Review Article

EFFICACY OF HYALURONIC ACID IN ALVEOLAR BONE REGENERATION: A SYSTEMATIC REVIEW

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ABSTRACT

This systematic review aims to evaluate the efficacy of hyaluronic acid (HA) in promoting bone regeneration in patients with maxillofacial alveolar bone defects. The review focuses on clinical outcomes, including bone volume and density, while exploring HA's underlying mechanisms in bone healing. A systematic literature search was conducted across multiple databases, including PubMed, Web of Science, Google Scholar, and the Cochrane Library, to identify clinical studies evaluating the role of HA in maxillofacial bone regeneration. Studies involving human subjects with maxillofacial alveolar bone defects treated with HA, alone or in combination with bone grafts, were included. We appraised the risk of bias and the level of evidence for all included studies using standardized tools. The systematic review included 4 studies with a total of 96 patients. The majority of studies reported significant improvements in bone volume and density following the local drug application of HA, with enhanced healing time compared to traditional bone grafts or other synthetic substitutes. The unique viscoelastic property and high water retention, HA was found to promote angiogenesis, reduce inflammation, and act as a scaffold, facilitating cellular migration and new bone formation. However, variability in assessment methods and HA formulations used made it challenging to standardize results across all studies. Hyaluronic acid shows promise as a biomaterial for enhancing bone regeneration in maxillofacial alveolar bone defects. However, further well-designed, large-scale clinical trials are necessary to establish standardized protocols and determine optimal HA formulations for predictable clinical success.

Key words: Hyaluronic acid, Bone regeneration, Water, Drug, Alveolar bone defects.

Introduction

Maxillofacial alveolar bone defects pose a significant clinical challenge in dentistry and maxillofacial surgery, particularly in the context of tooth loss, trauma, congenital anomalies, and periodontal disease [1]. Effective bone regeneration in these regions is critical to restore both function and esthetics. Over the years, various biomaterials have been used to facilitate bone healing, including autografts, allografts, xenografts, and synthetic substitutes [2]. Despite various advancements in these areas, the search for ideal materials that promote faster, safer, and more predictable bone regeneration continues.

A naturally occurring glycosaminoglycan in the body's connective tissues, hyaluronic acid (HA), has attracted substantial interest in regenerative medicine for its multifaceted roles in tissue repair, wound healing, and cellular growth [3]. With its unique viscoelastic properties, high water-retention capacity, and ability to form scaffolds conducive to cell migration, HA is widely used across various medical fields, including ophthalmology, dermatology, and orthopedics [4]. More recently, its application has extended into maxillofacial surgery, particularly in addressing bone defects. Alveolar bone defects in the maxillofacial region present significant clinical challenges, often resulting from trauma, infection, tooth loss, or surgical interventions like tumor resections. The treatment of these defects is critical, especially in contexts such as dental implant placement and oral rehabilitation, where successful bone regeneration directly affects patient outcomes [5].

Traditional methods for treating maxillofacial bone defects involve bone grafts, alloplastic materials, and growth factor applications. While these techniques have demonstrated success in promoting bone healing, they are often limited by factors such as donor site morbidity, infection risk, graft resorption, and prolonged healing times [6]. As the field of tissue engineering advances, there is growing interest in using biocompatible materials, such as HA, as adjuncts to enhance bone regeneration. HA's role in bone regeneration lies in its ability to support osteogenesis by creating a favorable microenvironment for osteoprogenitor cells recruitment, enhancing blood vessel formation, and promoting the synthesis of extracellular matrix components [7, 8]. Furthermore, HA can act as a carrier for growth factors, improving their local concentration at defect sites and sustaining their release over time [9].

Several preclinical and clinical studies have investigated the efficacy of hyaluronic acid for bone regeneration in maxillofacial alveolar bone defects, either as a single treatment or in combination with bone grafts or other regenerative materials [10-14]. These studies have demonstrated HA's ability to enhance osteogenesis,

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modulate the inflammatory response, and support the early stages of bone healing. Despite the promising results, variability in reported outcomes remains, and the precise mechanisms by which HA contributes to bone regeneration require further elucidation [15-17].

This systematic review aims to evaluate the efficacy of hyaluronic acid in the management of maxillofacial alveolar bone defects. By collating and integrating data from clinical studies, we aim to assess whether HA can improve clinical outcomes, such as bone volume and density, reduce healing time, and enhance overall patient satisfaction. This review will also explore the mechanisms through which HA influences bone regeneration and highlight any limitations or potential areas for future research in this promising field [18-22].

Aim

This systematic review aims to evaluate the efficacy of hyaluronic acid in promoting bone regeneration in patients with maxillofacial alveolar bone defects.

