J Stomatol Oral Maxillofac Surg 124 (2023) 101426

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Original Article

Clinical and radiographic assessment of cross-linked hyaluronic acid addition in demineralized bovine bone based alveolar ridge preservation: A human randomized split-mouth pilot study

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ARTICLE INFO

Article History:
Received 22 December 2022
Accepted 13 February 2023
Available online 16 February 2023

Keywords:
Bone grafting
Bone regeneration
Dental implants
Hyaluronic acid
Oral surgery
Socket preservation
Socket seal
Ridge preservation

ABSTRACT

Purpose: To investigate clinically and radiographically at 4 months post-operatively the outcomes of mixing demineralized bovine bone material (DBBM) with cross-linked hyaluronic acid in alveolar ridge preservation.
Material and Methods: Seven patients presenting bilateral hopeless teeth (14 teeth) were enrolled in the study, the test site contained demineralized bovine bone material (DBBM) mixed with cross-linked hyaluronic acid (xHyA) while the control site contained only DBBM. 4 months post-operatively prior to implant placement a Cone beam computed tomography (CBCT) scan was recorded and compared to the initial scan to assess the volumetric and linear bone resorption that occurred in both sites. Clinically, sites that needed further bone grafting at the implant placement stage were recorded. Differences in volumetric and linear bone resorption between both groups were assessed using Wilcoxon signed rank test. McNemar test was also used to evaluate difference in bone grafting need between both groups.
Results: All sites healed uneventfully, volumetric and linear resorption differences between the baseline and 4 months post-operatively were obtained for each site. The mean volumetric and linear bone resorption were respectively 36.56 ± 1.69%, 1.42 ± 0.16 mm in the controls sites and 26.96 ± 1.83%; 0.73 ± 0.052 mm in the tests sites. The values were significantly higher among controls sites (P=0.018). No significant differences were observed in the need for bone grafting between both groups.
Conclusion: Cross-linked hyaluronic acid (xHyA) appears to limit the post-extractional alveolar bone resorption when mixed with DBBM.

1. Introduction

Following tooth extraction, the alveolar socket is subject to resorption throughout the healing process, mainly observed in the first 8 weeks following extraction, and can cause up to 50%-dimensional reduction of the original ridge width [1]. The resorption is more pronounced on the buccal aspect of the ridge thus affecting the treatment prognosis when a prosthetically-driven implant placement is planned [1]. Therefore, maintaining adequate ridge volume by anticipating the risk of hard and soft tissue loss, is mandatory especially in the anterior sector [1].

In order to compensate this loss and achieve an aesthetically acceptable implant-supported prosthesis, different bone grafting techniques were proposed such as guided bone regeneration, onlay bone block and alveolar ridge preservation (ARP) [2]. The latter is a preventive procedure that consists of placing various biomaterials in the socket to limit post-extractional alterations. The two most used bone grafting materials are allografts and xenografts [2]. DBBM were proven to be biologically inert osteoconductive materials [3]. The ARP, however, aims at successful ridge reconstruction, i.e., new bone formation within the volume of the former socket [4]. Although xenografts offer a stable and acceptable bone volume maintenance, their healing period and the percentage of de novo bone formation remains their main drawback [5].

Abbreviations: ARP, alveolar ridge preservation; CBCT, cone beam computed tomography; DBBM, demineralized bovine bone material; HA, hyaluronic acid; xHya, Cross-linked hyaluronic acid; MBL, mean bone loss

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https://doi.org/10.1016/j.jormas.2023.101426
2468-7855/

Considering the aforementioned facts and to enhance the ARP outcomes, clinicians are searching to reduce the healing period in order to place the implants at the earliest convenience following tooth extraction. Hence, several growth factors were tested as biological adjuvants to promote the healing process and reduce the physiological post-extractive bone resorption [6].

The authors investigated the use of cross-linked hyaluronic acid (xHyA) gel as a biological adjuvant to xenograft in an attempt to boost the regeneration capabilities and limit post-extractional resorption [7]. In fact, hyaluronic acid an extracellular polymer of disaccharides administration appears to have a beneficial impact on healing process and bone cell response by stimulating mesenchymal cells proliferation, growth factors attraction and angiogenesis in situ [8]. However, the structure of latter is rapidly disintegrated through hydrolysis. Therefore, researchers have introduced xHyA as cross-linked hyaluronic acid with a slow degradation profile to maintain a longer presence and thus effect especially long biological processes such as bone healing [9].

The aim of this split mouth pilot study is to investigate clinically and radiographically at 4-months post-operatively the effects of xHyA against ridge resorption following DBBM ARP.

2. Materials and methods

2.1. Study design

This study is a split mouth, prospective, randomized, double blinded pilot study. The study protocol was approved by the university IRB (USJ-2019-167) and registered at the clinical trials.gov under the serial: NCT04377256.

The study followed the consort extension guidelines for pilot and feasibility studies. Patient enrolment started in May 2019 and ended in May 2022, during these two years 20 patients were screened positive for the study admissibility (Fig. 1).

Patients were informed about the treatment in detail and signed an informed consent. Accordingly, the participants knew about the freedom to quit the study whenever they want in agreement with the Helsinki declaration of medical research and they confirmed that the authors are allowed for the use of the data in scientific research.

Inclusion criteria:

- Age between 18 and 60.
- Patient presenting two contralateral hopeless teeth that needs and extraction and delayed implant placement.
- Bilateral teeth belonging to the same morphological group (mono, bi or multirooted).
- Patients that cannot receive immediate implant placement.
- Presence of more than 50% of the socket bone on both sites.
- Non-smoking patient.

