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Autogenous Mineralized Dentin versus Xenograft granules in Ridge Preservation for Delayed Implantation in Post-extraction Sites: A Randomized controlled clinical trial with an 18 months follow-up

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Abstract

Objectives: To test primary stability of delayed implants placed in post-extraction ridges preserved with autogenous mineralized dentin matrix (MDM) versus xenograft granules. Clinical, histological and pain experience outcomes were further assessed.

Material and Methods: From March 2018 to July 2020, patients requiring ridge preservation in preparation for delayed implant placement in post-extraction sites were included. Participants were randomly allocated to either the test (MDM) or control group (xenograft granules) prior to ridge preservation. Visual analogue scale and analgesic consumption were measured every day for a week. Six months after preservation, trephine cores were harvested for histomorphometry prior to implant placement. Implants were then placed, and implant stability was measured immediately as well as two months after placement. Marginal bone loss and presence of mucositis/peri-implantitis were registered up to 18 months after prosthetic loading.

Results: Fifty-two patients (66 implants) completed the study. MDM and xenograft groups presented similar primary (77.1 ± 6.9 versus. 77.0 versus. 5.9) and secondary (81.8 ± 5.1 versus. 80.1 ± 3.8) implant stabilities. The percentage of newly formed bone in MDM (47.3%) was significantly higher than xenograft (34.9%) ($p < .001$), and the proportion of residual graft was significantly lower (12.2% in MDM and 22.1% in xenograft) ($p < .001$). No significant differences were found as far as clinical, radiographic and patient-related outcomes.

Conclusions: Implants placed in sites preserved with MDM had similar primary stability in comparison to xenograft granules. MDM showed a significantly higher quantity of newly formed bone and lower amount of residual graft in histomorphometry results and equal clinical and patient-related outcomes.

KEYWORDS

bone regeneration, bone substitutes, clinical research, clinical trials, dental implants, guided tissue regeneration, histo-pathology, host mechanisms

Trial registration: ISRCTN11458658 (https://doi.org/10.1186/ISRCTN11458658).

1 | INTRODUCTION

After tooth extraction, the alveolar bone undergoes dimensional changes with a reduction in its buccal-lingual width, which may reach 50% (Atieh et al. 2015). This bone loss occurs mainly in the first 3 months post-extraction, after which there is a continuous process of resorption with an average of 0.5% to 1.0% per year (Araújo & Lindhe, 2005; Araújo et al. 2015; Cardaropoli et al. 2003; Couso-Queiruga et al. 2020; Vignoletti et al. 2012). However, an adequate bone width is a key prerequisite for placing dental implants, and, therefore, alveolar preservation is highly recommended (Hämmerle et al. 2012).

To minimize post-extraction ridge dimensional reduction, several approaches have been proposed under the concept of "alveolar ridge preservation" (Barootchi et al., 2019). A broadly recognized approach is the maintenance of bone walls through bone substitute (graft) delivery into the socket, where guided bone regeneration may be a requisite (Vignoletti et al., 2012; Vittorini Orgeas et al., 2013). Different types of bone substitutes may be used in, such as autogenous bone graft, demineralized freeze-dried bone allograft, calcium sulphate and synthetic hydroxyapatite bioglass, among others may be used. However, donor site morbidity, limited availability and associated costs may be relevant shortcomings of the latter bone substitute (Carlsen et al. 2013). Another autogenous matrix that is becoming popular is the patient's own extracted tooth. The extracted tooth can provide autogenous graft while eliminating the need for a secondary bone harvest site. Tooth-derived dentin grafts have been studied to learn whether teeth represent a viable alternative. Tooth-derived mineralized dentin matrix (DDM) showed similar composition to bone (Hee-Yung et al. 2014; Jeong et al. 2011; Joshi et al. 2016; Kim et al., 2014; Lee et al. 2011) and a viable option for alveolar bone augmentation following dental extraction (Gual-Vaqués et al. 2018; Kim et al. 2013; Li et al. 2017; Pang et al. 2017).

Recently, autogenous MDM graft was presented for bone regeneration procedures. Autogenous MDM differs from DDM by the absence of a demineralization process, that is time-consuming and expensive. The MDM processing devices transform about 95% of the patients' extracted tooth into a granulated mineralized dentin (particles of 250 μm to 1,200 μm in size) which represent a potential bone substitute in guided bone regeneration (GBR) procedures. Preclinical studies have provided information regarding the characteristics of MDM on bone regeneration compared to DDM (Koga et al., 2016; Moon et al., 2019). Nevertheless, clinical studies comparing MDM grafts with standard bone substitutes are scarce and, for that reason, a clinical trial would be of great interest.