Materials and Methods

Pico analysis

P (Population): Patients with maxillofacial alveolar bone defects

I (Intervention): Application of hyaluronic acid as an adjunct in bone regeneration treatments

C (Comparison): Conventional treatments without Hyaluronic acid

O (Outcome): Improved bone regeneration.

S (Study Design): Randomised clinical trials (RCTs), clinical trials

Structured question

Does the use of hyaluronic acid enhance bone regeneration outcomes in patients with maxillofacial alveolar bone defects compared to conventional treatment methodology?

A systematic literature review was conducted across multiple databases to evaluate the efficacy of hyaluronic acid for bone regeneration in people with maxillofacial alveolar bone defects. There were no restrictions placed on the publication date, and all the past articles were retrieved. The review was registered in PROSPERO - CRD420251069797.

To identify relevant studies for inclusion in this systematic review, we developed detailed search strategies for each database. The searches were constructed using a combination of controlled vocabulary (e.g., MeSH terms) and free-text keywords. Keywords were classified into four groups based on the PICO framework (Population, Intervention, Comparison, and Outcome). Keywords within each PICO group were combined using the OR operator, and the final searches for all four groups were combined using the AND operator to maximize the retrieval of pertinent articles. The Databases searched were PubMed, Cochrane, Web of Science, and Google Scholar.

The inclusion criteria for the review were studies that included only alveolar bone defects of the jaw and used only hyaluronic acid alone or with bone grafts. The studies had to be randomised controlled trials or clinical trials conducted on humans alone. Any study that was done on any bone other than the jawbone was excluded. If any other drug in combination with hyaluronic acid was used, it was also excluded from the review. Case reports, literature review, animal studies, etc., were not included [23-26].

Risk of bias was assessed using the RevMan (Cochrane Collaboration) framework **(Table 1)**. 2 articles had low risk of bias, and 2 had an intermediate risk of bias **(Figure 1)**.

Table 1. Risk Of Bias using the RevMan (Cochrane Collaboration) framework

STUDY	Random Sequencing Generation	Allocation Concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Alcântara *et al*. (2018)	Low	Low	Low	Low	Low	Low	Low
Mostafa *et al*. (2021)	low	Unclear	Unclear	low	Low	Low	Low
Abdelmabood *et al*. (2022)	High	High	Unclear	Unclear	Low	Low	Low
Abdelzaher *et al*. (2022)	Low	Low	Unclear	low	low	Low	Low

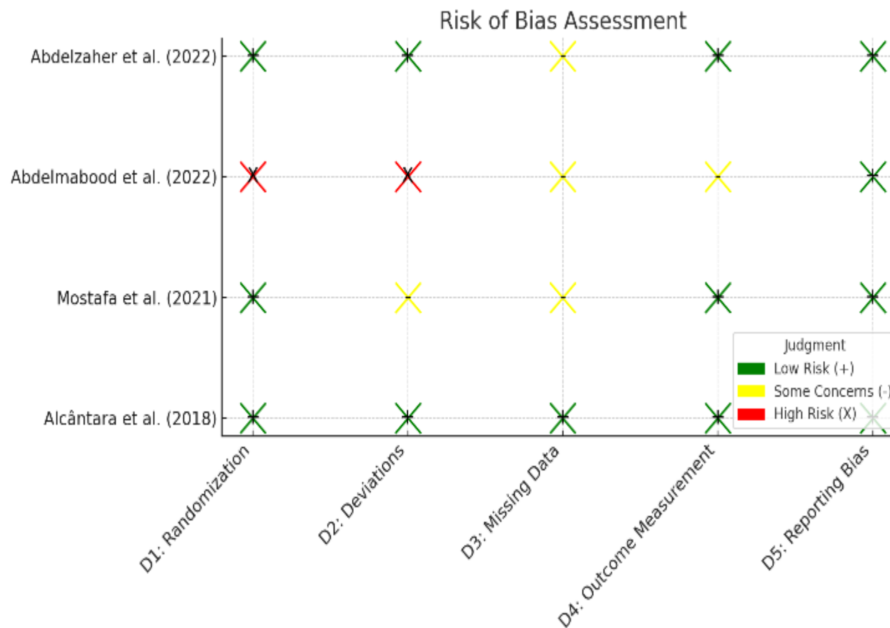

Figure 1. Risk of Bias Assessment

For all four studies, the level of evidence was checked using the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 **(Table 2)**.