Exclusion criteria:

- Age less than 18 or more than 60.
- Active acute infection and suppuration of the selected teeth.
- Presence of heavy metallic artefacts that can distort CBCT scans (amalgam, metallic crowns, implants).
- Bad oral hygiene and non-compliance.
- Systemic diseases interfering with bone healing.
- Active and progressive periodontal disease.

2.2. Randomization

Test and control sites were assigned following a coin toss procedure, the Surgeon (B.H.) couldn't be blinded due to the nature of study, however, the radiographic assessment was completely blinded, as the responsible investigator (R.W.) received the CBCTs without any indicative signs regarding the site allocation or other labelling.

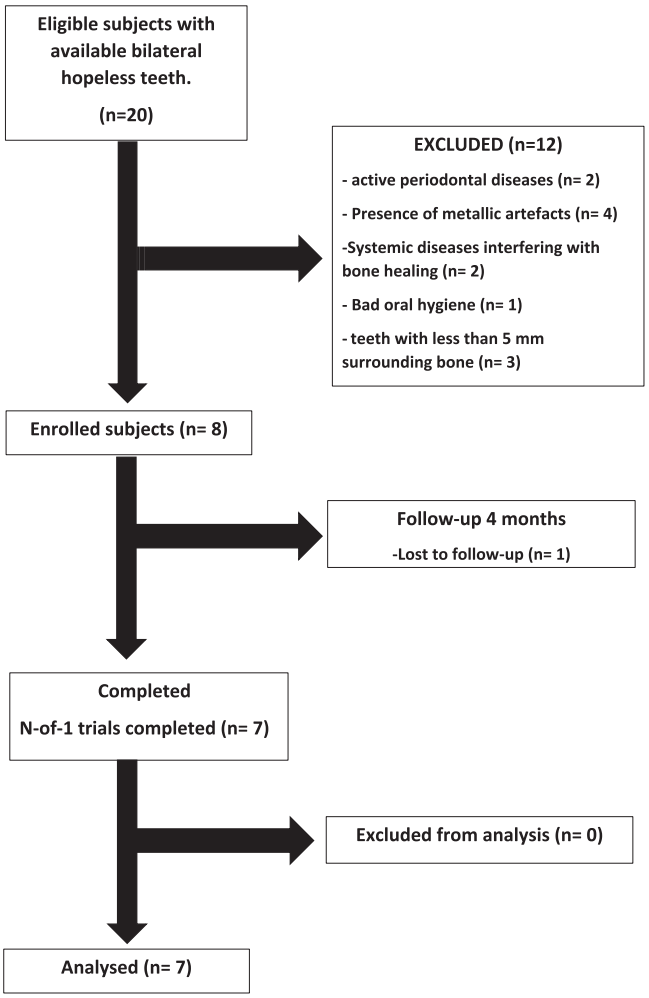

Fig. 1. Flowchart of the sample selection.

2.3. Treatment procedure

All surgical procedures were performed by the same operator B.H. A pre-operative clinical exam with a baseline CBCT scan (i-CAT®, Hatfield, PA, USA) was obtained for later radiographic comparison (Fig. 2a, b).

Following local anaesthesia (Septanest®, Septodont, Saint Maur des Fosses, France), the teeth were atraumatically extracted with the attempt to preserve the buccal plate (Fig. 3b). The sockets were debrided under copious saline irrigation using a Lucas curette (HU-friedy®, CHI, USA). The control site received DBBM solely (Bio-Oss®, Geistlich-Pharma AG, Switzerland), while the test site was filled with a mixture of DBBM and xHyA (Hyadent BG®, Regedent AG, Switzerland) (Fig. 3c). According to the individual socket diameter, two epithelio-connective tissue punches were harvested from the palate (Fig. 3d, e) and shaped as socket seal into both alveolae following the de-epithelialization of marginal tissue at their orifice (Fig. 3f). Lastly, a collagen fleece (CollaTape® Zimmer Biomet, USA.) was sutured at the donor site by 4.0 resorbable suturing material (Novosym®, B-Braun, Melsungen, Germany) for site protection.

Post-operative medication consisted of Antibiotics for 7 days 2 g/day orally (Amoxicillin Sandoz®, Basel, Switzerland). Non-steroidal anti-inflammatory drug (Ibuprofen 400 mg; Abbott Laboratories, Illinois, CHI, USA) was prescribed three times daily for three days, and a chlorhexidine mouthwash (0.12%), three times daily for two weeks.