In this single-blinded randomized clinical trial, implant stability of delayed implants placed in post-extraction ridges preserved with autogenous MDM versus xenograft granules was defined as the primary outcome. Also, clinical measurement, bone morphology and pain experience outcomes were assessed as secondary outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a single-centre, single-blinded, parallel-group, randomized clinical trial with balanced randomization (1:1) conducted in a private practice in Lisbon (Portugal), specialized in advanced oral surgery and implant rehabilitation, between March 2018 and June 2020. Ethical approval was provided by the Faculty of Dentistry of the University of Lisbon Ethical Committee (CES-FMDUL-9/3/2018) and followed the Helsinki declaration as revised in 2013. Each participant provided written informed consent following an adequate explanation prior to inclusion in the study. This trial was written, prepared and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guideline (Appendix S1) (Schulz et al. 2010).

Our null hypothesis was that ridges preserved with 100% MDM grafts present no significant different primary stability than ridge preservation with 100% xenograft granules for delayed implants placed in post-extraction sites.

2.2 | Participants

The inclusion criteria were as follows:

1. 18 years old or older,
2. Requiring alveolar preservation through GBR after tooth extraction prior to placement of dental implant,
3. Presenting with type 2 extraction sockets, and
4. With midfacial osseous dehiscence defect (Elian et al. 2007) classification and subclassification Type 2B with a dehiscence defect involving the middle one-third of the labial plate, approximately 7 to 9 mm from the free gingival margin (FGM) (Chu et al., 2015).

The exclusion criteria were as follows:

1. Heavy smokers (more than 10 cigarettes per day or an electronic cigarette dose of >6 mg/ml of nicotine),
2. Presence of active infection or severe inflammation in the intervention zone,
3. Relevant medical history that contraindicates implant surgery,
4. Immunosuppression (eg. HIV, solid-organ transplants),
5. Head and neck-irradiated patients in the past 5 years,
6. Regular intake of bisphosphonates, anticoagulants, or anti-inflammatories,
7. Chronic drug abuse or alcoholic habits,
8. Patients with poor oral hygiene (full-mouth plaque score and full-mouth bleeding score >15%) and lack of motivation,
9. Uncontrolled diabetes (reported levels of glycated haemoglobin exceeding 7%),
10. Uncontrolled and /or untreated periodontal disease,
11. Previous history of bone graft in the intervention zone,
12. Presence of acute endodontic lesion in the tooth to be extracted or in adjacent teeth.

Sociodemographic information included age, gender, education, smoking habits and medical and dental history.

Patients with recent history of periodontal treatment have been treated for their periodontal condition previously. These patients had been inserted in a supportive periodontal treatment (SPT), with regular intervals between appointments, adapted to each patient (between 3 and 6 months). Then, surgery in these patients was only performed when good control of bacterial plaque (<15%) was achieved, with an adequate attendance to SPT, absence of periodontal pockets depths (PPD) (PPD <4 mm) and without bleeding on probing (BOP).

2.3 | Randomization

Each participant was assigned in ascending order at the enrolment visit. Patients were randomly assigned in a 1:1 ratio to either the test group (MDM +delayed implant) or the control group (xenograft +delayed implant) using an online randomization tool (https://www.randomizer.org/). Allocation concealment was done with opaque envelopes, which were opened by the surgeon immediately after tooth extraction and before the graft delivery procedure. The sequence of envelopes was done, a priori, by a non-involved researcher.

2.4 | Blinding

Participants were blinded to the allocated arm as well as the statistician (L.P.) and the pathological anatomy technician (G.B.). The clinical surgeon (A.S.) examined and registered post-surgical complications and clinical outcomes of interest.

2.5 | Interventions

In both groups, minimally invasive atraumatic tooth extraction was performed (Saund & Dietrich, 2013). Surgery was performed under local anaesthesia using 4% articaine HCl with epinephrine (1:100,000). Both sites from mono- and multiradicular teeth were considered. In both procedures, a full thickness flap was performed with a 15C blade, after intrasulcular incision, to access the vestibular bone dehiscence. Atraumatic extraction was achieved using periotomes (PT1 and PT5, Hu-Friedy, Chicago, Illinois, USA) and avoiding forceps use. When forceps were necessary, precautions were taken to avoid damaging marginal bone. In multiradicular teeth, roots were separated by high-speed drills. After extraction, the alveolus was meticulous handled with a Lucas mini cutter (#611748, Hu-Friedy, Chicago, Illinois, USA). Then, the assigned graft material was placed inside the alveolus according to its manufacture protocol (Figure 1). Both materials (MDM; or xenograft) were prepared in a separate room. The administration of the allocated material was done 15 min after tooth extraction to maintain patients blinded. In the control group, xenograft (Bio-Oss®, Geistlich, Switzerland) was placed in the alveolus (Figure 2).