Table 2. Level of Evidence based on Oxford Centre for Evidence-Based Medicine (OCEBM) - 2011

Reference	Study Design	Level of Evidence	Blinding	Sample Size
Alcântara *et al*. (2018)	Randomised triple-blind clinical trial	Level 2	Triple blinded	N = 32
Mostafa *et al*. (2021)	Pilot study (RCT)	Level 2	Not Reported	N = 20
Abdelmabood *et al*. (2022)	Comparative study (non-randomised)	Level 3	Not Reported	N = 24
Abdelzaher *et al*. (2022)	Randomised clinical trial	Level 2	Not Reported	N = 20

Results and Discussion

The initial electronic search yielded 521 articles. Of these, 83 were identified as duplicate records and removed. We then excluded 434 articles after reviewing their titles and abstracts for irrelevance to our topic. The remaining four articles were selected based on the assessment of their full-text core data. These four studies formed the final evidence base and were consolidated for the systematic review, as depicted in **Figure 2**.

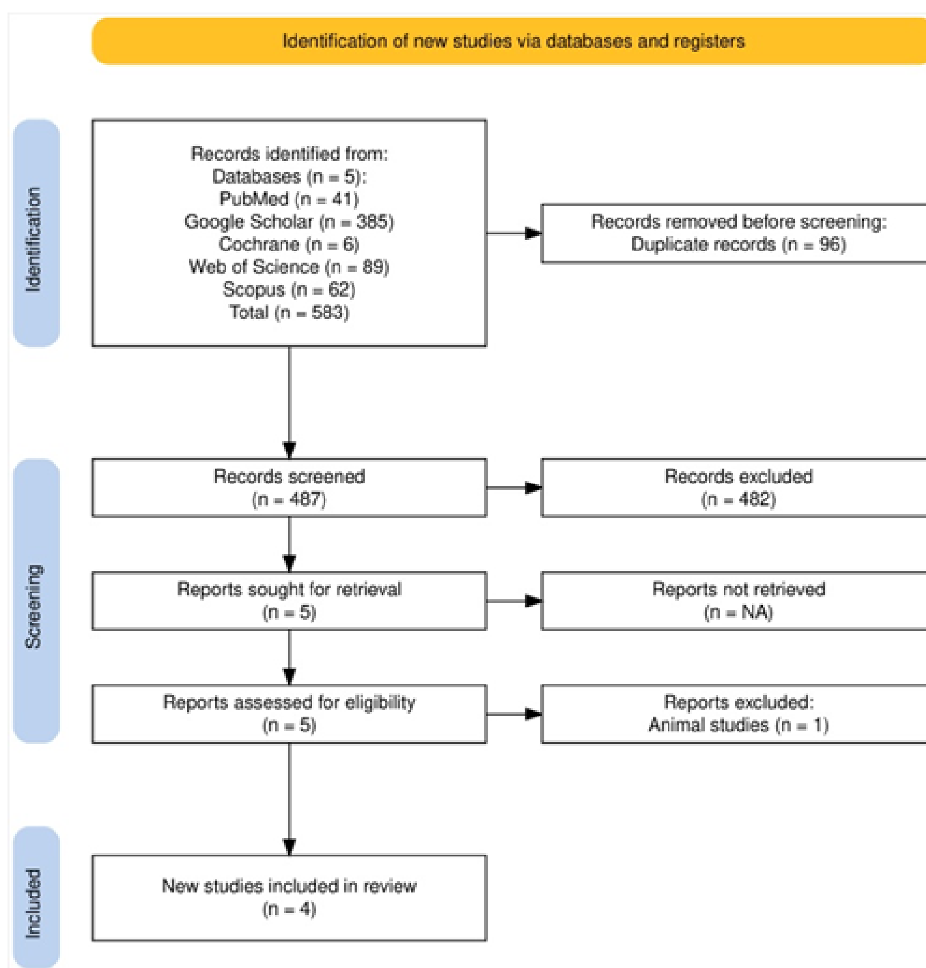

Figure 2. PRISMA Flowchart of Data Extraction for Systematic Review

Data extraction was done for all four studies **(Table 3)**. Of the 4 studies, 3 used HA in extraction sockets and 1 used it in post-cyst enucleation bony sockets. In all studies, bone formation was checked. 3 studies used CBCT as an assessment tool, and 1 study checked socket length. The follow-up period was variable: 2 studies had a follow-up period of 3 months, 1 study had a follow-up period of 6 months, and 1 had only a 10-day follow-up. All studies showed positive results for HA in bone regeneration compared with the control group [27-42].