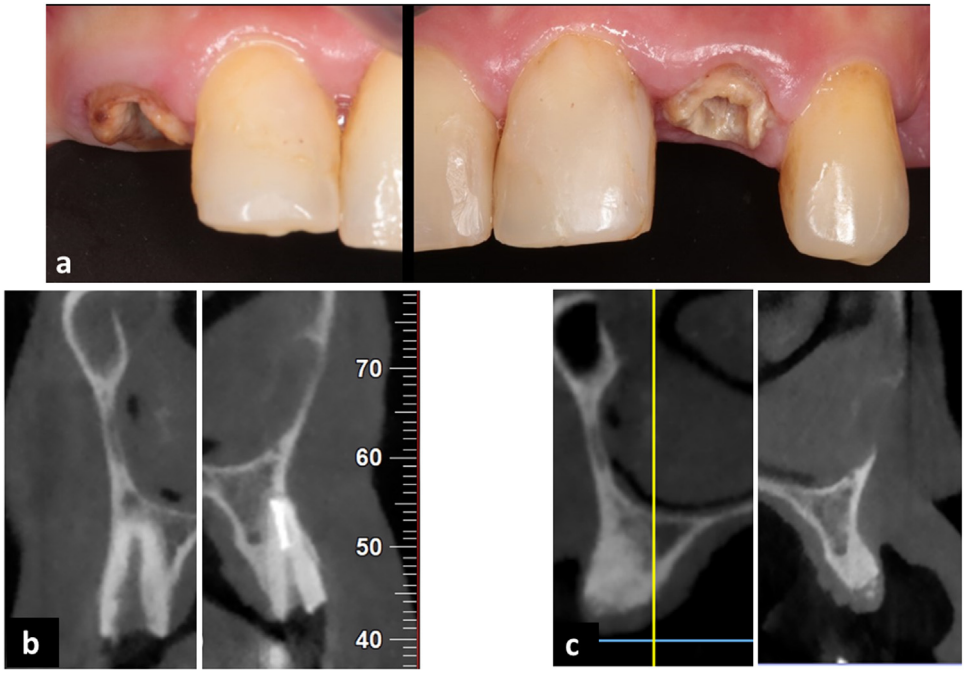

Fig. 2. (A) Pre-operative clinical photo, (b) pre-operative CBCT showing the teeth, (c) post-operative CBCT showing the bone healing 4 months after the grafting.

The healing was uneventful, only minor swelling and pain were observed. There was no evidence of necrosis or suppuration. Four months later a second CBCT scan was obtained prior to implant placement (Fig. 2c), and all patients received the dental implants (Tapered screw vent® Zimmer Biomet, CHI, USA) without early or delayed complications or failures till date.

To approve the tissue quality within the attributed volume exemplary, core biopsies from both sites retrieved at implant placement.

2.4. Outcomes identification

The assessed outcomes of this study are as follow:

1 Radiographic volumetric resorption percentage.
2 Radiographic linear resorption distance.
3 The need of further bone grafting at implant placement surgery.

2.5. Radiographic assessment techniques

Radiographic assessment and comparison of the seven cases was performed by one investigator (R.W.), who repeated the measurements one month later to assess the intraclass correlation coefficient. For estimation of the alveolar ridge volumetric change, pre- and post-operative CBCT scans were superimposed using a semi-automatic

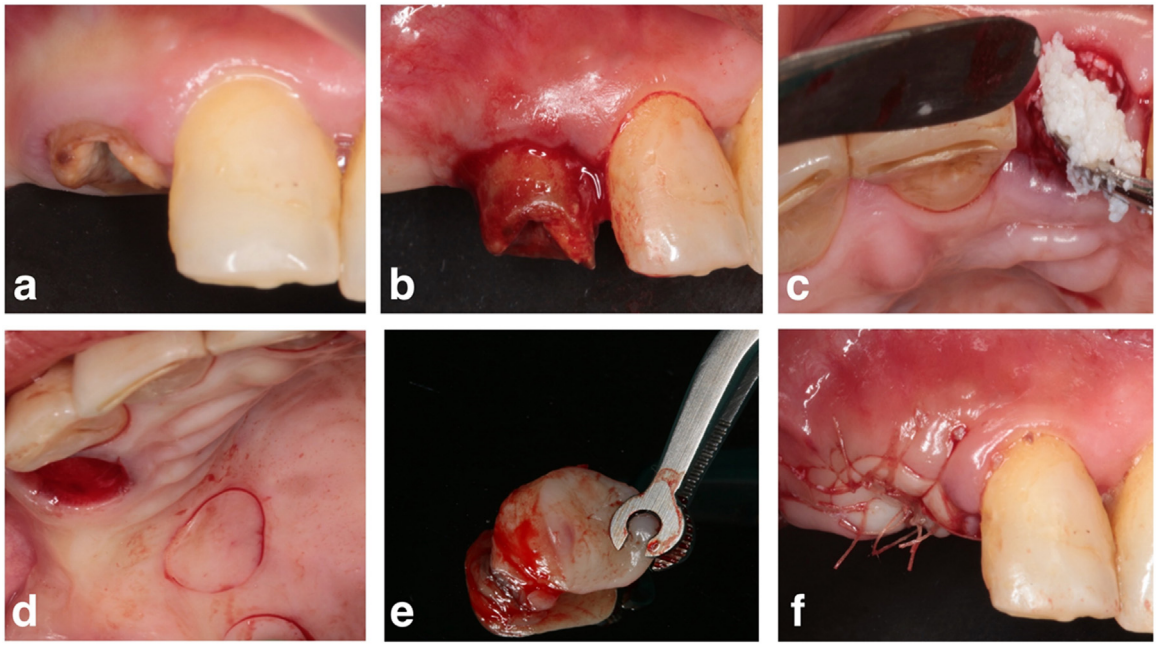

Fig. 3. Surgical sequence: (a) pre-operative photo, (b) atraumatic extraction, (c) socket filling, (d) epithelio-connective tissue punches harvesting from the palate, (e) the epithlio-connective graft, (f) post-operative photo.