For the test group, we followed the manufacturer protocol for MDM (Smart Dentin Grinder®, KometaBio Inc., USA) (Appendix S2). Remaining soft tissues were carefully removed from the tooth and adequately dried. Each tooth was placed inside the milling chamber where it was pulverized and sorted into two compartments: 1) particles of diameter between 250 and 1,200 μm; and 2) particles of diameter below 250 μm, which were discarded. Then, the particulate was immersed in a cleanser solution (0.5 M NaOH and 30% (v/v) alcohol) for 5 min, replaced by a saline solution of phosphate-buffered saline (PBS) for two quick rinses. Finally, the saline solution was carefully removed with sterile gauze, and the final graft material was kept in temperature room for clinical use (Binderman et al. 2012).

In both groups, the allocated material was covered with a resorbable barrier membrane (Bio-Gide, Geistlich, Switzerland). Primary closure of the surgical site was done with a free gingival graft harvested from the palate and sutured with non-resorbable synthetic monofilament suture made of polyamide polymers (Dafilon® 5/0m B/Braun Surgical, Spain).

At post-operative care, both groups of patients were instructed to rinse twice a day with 0.10% chlorhexidine gluconate solution (Eludril

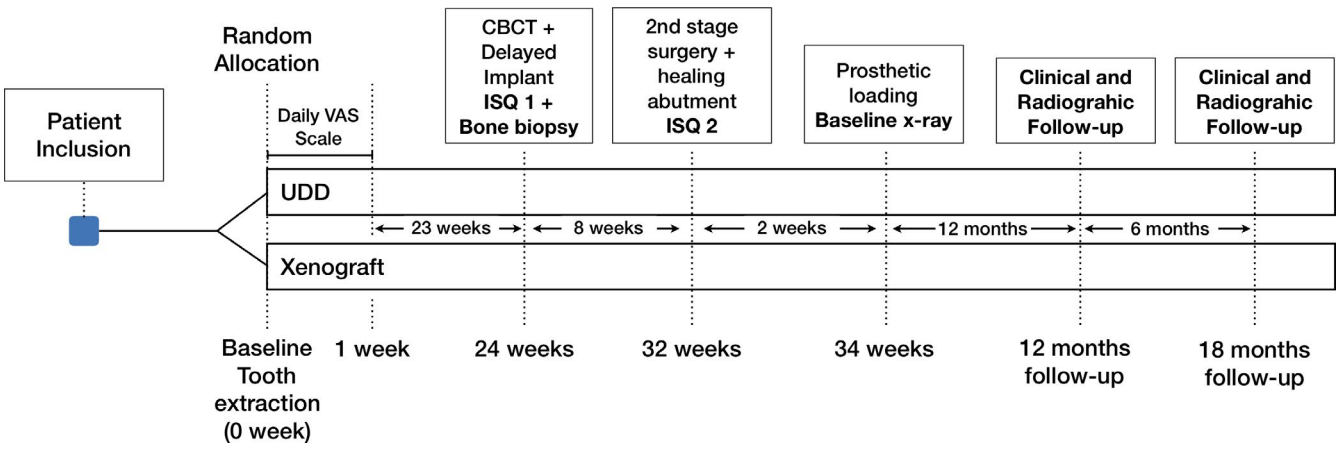

FIGURE 1 Study timeline

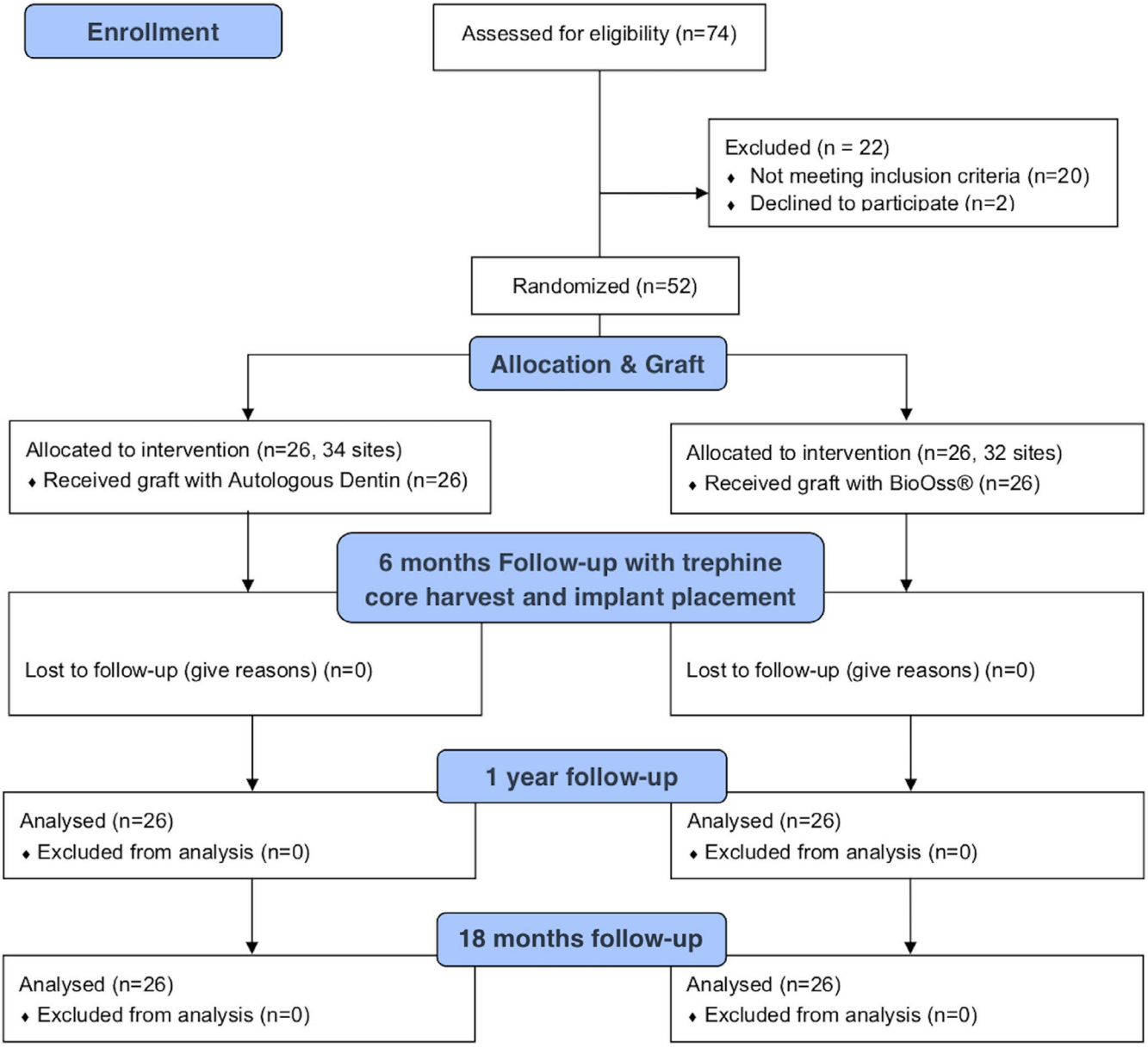

FIGURE 2 Flow diagram according to the CONSORT

Classic, Pierre Fabre Oral Care) and to take oral antibiotics, amoxicillin plus clavulanate potassium (875mg/125mg) every 12 hr for 8 days, or 500 mg of azithromycin in cases of allergy to penicillin, once a day for 3 days, non-steroidal anti-inflammatory drug (ibuprofen 600mg) every 12 hr for 4 days. An analgesic was prescribed to be taken immediately after surgery (300 mg clonixin, 1 pill), or when necessary, during follow-up. All post-operative care was registered in a diary for further analysis.

