: Contd...

| Item           | Recommendation | Nakas et al. (2017) [31] | Fernandez-Gonzalez et al. (2016) [32] | Venkataramana, Kumar et al. (2014) [31] | Ortega et al. (2012) [29] | Fujimura et al. (2009) [26] | Liu et al. (2004) [27] | Adachi et al. (1994) [26] |
|----------------|----------------|--------------------------|--------------------------------------|--------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Interpretation/ scientific implications | 17              | Yes                      | Yes                                  | Yes                                  | Yes                      | Yes                      | Yes                      | Yes                      |
| Generalizability/translation | 18              | No                       | Yes                                  | Yes                                  | No                       | Yes                      | Yes                      | No                       |
| Funding        | 19              | No                       | No                                   | No                                   | Yes                      | Yes                      | No                       | No                       |

Before applying these findings to human studies, it is preferable to examine the dosage and frequency of locally administered bisphosphonates in similar settings. It is also critical to do animal research to determine the effect of locally administered bisphosphonate's long-term local and systemic effects. It would also be significant if such research were to become more standardized and the approach to evaluating the outcome events was more relevant to the tooth movement's three-dimensional aspect. Additionally, potential sources of bias should be resolved, and future research should replicate as closely as possible, scenarios encountered in clinical practice.

Conclusion

This systematic review found that bisphosphonates effectively limit orthodontic tooth movement around the application site without affecting adjacent sites. More potent bisphosphonates in smaller doses or less frequent bisphosphonates in higher frequencies have been proposed to improve outcomes. However, the data quality is insufficient to recommend a protocol for bisphosphonate administration for anchoring control. Long-term studies evaluating various types, frequencies, and dosages of bisphosphonates are required to clarify the effects on orthodontic tooth movement.

Data availability

Data available on request.

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Conflicts of interest

There are no conflicts of interest.

References

1. Roberts-Harry D, Sandy J. Orthodontics. Part 9: Anchorage control and distal movement. Br Dent J 2004;196:255–263.
2. Block MS, Hoffman DR. A new device for absolute anchorage for orthodontics: A dream or reality? J Orthod 1995;22:251–256.
3. Young KA, Melrose CA, Harrison JE. Skeletal anchorage systems in orthodontics: A dream or reality? J Orthod 2001;28:21–26.
4. Consolaro A, Minis-plants and miniimplants: sub-absolute and absolute anchorage. Dent Press J Orthod 2014;19:30–38.
5. Consolaro A, Minis-plants and miniimplants: bone remodeling and adhesion. Dent Press J Orthod 2015;20:16–31.
6. Power sample estimates in most studies is low, which only one study was able to be performed. Before applying these findings to human studies, it is preferable to examine the dosage and frequency of locally administered bisphosphonates in similar settings. It is also critical to do animal research to determine the effect of locally administered bisphosphonate's long-term local and systemic effects. It would also be significant if such research were to become more standardized and the approach to evaluating the outcome events was more relevant to the tooth movement's three-dimensional aspect. Additionally, potential sources of bias should be resolved, and future research should replicate as closely as possible, scenarios encountered in clinical practice.
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6. Diar-Bakirly S, Feres MF, Saltaji H, Flores-Mir C, El-Bialy T. Effectiveness of the transpalatal arch in controlling orthodontic anchorage in maxillary premolar extraction cases: A systematic review and meta-analysis. Angle Orthodontist 2017;87:147-58.

7. Fleisch H. Bisphosphonates in Bone Disease: From the Laboratory to the Patient. Amsterdam, Netherlands: Elsevier; 2000.

8. Fleisch H. Development of bisphosphonates. Breast Cancer Res 2002;4:30-4.

9. Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, et al. Cellular and molecular mechanisms of action of bisphosphonates. Cancer 2000;2961-78.

10. Wood J, Bonjean K, Ruetz S, Bellahcène L, Foidart JM, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002;302:1055-61.

11. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. Ann Pharmacother 2005;39:668-77.

12. Kim TW, Yoshida Y, Yokota K, Sasaki T. An ultrastructural study of the effects of bisphosphate administration on osteoclastic bone resorption during relapse of experimentally moved rat molars. Am J Orthod Dentofac Orthop 1999;115:645-53.

13. Keles A, Grunes B, Difuria C, Gagari E, Srinivasan V, Darendeliler MA, et al. Inhibition of tooth movement by osteoprotegerin vs. pamidronate under conditions of constant orthodontic force. Eur J Oral Sci 2007;115:131-6.