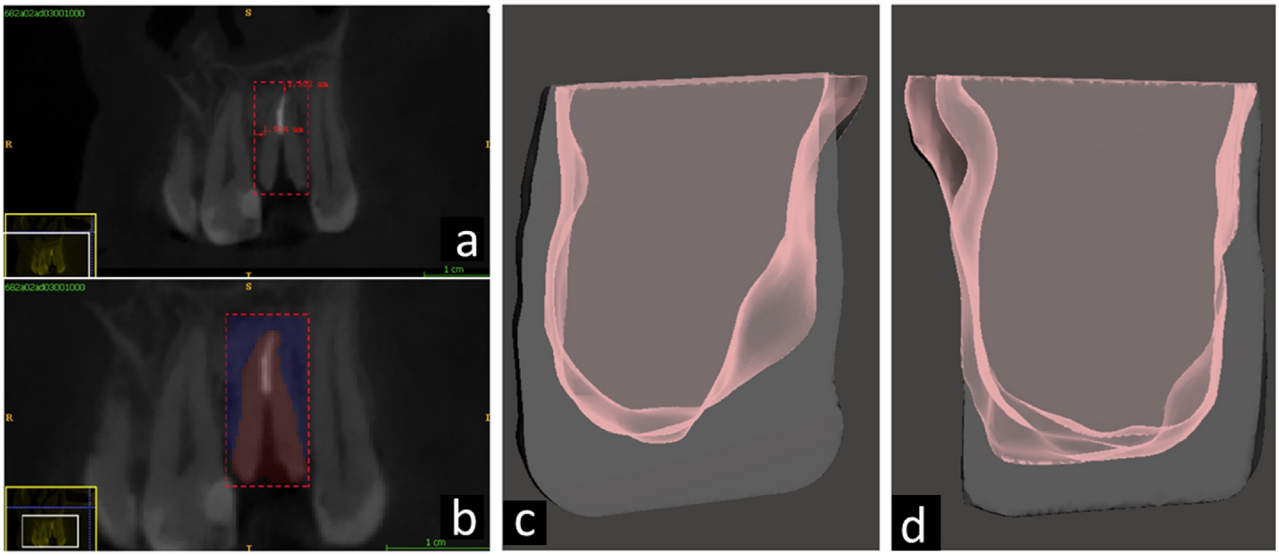

Fig. 4. Three-dimensional analysis of the pre- and post-operative CBCTs: (a) region of interest (ROI) demarcation prior to segmentation, (b) three threshold based semi-automatic contour segmentations: tooth (red), surrounding pre-operative socket bone (blue) and post-operative bone of the ROI. (c) Superimposed volumetric result of the control site (Grey color represents the pre-operative socket while the pale pink presents the post-operative ridge. (d) Superimposed Volumetric result of the test site.

contour segmentation software (ITK-SNAP, U.S. National Institute of Biomedical Imaging and BioEngineering, USA).

The process involves setting a threshold value that separates the desired tissue or structure from the surrounding tissues based on CBCT values or intensity levels. The pixels with values above the threshold are designated as the region of interest, while those below are disregarded. The threshold value can be adjusted to fine-tune the segmentation results.

A standardized region of interest (ROI) was calibrated for all sites, determined by following reference points (Fig. 4a):

- Apico-coronally: Coronally the most crestal bone peak was detected mesially and distally; apically, an artificial line was drawn 1.5 mm below the most apical point of the root tip across the apical base of the socket.
- Mesio-distally: limited by an artificial line at 1.5 mm distance of the most mesial and distal surface of adjacent tooth or implant.
- Bucco-lingually: limited to the mostly detectable bone width extension.

Three threshold based semi-automatic active contour segmentations in the above ROI were performed as follows (Fig. 4b):

1 Tooth root segmentation was realized to be able to differentiate the buccal bone from the root surface in the second segmentation.
2 pre-operative alveolar socket segmentation which included the alveolar bone surrounding the root and the part of first segmentation (root) which was located inside the bone socket (apically to the line connecting the most coronal lingual and buccal bone points at each slice).
3 post-operative alveolar bone segmentation (4 months post-op).

The volume of the pre- and post-operative bone was then measured using the volumes and statistical tool of the software (Fig. 4c, d). In order to calculate the volumetric resorption rate (Percentage), the following mathematical equation was used:

$$\left[\left(V_{Pre-op} - V_{post-op}\right)/V_{Pre-op}\right] \quad X\,100.$$

As for the linear resorption, segmentations were exported as stereolithography files (STL) and then imported to the Autodesk Meshmixer software (Autodesk research, CA, USA) where the outer surface of the pre- and post- models was separated and saved as two distinct STL meshes.

The mean linear distance between the pre-operative and post-operative mesh (mean resorption) was calculated using a specialized comparative software (Cloudcompare, EDF R&D Energy research and development, France.) (Fig. 5).

2.6. Histological assessment

Bone cores were fixed using 4% paraformaldehyde then following a decalcified protocol they were stained using Giemsa-Paragon stain in order to observe residual particles and newly formed bone.

Histological images (Fig. 6a,d) were saved in .JPEG (Joint Photographic Experts Group) format and imported in the ImageJ software (ImageJ NIH Image, WI, USA.), where the total calcified tissues were first isolated from the soft tissues using the gray value segmentation option (Fig. 6b,e). Finally using a more sensitive gray scale filter, newly formed bone was distinguished from the old calcified structures (Fig. 6c,f)

2.7. Clinical outcome assessment technique

Implants were placed in a prosthetically driven position using surgical guides. At implant placement, sites which were in need for additional bone grafting due to thread exposure by fenestration or dehiscence in the buccal bone wall were counted according to the site and implant position.

2.8. Statistical analysis

Descriptive statistics were used to summarize the patients' characteristics. The data were expressed as the mean ± standard deviation. The Wilcoxon signed-rank test was used to determine differences in volumetric and linear resorption between both sites (tests and controls) among the same patient. McNemar test was used to figure out the difference in bone grafting need between control and test sites pairwise. Statistical analysis was conducted using Stata data analysis and statistical software (Stata 15. MP, TX, USA).