After a healing period of six months, a cone beam computed tomography (CBCT) scan was carried out to plan implant placement (CRANEX™ 3Dx from SOREDEX™). Radiodensity was registered (measured as Hounsfield Units). For both groups (test and control), the grafted site was exposed and a trephine core was taken using a trephine bur (outer diameter 2.35 mm, inner diameter 2.30 mm, length). Biopsies from all 66 sites were processed and analysed. The harvested core was immediately preserved in a 10% formalin solution and sent for histologic analysis. During implant insertion, no addition of graft material was necessary (Figure 1).

2.6 | Outcomes

2.6.1 | Implant stability and clinical outcomes

Primary implant stability was defined as the primary outcome of this study. A resonance frequency analyser (Osstell IDx Mentor, Osstell AB, Goteborg, Sweden) was used to record implant stability, as the average between buccolingual and mesiodistal measures (ISQ). We collected primary stability (baseline) and secondary stability (2-month after placement) ISQ values.

The diagnosis of peri-implant mucositis and peri-implantitis was made following the 2017 world workshop case definitions and diagnostic consideration (Berglundh et al., 2018; Renvert et al., 2018).

Keratinized tissue width (KTW) was measured using a UNC-15 periodontal probe (Hu-Friedy, Chicago, Illinois, USA), mid-facially from the gingival margin to the mucogingival junction of the extracted tooth at baseline. The measurement of KTW during follow-ups was made from the top of the gingival margin to the mucogingival junction of the implant crown (follow-up measurements).

2.6.2 | Radiographic analysis

Digital periapical radiographs were made via VistaScan image plate scanner (Durr Dental AG, Bietigheim-Bissingen, Germany) using the DBS-Win software (Dürr Dental AG, Bietigheim-Bissingen, Germany). Radiographs were carried out before tooth extraction, immediately after GBR, 6 months after GBR, during implant placement, at baseline (prosthetic loading), and after prosthesis loading (at 12 and 18 months of follow-up).