Table 3. Data Extraction Table

S. No	Study Design	Reference	Sample Size	Population	Intervention group	Control group	Outcome measures assessment method	Results	Follow-Up Time
1	In Vivo	Alcântara *et al.* (2018)	N = 32	Patients undergoing dental extractions.	Hyaluronic acid gel	No drugs used	CBCT Morphometric evaluation and fractal dimension analysis	Hyaluronic acid is an effective adjunctive treatment for bone repair in dental sockets.	3 months
2	In Vivo	Mostafa *et al.* (2021)	N = 20	Patients requiring simple dental extractions.	Hyaluronic acid gel	No drugs used	Socket length	Hyaluronic acid gel in simple dental extraction sockets has a positive effect on bone healing.	10 days
3	In Vivo	Abdelmabood *et al.* (2022)	N = 24	Patients undergoing enucleation of mandibular cysts	Hyaluronic acid gel	Ozone gel	CBCT	Hyaluronic acid proved to be more effective than ozone gel.	6 months

4	In Vivo	Abdelzaher *et al*. (2022)	N = 20	Patients needing socket preservation post-extraction	Hyaluronic acid with xenogenic bone graft	Xenogenic bone graft	CBCT	Hyaluronic acid with bone graft is significantly better than xenogenic bone graft alone.	3 months

The current systematic review aimed to assess the efficacy of hyaluronic acid (HA) in promoting bone regeneration in patients with maxillofacial alveolar bone defects. A naturally occurring polysaccharide, hyaluronic acid, is widely used for its roles in tissue repair, modulation of inflammation, and angiogenesis, which are critical for bone healing [43]. This review synthesizes four relevant clinical studies and provides insight into the potential advantages and limitations of HA for bone regeneration in the maxillofacial region [44-46].

Hyaluronic acid (HA) plays a crucial role in bone regeneration through various interconnected biological processes. Its structural properties provide hydration that supports cell adhesion, proliferation, and migration, particularly for osteoprogenitor cells and fibroblasts, which differentiate into osteoblasts responsible for bone formation. HA also enhances blood vessel formation by promoting the release of vascular endothelial growth factor (VEGF), thereby facilitating new blood vessel formation, which is essential for adequate nutrient supply. Furthermore, HA modulates the inflammatory response, reducing excessive inflammation that can hinder healing, while simultaneously serving as a scaffold that supports extracellular matrix (ECM) formation, thereby enhancing bone strength and mineralization. Additionally, HA can sustain the release of growth factors, such as bone morphogenetic proteins (BMPs), thereby further promoting osteogenesis and improving overall bone healing [47-49].

According to the article by Alcântara *et al*. (2018), in this randomized triple-blind clinical trial, Alcântara *et al*. (2018) explored the effect of HA on bone repair in human dental sockets post-extraction. The study demonstrated that HA use significantly accelerated bone formation compared with the control group. The authors reported enhanced early healing in patients who received HA treatment, with clinical and radiographic assessments confirming greater bone deposition in HA-treated sockets [50].

The results suggest that HA contributes to early-stage osteogenesis, likely by retaining moisture, modulating inflammation, and creating a conducive environment for bone precursor cells. By enhancing the early phases of bone repair, HA might reduce healing time after dental extractions, which is especially beneficial for preparing alveolar ridges for implant placement. However, the study also noted that the long-term effects of HA on bone quality require further investigation [51, 52].

Mostafa *et al*. (2021) conducted a pilot study to evaluate the impact of HA gel on the healing of simple dental extraction sockets. Similar to Alcântara *et al*. this study highlighted that HA application resulted in improved healing outcomes, both clinically and radiographically. The study showed that patients treated with HA exhibited faster soft tissue healing, and bone regeneration was more uniform in the HA group compared to controls [53].

The authors attributed these findings to HA's anti-inflammatory and wound-healing properties. HA's ability to minimize inflammation and enhance angiogenesis likely plays a significant role in reducing post-extraction complications, leading to faster and more predictable bone regeneration. Nevertheless, the pilot nature of the study, with a relatively small sample size, limits the generalizability of the results. Larger-scale studies are needed to confirm these findings and to explore the optimal concentration and formulation of HA for clinical use [54, 55].

In this comparative study, Abdelmabood *et al*. (2022) assessed the efficacy of hyaluronic acid and ozone gel in bone healing following the enucleation of mandibular odontogenic cysts. The results indicated that while both HA and ozone gel improved bone healing compared to the control group, HA demonstrated superior outcomes in terms of new bone formation and radiographic density at three and six months post-operation [56].

This study further supports the osteogenic potential of HA in maxillofacial bone defects, suggesting that HA's biochemical properties, including its ability to support cellular proliferation and modulate inflammatory responses, make it more effective than other biomaterials like ozone gel. The study also pointed out that the early bone remodeling process was more efficient in the HA-treated group, which has significant implications for accelerating the recovery period after cyst enucleation [57].