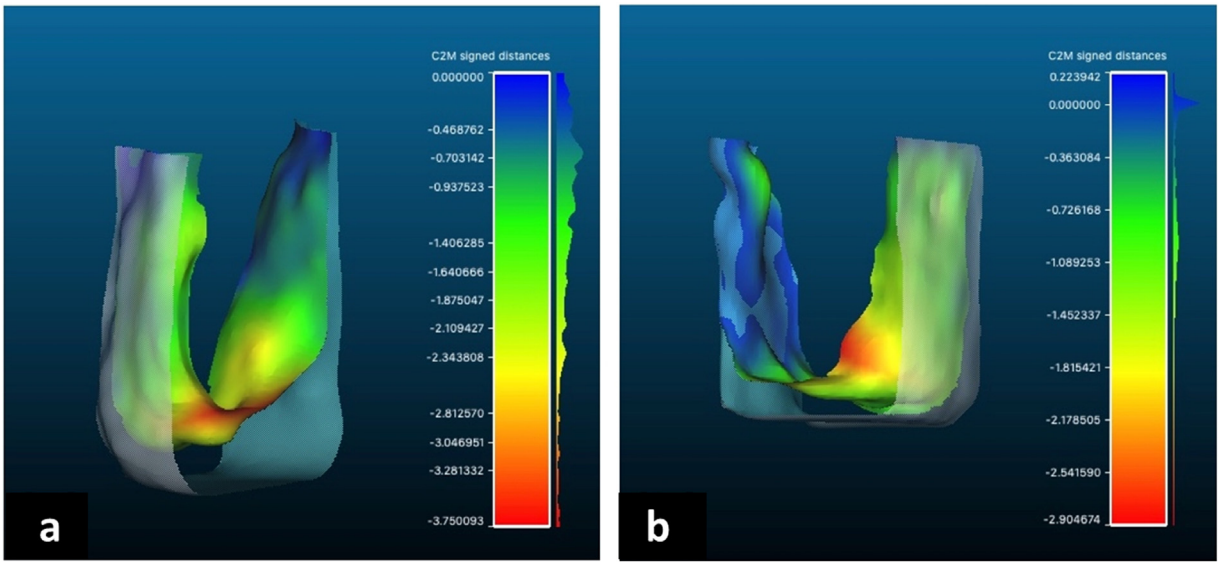

Fig. 5. A software-generated colour map showing the linear resorption based on the distance between the pre- and post-operative meshes extracted from the three-dimensional models: (a) Control site, (b) test site.

3. Results

Seven out of twenty foreseen patients with two contralateral hopeless teeth each, were included and analysed in this randomized pilot study. The demographic data of the participants is featured in Table 1 (Table 1). Values of intraclass correlation coefficient for the volumetric bone resorption ranged from 0.9 to 1 among both controls and tests sites, which demonstrated a perfect intraobserver agreement.

3.1. Radiographic assessments

The superimposed baseline and 4 months post-operative scans revealed for both, the volumetric and the linear resorption a significantly less expressed rate in the test sites which consisted of the DBBM and xHyA combination (P = 0.018, respectively) compared to the control group with DBBM alone. The mean difference in volumetric and linear resorption at each of the controls and tests sites are presented in Table 2. No significant differences were observed between the sites that needed bone grafting and the presence of xHyA in this site (P=0.15).

3.2. Histological observations

The particulate DBBM bone substitute used without additives appeared to be embedded in connective tissue instead of getting part of newly formed bone, especially in the coronal portion of the disclosed specimen (turquoise arrows in Fig. 6a). Furthermore, as previously reported [5], the biopsy presented a high amount of residual DBBM graft material (white area, Fig. 6b) and only a limited area of newly formed bone (white areas, Fig. 6c). On the contrary, the combination of DBBM with xHyA was associated with a greater level of homogenous incorporation of DBBM graft particles into newly formed bone throughout the complete biopsy (Turquoise/red arrows,

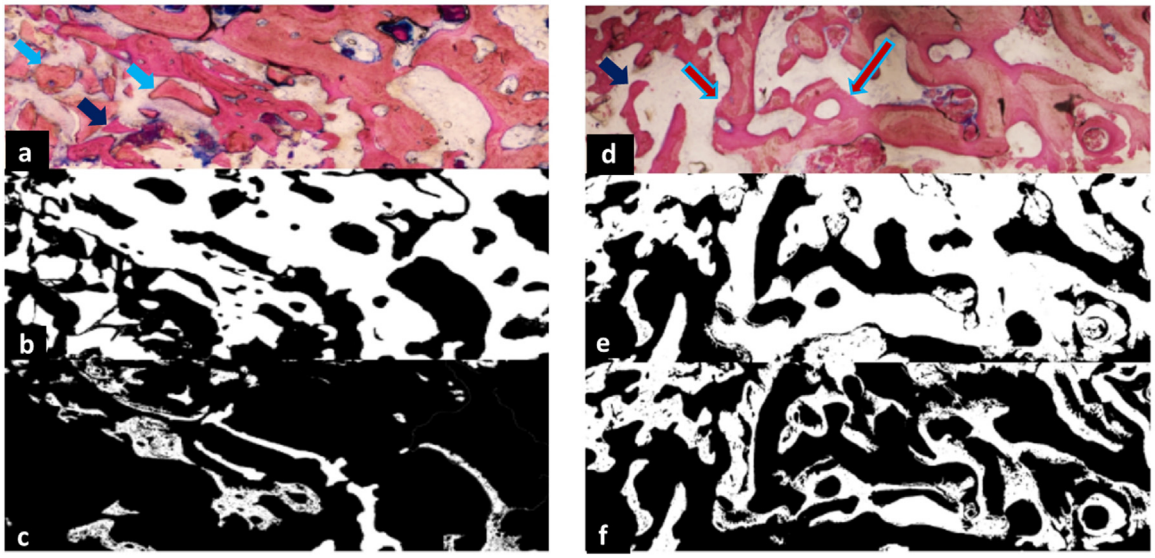

Fig. 6. Histological comparison between core biopsies taken from control site (a) and test site (d). (b) and (e): Threshold based pictures showing the total calcified tissues in white respectively in control and test sites, (c) and (f): Threshold based picture showing the new bone formation in white. The turquoise arrows indicate the particulate graft residues embedded in newly formed soft tissue while turquoise/red arrows indicate those embedded into newly formed bone. Dark blue arrows indicate newly formed bone.