Radiographs were taken using parallelometry technique through Rinn XCP positioners (Dentsply, Constanz, Germany), in which the central radius of the X-ray beam is perpendicular to the implant in order to have the least possible distortion. Radiographic distortion calibration value was calculated by measuring the apical-coronal length of the implant to the nearest 0.01 mm. Regarding the periapical radiographic distortion calibration after implant placement, 12 and 18 months after functional loading, the distortion was evaluated based on the implant placed size and its measurement on digital radiography.

2.6.3 | Histomorphometric analysis

Bone tissues harvested from the trephine cores were processed for histological assessment. Samples were fixed in formaldehyde and decalcified overnight in a tissue floatation bath (TBD). Then, specimens were dehydrated by crescent alcohols concentrations, cleared in xylene and infiltrated in paraffin. The samples were embedded and cut on the median longitudinal axis at 3 μm paraffin sections for haematoxylin and eosin staining with a Microm HM 355S microtome (Thermo Scientific, USA). Digital images from a light microscope (Leica DMLB) connected to a computer and camera device (camera DFC290 HD and Leica Application Suite Software, Leica, Wetzlar, Germany). Quantitative evaluations were made using ImageJ (Image Tool 3.0 software, Department of Dental Diagnostics Science, University of Texas Health Science Center, USA). The assessment included (1) percentage of newly formed bone area compared to total area, (2) percentage of residual bone substitute material area compared to total area and (3) percentage of soft tissue component compared to total area (as the subtraction of the percentage of newly formed bone and residual bone from the total area). This set of analyses was carried out by one examiner (G.B.) blinded to the type of graft material delivered.

2.6.4 | Patient-related outcomes

Patient's pain and discomfort perceptions were rated, during a 7-day consecutive period after the allocated intervention (Figure 1). For this purpose, we used the visual analogue scale (VAS) score (0–10), using “No Discomfort” and “Worst Discomfort” as anchors. Further, the frequency of analgesic consumption was registered by the patient during the same follow-up period.

2.7 | Sample size

Sample size calculation was performed based on previous data by (Li et al. 2018), indicating that a minimum number of 24 individuals was needed to determine a 0.7 difference in stability value (ISQ) with a standard deviation (*SD*) of 0.85, the primary outcome of this study, between groups immediately after surgery (85% power, with a 5%, two-sided, significance level). Considering a 10% dropout rate, a final number of 26 participants per group was set as the minimum required sample.

2.8 | Statistical analysis

The statistical analysis approach was based on patient as a unit. Data analysis was performed using SPSS Statistics version 26.0 for Windows (Armonk, NY: IBM Corp.). Explicit comparison of mean values was not performed by Student's *t* test, since data assumptions for the test applicability were not met (normality and homoscedasticity). Group data comparison was alternatively performed by the Mann–Whitney test. Chi-square test was used for comparisons of categorical variables between the groups. A mixed linear model was applied for the clinical outcomes that were measured at more than one time point during follow-up (Bleeding on Probing and Marginal Bone Loss), taking into account the existence of more than one site per patient. The level of statistical significance was set at 5% in all inferential analyses.

3 | RESULTS

3.1 | Participants and baseline data

From a total of 74 patients who attended the clinic, 52 patients (and 66 sites) met the inclusion criteria and were enrolled in the study (Figure 3). The sociodemographic information of the included patients is depicted in Table 1. Overall, age, gender distribution and smoking habits were similar between the groups ($p > .05$). All

participants completed the study timeframe and were included in the analyses.

All patients presented no need for additional GBR at time of implant placement. Post-operative infection or wound dehiscence was not observed in both groups, and all dental implants were placed as planned (Table 1). All grafted sites healed uneventfully.

3.2 | Implant stability and clinical outcomes

Primary stability ($p = .807$), secondary stability ($p = .054$) and change in stability (T1-T0) ($p = .108$) between both groups showed no significant differences (Table 2). There were statistically significant differences between both groups regarding implant length ($p = .040$). Furthermore, radiodensity was significantly higher in the control group ($p < .001$). Implant location, average tooth extraction time and presence of thin phenotype were not significantly different between groups ($p > .05$) (Table 3). In both groups, keratinized gingival width was reduced, and no differences were found between the test and control groups.

3.3 | Histomorphometry

All the 66 harvested trephine cores were analysed for the quantity of newly formed bone and for residual bone graft material (Table 3). The percentage of grafted material presented in the harvested cores was significantly lower in MDM when comparing to control ($p = .001$) (and graphically presented n Figure 4). The percentages of newly formed bone were 47.3% (±14.8%) for MDM and 34.9% (±13.2%) for xenograft granules, exhibiting a significant difference ($p < .001$). The percentage of soft tissue present showed no significant differences between the groups ($p = .346$).