However, the study faced some limitations, particularly in terms of the variability in cyst sizes and the extent of bone defects, which could have influenced the results. Future studies with more standardized defect sizes and a longer follow-up period could provide clearer conclusions about HA's long-term efficacy in this context [56].

In a randomized clinical trial, Abdelzaher *et al*. (2022) evaluated the use of HA in combination with a xenogenic bone graft for post-extraction socket preservation. The study found that the addition of HA to the bone graft significantly enhanced bone volume and density compared to the bone graft alone [58]. Clinical and radiographic assessments revealed that the HA group had more uniform bone

regeneration and better alveolar ridge preservation, critical for subsequent implant placement.

This study highlights the synergistic effect of HA when used alongside traditional bone graft materials. The combination of HA with xenogenic bone grafts may enhance the regenerative potential of the graft by providing a hydrated matrix that supports cellular migration and proliferation [59]. This finding suggests that HA could be a valuable adjunct in clinical settings where rapid and predictable bone regeneration is needed, such as in implantology. However, the study also noted some concerns related to the cost-effectiveness of using HA in routine clinical practice, which may limit its widespread adoption despite its demonstrated benefits.

The collective findings from these four studies suggest that hyaluronic acid has a significant positive impact on bone regeneration in maxillofacial alveolar bone defects. Across various clinical scenarios, from simple dental extractions to more complex bone defects associated with cyst enucleation and socket preservation, HA consistently improved clinical and radiographic outcomes compared to control treatments [60].

The primary mechanisms by which HA appears to enhance bone regeneration include its anti-inflammatory effects, ability to modulate the early stages of healing, and promotion of angiogenesis, which are essential for the establishment of new bone [61]. Furthermore, HA's hydrophilic nature creates an optimal environment for bone precursor cells, fostering faster and more predictable bone formation. The studies by Alcântara *et al*. (2018) and Mostafa *et al*. (2021) underscored HA's efficacy in accelerating early bone repair, while Abdelmabood *et al*. (2022) and Abdelzaher *et al*. (2022) demonstrated HA's role in improving both short- and long-term bone regeneration outcomes.

Despite the promising results, there are several limitations that need to be considered. Firstly, the included studies exhibit considerable heterogeneity in sample sizes, treatment protocols, and outcome measures, making it challenging to generalize findings across different clinical contexts. Many studies had limited sample sizes, which may reduce statistical power and reliability. Additionally, the follow-up periods varied, with some studies assessing outcomes only in the short term, potentially missing long-term effects of hyaluronic acid (HA) on bone regeneration. The quality of the studies also varied, with several exhibiting a higher risk of bias due to factors such as inadequate randomization and lack of blinding. Inconsistencies in outcome measures across studies further complicate the synthesis of results. Additionally, the optimal concentration and formulation of HA remain unclear, with different studies employing various HA preparations. The economic feasibility of incorporating HA into routine clinical practice also requires further evaluation, especially in resource-limited settings. Moreover, potential confounding factors, including patient-related variables, were often not adequately controlled for, resulting in challenges when attempting to isolate the particular effects of HA. Lastly, publication bias may influence the perceived efficacy of HA, as studies with positive outcomes have a higher chance of getting published. Collectively, these limitations highlight the need for further research with larger, well-designed studies to provide more robust evidence regarding the role of HA in bone regeneration.

Future research efforts must prioritize large-scale, multicenter Randomized Controlled Trials (RCTs) employing standardized methodologies to enhance comparability and reliability. Studies should aim for longer follow-up periods to assess the long-term effects of HA on bone quality and density, particularly concerning dental implant success. Additionally, investigating the optimal concentration and formulation of HA, as well as its combined effects with other regenerative materials, would provide valuable insights. Exploring the underlying biological mechanisms of HA in bone healing at the cellular and molecular levels is crucial for understanding its therapeutic potential. Furthermore, addressing potential confounding variables, such as patient demographics and systemic health conditions, will improve the robustness of findings. Ultimately, these efforts will contribute to a clearer understanding of HA's role in bone regeneration and guide its clinical application in maxillofacial surgery.

Conclusion

In conclusion, hyaluronic acid appears to be a valuable biomaterial for enhancing bone regeneration in maxillofacial alveolar defects. Its ability to promote early healing, modulate inflammation, and support bone formation makes it a promising adjunct to traditional bone grafting techniques. However, further high-quality studies are required to confirm its long-term efficacy and establish standardized protocols for its clinical use.

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