Table 1
Demographic data of the study. GBR: guided bone regeneration, DBBM: demineralized bovine bone material, xHya: Cross linked hyaluronic acid.

Study demographics	
Number of patients	7
Mean age	52.65
Tooth type	
Maxillary mono radiculars/ Maxillary Bicusps/ Maxillary molars	4/4/2
Mandibular Bicusps/ Mandibular molars	2/2
GBR procedure at implant placement	
DBBM	**xHya-DBBM**
2	0

Table 2
Volumetric and linear resorption values (mean ± SD) in control and test sites at 4 months postoperatively.

	4 months	P-value
Volumetric resorption percentage in control sites (%)	36.56 ± 1.69	
Volumetric resorption percentage in test sites (%)	26.96 ± 1.83	
Volumetric resorption rate between both sites (%)	9.59 ± 1.79	0.018*
Linear resorption distance in control sites (Millimetres)	1.42 ± 0.16	
Linear resorption distance in test sites (Millimetres)	0.73 ± 0.052	
Linear resorption differences between both sites (Millimetres)	0.69 ± 0.16	

Fig. 6d). Presence of xHyA resulted in a reduced amount of residual graft particles and a greater amount of newly formed bone in intimate proximity to the residues of particulated graft (Fig. 6e and 6f).

3.3. Post hoc power analysis

The difference in bone grafting need between controls and tests in this pilot small patient cohort was clinically relevant but not statistically significant. To assess statistical significance, the required sample size for future studies should be 20 if the same patient is used for both sites and 40 if both sites are assessed independently; power of study=80%, alpha=0.05.

4. Discussion

DBBM is one of the recommended biomaterials to use when performing an ARP due to its dimensional stability and low resorption rate [10]. However, it is biologically inert which means that it only functions as a scaffold with a low tendency for resorption [11]. De novo bone formation rate and healing time might represent the major vulnerabilities which characterize the DBBM particulate [5]. Henceforth, researchers and practitioners started the bio-activation of inert biomaterials with different biological adjuncts such as xHyA, platelet rich fibrin, enamel matrix derivates or others [12]. The variety of adjuncts and the contradictory results in the studies indicated that further research effort should prove clinically a theoretically proven concept [13]. The aim of this prospective split mouth study was to evaluate clinically and radiographically the impact of xHyA addition to the DBBM in socket preservation.

The approach used to assess the alterations in this study has been successfully implemented as non-invasive evaluation method in humans by the group of Chappuis et al. and Araujo et al. previously [14]

It is known that coverage of the orifice after grafting the socket resulted in a sufficiently better volume preservation by means of less horizontal bone resorption [15]. The rationale of using Socket Seal technique with a free gingival punch instead of an open membrane cover with a collagen membrane was related to previously reported improved volume preservation in the horizontal aspect [15] and to omit any effect which may be associated with the presence of other foreign biomaterial except the bone substitute itself [16].

4.1. Key findings

In this study, the authors tried to minimize biases at different stages that could affect the study's precision and reproducibility. First, patients were carefully enrolled according to a strict selection criterion that homogenized the extraction sockets in terms of morphological shape, second the use of a novel fully computerized radiographic assessment software helped by far to standardize the measured outcomes.

The combination of xHyA mixed with DBBM showed statistically both, a significantly lower volumetric resorption (26.96 ± 1.83%) and a linear resorption rate (0.73 ± 0.052 mm), respectively, compared to outcome achieved by using DBBM alone (36.56 ± 1.69%) (1.42 ± 0.16 mm). Thus, the clinical need in additional bone grafting was dominant in sites treated by DBBM alone.

The reported results are in agreement with the outcomes reported by numerous studies which illustrated the supportive role of HA in soft and hard tissue grafting [7,17–21]. HA is a major component of the extracellular matrix and is composed of a straight chain of glycosaminoglycan carbohydrate polymer [20]. Depending on its molecular weight, HA can stimulate the neovascularization process by increasing Vascular endothelial growth factor availability in-situ and has an important role in promoting bone formation and mineralization by altering the graft/clot morphology in a way to form a rigid 3D scaffold that acts as a reservoir for different attracted bone growth factors [20,22]. Moreover, HA is involved in the mediation of cellular signalling, differentiation and regulation of mesenchymal cell proliferation/adhesion through its direct influence on the CD44 trans-membrane receptors [8]. It is also known for its bacteriostatic, fungistatic, anti-inflammatory and anti-oedematous properties [23]. xHyA, composed of natural and crosslinked high-molecular HA was conceptualized to consolidate all the above-mentioned biological properties. A recent in vitro study confirmed xHyA contribution to the overexpressed rate of bone proteins transcribed by osteoblast-like cells in an air-lift model [24]

4.2. Comparison with other studies

The reported results for socket volume shrinkage after using DBBM alone are in good alignment with several previous studies which evaluated the mean bone loss (MBL) when using xenografts in ARP. Thus, one previous study stated a resorption rate of 1.5 mm ± 0.70 4 months after using DBBM solely [25]. In the systematic review, Majzoub et al. calculated an overall MBL with 1.47 mm in horizontal and 0.68 mm in vertical dimension 6 months postoperatively, when DBBM was used exclusively [26]. Despite the different measurement techniques applied in the different studies, the values presented there appear similar to those obtained in the present study. Furthermore, 11.5% of subjects treated with a DBBM alone for ARP needed a supplementary bone grafting at the implant placement step [27].