14. Karras JC, Miller JR, Hodges JS, Beyer JP, Larson BE. Effect of alendronate on orthodontic tooth movement in rats. Am J Orthod Dentofac Orthop 2009;136:843-7.

15. Sirisoontorn I, Hotokezaka H, Hashimoto M, Gonzales C, Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, et al. Preferred reporting items for systematic review and meta‑analysis protocols (PRISMA‑P) 2015: Elaboration and elaboration. J Clin Epidemiol 2017;86:62-69.

16. Cumpton M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: A new edition of the cochrane handbook for systematic reviews of interventions. Cochrane Database of Syst Rev. 2019. doi: 10.1002/14651858.ed000142.

17. Kaipatur NR, Wu Y, Adeeb S, Stevenson TR, Major PW, Doschak MR. Impact of bisphosphonate drug burden in alveolar bone during orthodontic tooth movement in a rat model: A pilot study. Am J Orthod Dentofac Orthop 2013;144:557-67.

18. Salazar M, Hernández L, Ramos AL, Salazar Bde O, Micheletti KR, Panahos LR, et al. Effect of alendronate sodium on tooth movement in ovariectomized rats. Arch Oral Biol 2015;60:776-81.

19. Brunet MD, Araujo CM, Johann AC, Camargo ES, Tanaka OM, Guariza O Filho. Effects of zoledronic acid on orthodontic tooth movement in rats. Braz Dent J 2016;27:515-23.

20. Franzoni JS, Soares FMP, Zaniboni E, Vedovello Filho M, Santamaria MP, Dos Santos GMT, et al. Zoledronic acid and alendronate sodium and the implications in orthodontic movement. Orthod Craniofac Res 2017;20:164-9.

21. Suzuki H, Band K, Tada H, Kiyama T, Oizumi T, Funayama H, et al. Observations of lipopolysaccharide-induced production of IL-1α and IL-1β in mice given intravenous zoledronate (a non-containing bisphosphonate) and its prevention by clodronate (a non-nitrogen-containing bisphosphonate). Biol Pharm Bull 2019;42:164-72.

22. Wu D, Meng B, Cheng Y, Gan L, Huang P, Cao Y. The effect of risendronate on orthodontic tooth movement in ovariectomized rats. Arch Oral Biol 2019;105:59-64.

23. Venkataraman V, Chidambaram S, Reddy BV, Goud EV, Afafath M, Krishnan S, et al. Impact of bisphosphonate on orthodontic tooth movement and osteoclastic count: An animal study. J Int Oral Health 2014;6:1-8.

24. Adachi H, Igarashi K, Mitani H, Shinoda H. Effects of topical administration of a bisphosphonate (risendronate) on orthodontic tooth movements in rats. J Dent Res 1994;73:1478-86.

25. Liu L, Igarashi K, Haruyama N, Saeki S, Shinoda H, Mitani H. Effects of local administration of clodronate on orthodontic tooth movement and root resorption in rats. Eur J Orthod 2014;26:469-73.

26. Fujimura Y, Kitaura H, Yoshimatsu M, Eguchi T, Kohara H, Morita Y, et al. Influence of bisphosphonates on orthodontic tooth movement in mice. Eur J Orthod 2009;31:572-7.

27. Ortega AJ, Campbell PM, Hinton R, Naidu A, Buschang PH. Local application of zoledronate for maximum anchorage during space closure. Am J Orthod Dentofac Orthop 2012;142:780-91.

28. Fernández‑González FJ, López‑Caballo JL, Cañigral A, Menéndez‑Díaz I, Brizuela A, de Cos FJ, et al. Osteoprotegerin and zoledronate bone effects during orthodontic tooth movement. Orthod Craniofac Res 2016;19:54-64.

29. Nakaš E, Lauć T, Tiro A, Džemidžić V, Zukanović A, Franić M, et al. Dosage- and time-dependent effects of clodronate on orthodontic tooth movement. Bosn J Basic Med Sci 2017;17:23-8.

30. Venkataraman V, Kumar SS, Reddy BV, Cherukuri AS, Sigamani KR, Chandrasekhar G. Administration of bisphosphonate (ibandronate) impedes molar tooth movement in rabbits: A radiographic assessment. J Pharmacy Bioall Sci 2014;6:165-70.

31. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Riks‑Hoitinga M, Langendam MW. SYRCLE’s risk of bias tool for animal studies. BMC Med Res Methodol 2014. doi: 10.1186/1471-2288-14-43.

32. Kilkenney C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research. Osteoarthritis Cartilage 2012;20:256-60.