3.4 | Peri-implant and patient-reported outcomes

No significant differences were found between the groups in regard to bleeding on probing and marginal bone loss; we found no significant differences were found between the groups at baseline and at each follow-up timeframe (6, 12 and 18 months) (Table 4). No significant results were found regarding keratinized gingival width and occurrence of peri-implant mucositis.

Pain experience through the VAS scale was found to be significantly higher one day after surgery in the control group ($p = .014$), though this difference vanished over the course of seven days follow-up (Appendix S3).

4 | DISCUSSION

The main purpose of this randomized clinical trial was to compare the primary implant stability of implants placed in post-extraction sites filled with MDM versus xenograft granules. Our results showed that MDM presented similar primary and secondary implant stability

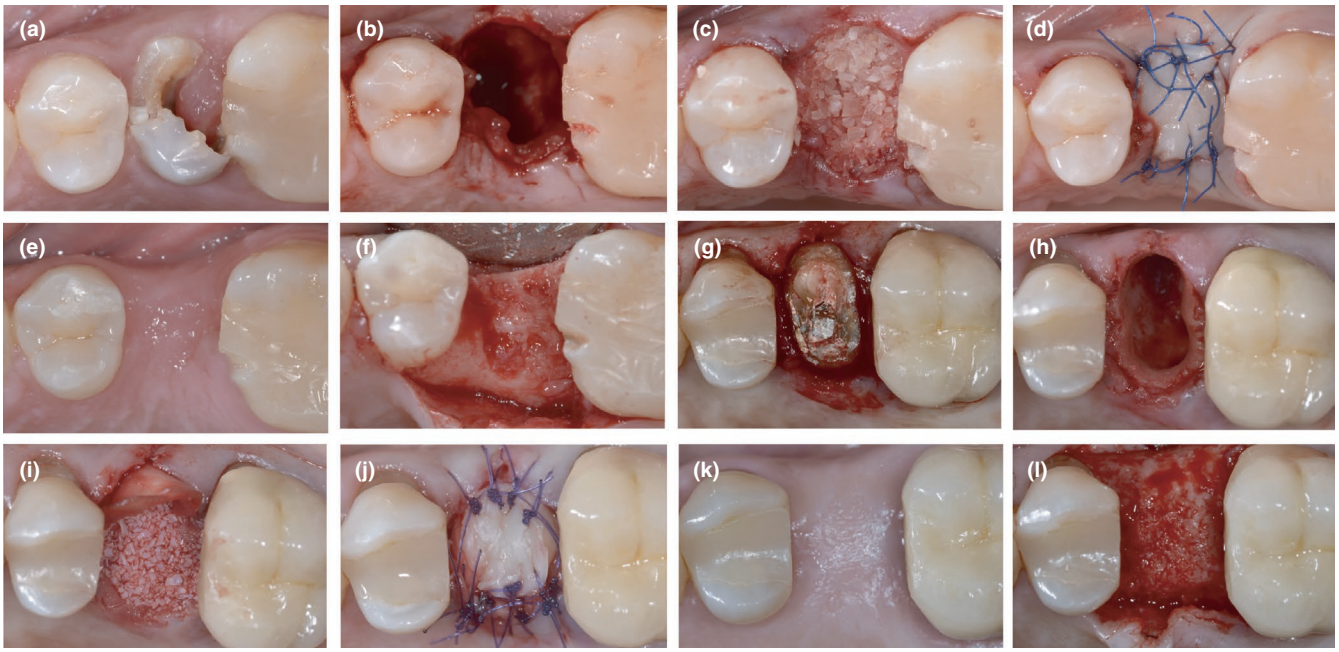

FIGURE 3 Schematic representation of the surgical procedures in the test (MDM) and control group (Bio-Oss®). In the test group, initial presentation (a), followed by minimally invasive surgery (b), wound healing filled with MDM (c), suture with graft (d), six months of follow-up after surgery (e) and bone presentation after opening for implant placement (f). In the control group, initial presentation (g), followed by minimally invasive surgery (h), wound healing filled with Bio-Oss® (i), suture with graft (j), six months of follow-up after surgery (k) and bone presentation after opening for implant placement (l)

TABLE 1 Participants characteristics for test (MDM) ($n = 26$) and control (Xenograft) ($n = 26$) groups

Variable	MDM	Xenograft	*p*-value*
Age (years), mean (*SD*) [Min-Max]	56.8 (12.3) [28–75]	61.5 (13.1) [38–88]	.211
Sex, *n* (%)			
Female	15 (57.7)	16 (61.5)	.988
Male	11 (42.3)	10 (38.5)	
No. of extracted teeth, mean (*SD*)	1.2 (0.4)	1.3 (0.5)	.638
Smoking habits, *n* (%)			
Non-smokers	23 (88.5)	25 (96.2)	.614
Light smokers	3 (11.5)	1 (3.8)	

*Chi-square test for categorical variables and Mann–Whitney test for continuous variables.