To the best of authors knowledge, limited scientific evidence is available concerning the direct effect of HA on human alveolar bone healing, especially with respect to volume shrinkage. The data from human studies is oscillating between different HA formulations, different substitutes other than DBBM and diversely distributed assessment techniques/outcomes. Therefore, heterogenous results were reported. Lorenz et al. [28] and Bladini et al. [29] showed an acceleration in bone formation when HA was applied together with alloplastic [28] material and autogenous bone [29] in extraction sockets. Alcântara et al. [30] found a significantly higher rate of new bone formation at an early timepoint of 30 days after extraction sockets were filled with HA. Nevertheless, the rate of new bone formation was equalized by day 90 in both groups, as the rate of volume shrinkage

did, respectively. Eeckhout et al. [31] investigated the effect of HA on the socket healing and disclosed a non-significant effect of HA. However, in contrary to the abovementioned studies the group used HA only outside the extraction socket applying a layer on top of a collagen matrix which covered the grafted socket. The socket itself was filled just with DBBM without HA addition.

The measured effect on an improved preservation of the grafted volume under HA presence was previously observed by Stiller et al., who used it for sinus augmentation with a synthetic graft material [32]. After 6 months, the test group with HA resulted in a significantly higher rate of new bone formation as well as in significantly less volume shrinkage than the control group with the graft material alone.

Despite the fact that histological evaluation was not between the aims of our study, minimally invasive biopsies were taken to ensure the grafted bone quality. The results favoured the combination of particulated graft with xHyA versus graft material alone. It appears that the presence of xHyA featured increased amount of newly formed bone, less soft tissue protrusion into the former socket and a diminished amount of residual graft particles.

4.3. Study limitations

This paper represents a pilot project for a lager randomized controlled trial with a subject number of at least 20 patients, if a split mouth design should be continued. Histomorphometric analysis and a longer healing period should be included in order to better understand the histological nature of the newly formed bone and the behaviour of the socket area at extended healing stages.

Author Contribution

Dr. Bachar Husseini: Conceptualization, surgical workflow
Dr. Ralph Wak: Data analysis and methodology.
Dr. Georges Khoury: Surgical technique development
Dr. Nabil Ghosn: assessment techniques.
Dr. Tala El; Ghoul: Statistical analysis, writing
Dr. Chloe Karen Abboud: Writing and grammar correction.
Pr.Anton Freidmann: project administration, review and editing.
Pr. Ronald Younes: Supervision

One Sentence summary: The addition of hyaluronic acid to xenograft particles during a ridge preservation procedure might limit the bone resorption.

Conflict of interest

The authors report no conflicts of interest related to this study.

Acknowledgment

The manuscript was not presented as part at a conference/convention/meeting.

References

[1] Chappuis V, Araújo MG, Buser D. Clinical relevance of dimensional bone and soft tissue alterations post-extraction in esthetic sites. Periodontol 2017;73:73–83 2000. doi: 10.1111/prd.12167.
[2] Kalsi AS, Kalsi JS, Bassi S. Alveolar ridge preservation: why, when and how. Br Dent J 2019;227:264–74. doi: 10.1038/S41415-019-0647-2.
[3] Moussa NT, Dym H. Maxillofacial Bone Grafting Materials. Dent Clin N Am 2020;64:473–90. doi: 10.1016/J.CDEN.2019.12.011.
[4] Araújo MG, Silva CO, Misawa M, Sukekava F. Alveolar socket healing: what can we learn? Periodontol 2015;68:122–34 2000. doi: 10.1111/PRD.12082.
[5] de Risi V, Clementini M, Vittorini G, Mannocci A, de Sanctis M. Alveolar ridge preservation techniques: a systematic review and meta-analysis of histological and histomorphometrical data. Clin Oral Implants Res 2015;26:50–68. doi: 10.1111/CLR.12288.
[6] Geurs N, Ntounis A, Vassilopoulos P, van der Velden U, Loos BG, Reddy M. Using growth factors in human extraction sockets: a histologic and histomorphometric evaluation of short-term healing. Int J Oral Maxillofac Implants 2014;29:485–96. doi: 10.11607/JOMI.3408.
[7] Arpağ OF, Damlar İ, Altan A, Tatli U, Günay A. To what extent does hyaluronic acid affect healing of xenografts? A histomorphometric study in a rabbit model. J Appl Oral Sci 2018;26. doi: 10.1590/1678-7757-2017-0004.
[8] Moseley R, Waddington RJ, Embery G. Hyaluronan and its potential role in periodontal healing. Dent Update 2002;29:144–8. doi: 10.12968/DENU.2002.29.3.144.
[9] Bayer IS. Hyaluronic acid and controlled release: a review. Molecules 2020;25. doi: 10.3390/MOLECULES25112649.
[10] Hämmerle CHF, Araújo MG, Simion M. Evidence-based knowledge on the biology and treatment of extraction sockets. Clin Oral Implants Res 2012;23:80–2. doi: 10.1111/J.1600-0501.2011.02370.X.
[11] Valentini P, Bosshardt D. 20-year follow-up in maxillary sinus floor elevation using bovine-derived bone mineral: a case report with histologic and histomorphometric evaluation. Int J Oral Maxillofac Implants 2018;33:1345–50. doi: 10.11607/jomi.6884.
[12] del Amo FS-L, A Monje. Efficacy of biologics for alveolar ridge preservation/reconstruction and implant site development: an American Academy of Periodontology best evidence systematic review. J Periodontol 2022. doi: 10.1002/JPER.22-0069.
[13] Donos N, Dereka X, Calciolari E. The use of bioactive factors to enhance bone regeneration: a narrative review. J Clin Periodontol 2019;46:124–61. doi: 10.1111/jcpe.13048.
[14] Chappuis V, Engel O, Reyes M, Shahim K, Nolte LP, Buser D. Ridge alterations post-extraction in the esthetic zone: a 3D analysis with CBCT. J Dent Res 2013;92. doi: 10.1177/0022034513506713.
[15] del Fabbro M, Tommasato G, Pesce P, Ravidà A, Khijmatgar S, Sculean A, et al. Sealing materials for post-extraction site: a systematic review and network meta-analysis. Clin Oral Investig 2022;26:1137–54. doi: 10.1007/S00784-021-04262-3/FIGURES/5.
[16] Friedmann A, Meskeleviciene V, Yildiz MS, Götz W, Park JC, Fischer KR. Open healing of contained and non-contained extraction sockets covered with a ribose cross-linked collagen membrane: a pilot study. J Periodontal Implant Sci 2020;50:1–12. doi: 10.5051/JPIS.2000400020.
[17] Martínez-Sanz E, Ossipov DA, Hilborn J, Larsson S, Jonsson KB, Varghese OP. Bone reservoir: injectable hyaluronic acid hydrogel for minimal invasive bone augmentation. J Control Release 2011;152:232–40. doi: 10.1016/J.JCONREL.2011.02.003.
[18] Zou L, Zou X, Chen L, Li H, Mygind T, Kassem M, et al. Effect of hyaluronan on osteogenic differentiation of porcine bone marrow stromal cells in vitro. J Orthop Res 2008;26:713–20. doi: 10.1002/JOR.20539.
[19] Raines AL, Sunwoo M, Gertzman AA, Thacker K, Guldberg RE, Schwartz Z, et al. Hyaluronic acid stimulates neovascularization during the regeneration of bone marrow after ablation. J Biomed Mater Res A 2011;96:575–83. doi: 10.1002/JBM.A.33012.
[20] Zhao N, Wang X, Qin L, Zhai M, Yuan J, Chen J, et al. Effect of hyaluronic acid in bone formation and its applications in dentistry. J Biomed Mater Res A 2016;104:1560–9. doi: 10.1002/JBM.A.35681.
[21] Dogan E, Dursun E, Tosun E, Bilgic E, Akman AC, Orhan K, et al. Evaluation of hyaluronic matrix efficacy in sinus augmentation: a randomized-controlled histomorphometric and micro-computed tomography analysis. Int J Oral Maxillofac Surg 2017;46:931–7. doi: 10.1016/J.IJOM.2017.03.003.
[22] Al-Khateeb R, Olszewska-Czyz I. Biological molecules in dental applications: hyaluronic acid as a companion biomaterial for diverse dental applications. Heliyon 2020;6. doi: 10.1016/j.heliyon.2020.e03722.
[23] Aya KL, Stern R. Hyaluronan in wound healing: rediscovering a major player. Wound Repair Regen 2014;22:579–93. doi: 10.1111/WRR.12214.
[24] Nobis B, Ostermann T, Weiler J, Dittmar T, Friedmann A. Impact of cross-linked hyaluronic acid on osteogenic differentiation of SAOS-2 cells in an air-lift model. Materials 2022:15. doi: 10.3390/ma15196528.
[25] Llanos AH, Sapata VM, Jung RE, Hämmerle CH, Thoma DS, César Neto JB, et al. Comparison between two bone substitutes for alveolar ridge preservation after tooth extraction: cone-beam computed tomography results of a non-inferiority randomized controlled trial. J Clin Periodontol 2019;46:373–81. doi: 10.1111/JCPE.13079.
[26] Majzoub J, Ravida A, Starch-Jensen T, Tattan M. The influence of different grafting materials on alveolar ridge preservation: a systematic review. J Oral Maxillofac Res 2019;10. doi: 10.5037/JOMR.2019.10306.
[27] Avila-Ortiz G, Gubler M, Romero-Bustillos M, Nicholas CL, Zimmerman MB, Barwacz CA. Efficacy of alveolar ridge preservation: a randomized controlled trial. J Dent Res 2020;99:402–9. doi: 10.1177/0022034520905660.
[28] Lorenz J, Barbeck M, Kirkpatrick C, Sader R, Lerner H, Ghanaati S. Injectable bone substitute material on the basis of β-TCP and hyaluronan achieves complete bone regeneration while undergoing nearly complete degradation. Int J Oral Maxillofac Implants 2018. doi: 10.11607/jomi.6026.
[29] Baldini A, Zaffe D, Nicolini G, Baldoni M, Baldini DA. Bone-defects healing by high-molecular hyaluronic acid: preliminary results. Ann Stomatol (Roma) 2010;1:2.
[30] Alcântara CEP, Castro MAA, de Noronha MS, Martins-Junior PA, de Melo Mendes R, Caliari MV, et al. Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial. Braz Oral Res 2018;32. doi: 10.1590/1807-3107BOR-2018.VOL32.0084.
[31] Eeckhout C, Ackerman J, Glibert M, Cosyn J. A randomized controlled trial evaluating hyaluronic acid gel as wound healing agent in alveolar ridge preservation. J Clin Periodontol 2022;49:280–91. doi: 10.1111/JCPE.13589.
[32] Stiller M, Kluk E, Bohner M, Lopez-Heredia MA, Müller-Mai C, Knabe C. Performance of β-tricalcium phosphate granules and putty, bone grafting materials after bilateral sinus floor augmentation in humans. Biomaterials 2014 Mar;35 (10):3154–63. doi: 10.1016/j.biomaterials.2013.12.068.