TABLE 3 Implant and histomorphometry characteristics for test (MDM) ($n = 26$) and control (Xenograft) ($n = 26$) groups

Variables	MDM	Xenograft	*p*-value*
Implant location, *n* (%)			
Anterior	12 (35.3)	19 (59.4)	.083
Posterior	22 (64.7)	13 (30.6)	
Site Radiodensity (UI), mean (*SD*)	848.5 (205.0)	1,080.9 (154.3)	<.001
Phenotype thin, *n* (%)	7 (20.6)	5 (15.6)	.752
Length of placed implant (mm), mean (*SD*)	11.1 (0.8)	11.6 (0.8)	.004
Diameter of the placed implant (mm), mean (*SD*)	3.8 (0.4)	3.6 (0.3)	.040
Tooth extraction time (minutes), mean (*SD*)	23.2 (5.0)	21.5 (4.4)	.176
Reported pain, *n* (%)	10 (29.4)	10 (31.3)	.904
Hematoma, *n* (%)	9 (26.5)	6 (18.8)	.596
Dehiscence, *n* (%)	13 (38.2)	15 (46.9)	.549
Membrane exposure, *n* (%)	4 (11.8)	4 (12.5)	.968
Graft exposure, *n* (%)	0 (0.0)	0 (0.0)	-
Free gingival graft mortality, *n* (%)	0 (0.0)	0 (0.0)	-
Peri-implant Mucositis, *n* (%)	2 (5.9)	3 (9.4)	.668
Peri-implantitis, *n* (%)	0 (0.0)	0 (0.0)	-
Grafted bone (%), mean (*SD*)	12.2 (7.7)	22.1 (10.9)	.001
New bone (%), mean (*SD*)	47.3 (14.8)	34.9 (13.2)	<.001
Soft tissue (%), mean (*SD*)	40.5 (17.6)	42.9 (9.6)	.346

*Chi-square test for categorical variables and Mann–Whitney test for continuous variables.

to sites preserved with xenograft granules, both in combination with FGG and porcine collagen membrane. Also, there were no differences in clinical and patient-related outcomes. However, higher percentage of newly formed bone and lower percentage of grafted material were found in the MDM group.

To the best of our knowledge, this randomized trial may be the first to compare implant stability of implants placed in sockets preserved with MDM versus a xenograft. Concerning the histomorphometry characteristics, the lower proportion of graft material and higher percentage of newly formed bone found in MDM is not in agreement with previous studies (Pang et al. 2017; Um et al. 2018). A possible reason is that previous studies only performed histomorphometry in subset of the sample of demineralized dentin grafts. These results in the MDM sample may be due to the similarity of dentin composition with human bone, and its bone induction potential demonstrated after grafting with decalcified dentin (Kim et al. 2015; Moharamzadeh et al. 2008; Murata et al. 2011; Yeomans & Urist, 1967). However, other studies also reported similar histomorphometry results (Andrade et al., 2020; Del Canto-Díaz et al., 2019; Pohl et al., 2020). A potential advantage of MDM grafts is the harvesting process that may prevent the exposure to viruses and bacteria, which may occur in grafts of animal origin even with its sterilization protocol (Bhattacharjya et al. 2016; Kim et al. 2016; Pang et al. 2017; Valdec et al. 2017).

Regarding the available data on MDM, a number of preclinical (Calvo-Guirado et al., 2018; Kadkhodazadeh et al., 2015) and clinical studies (Andrade et al., 2020; I. Binderman et al., 2014; Del Canto-Díaz et al., 2019; Dwivedi & Kour, 2020; Nadershah & Zahid, 2019; Pohl et al., 2020) have evaluated its efficacy. In some studies, MDM was combined either with platelet-rich fibrin (Pohl et al., 2020) or with leukocyte-platelet-rich fibrin and fibrinogen (Andrade et al., 2020), which hampers comparability with the present results. Radiologically, the socket seemed to be positively preserved and our results are in line with previous studies (Andrade et al., 2020; Dwivedi & Kour, 2020; Pohl et al., 2020).

TABLE 2 Follow-up implant stability for test (MDM) ($n = 26$) and control (Xenograft) ($n = 26$) groups

Variable	Group	T0 (Primary stability)	*p*-value*	T1 (Secondary stability) (2 months)	*p*-value*	Δ (T1-T0)	*p*-value*
ISQ, mean (*SD*)	MDM	77.1 (6.9)	.807	81.8 (5.1)	.054	4.7 (5.4)	.108
	Xenograft	77.0 (5.9)		80.1 (3.8)		3.1 (4.7)	

*Mann–Whitney test

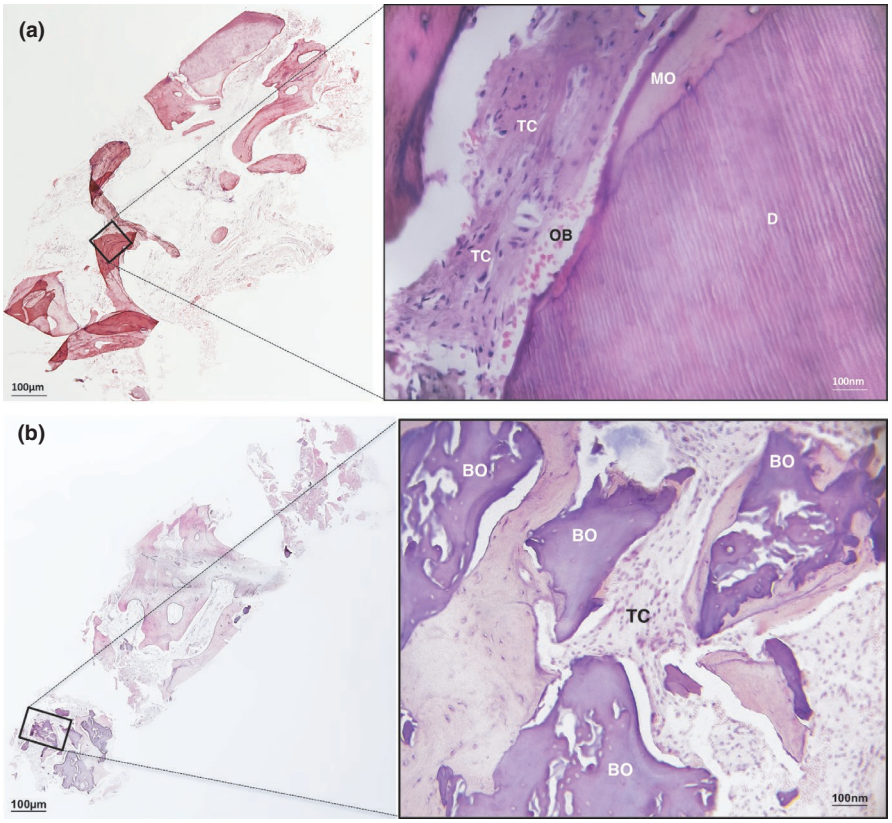

FIGURE 4 Histological specimens of test (MDM and control group (Bio-Oss®) with haematoxylin and eosin staining. (a), histological presentation of a trephine core of a MDM sample, with the presence of connective tissue (TC), dentin (D), odontoblasts (OD) and bone matrix (MO). (b), histological presentation of a trephine core of a control sample, with the presence of bone (BO) and connective tissue (TC)

TABLE 4 Follow-up clinical outcomes for test (MDM) ($n = 26$) and control (Xenograft) ($n = 26$) groups

Variable	Group	T0 (Baseline)	T1 (6 months)	T2 (12 months)	T3 (18 months)	Δ (T3-T0)	*p*-value
Bleeding on Probing (%), mean (*SD*)	MDM	0.0 (0.0)	0.0 (0.0)	2.9 (9.6)	2.9 (8.7)	-	.706 (a)
	Xenograft	0.0 (0.0)	0.0 (0.0)	3.1 (13.0)	3.7 (12.5)	-	
Marginal Bone Loss (mm), mean (*SD*)	MDM	0.0 (0.0)	0.10 (0.21)	0.23 (0.35)	0.35 (0.89)	-	.546 (a)
	Xenograft	0.0 (0.0)	0.13 (0.20)	0.42 (0.75)	0.42 (0.75)	-	
Keratinized Gingival Width (mm), mean (*SD*)	MDM	4.3 (1.0)	-	-	3.1 (1.0)	−1.2 (0.8)	.078 (b)
	Xenograft	4.7 (0.9)	-	-	3.5 (1.0)	−1.2 (0.9)	

Note: (a) referred to the interaction time*group, obtained within a mixed linear model analysis (b) Mann–Whitney test.

Regarding the clinical efficacy for alveolar preservation, our results show that MDM presented similar clinical performance, radiographic measurements and patient-related outcomes as the control group. Conclusively, these outcomes point to a comparable efficacy to that of inorganic bovine bone material and a viable option for socket preservation after tooth extraction for implant placement. Investigations using demineralized dentin matrix also reported similar conclusions (Kim, 2015; Kim et al., 2014; Kim et al. 2015; Pang et al. 2017), though we believe that more clinical trials are warranted to render robust and consistent conclusion on the potential of MDM for these surgical procedures.

This clinical trial has numerous strengths, including the novelty of such comparison and the strict methodology employed throughout the trial. Furthermore, histomorphometry was successfully performed on all samples and not just on a subset as previously done (Cardaropoli et al. 2019; Mazor et al., 2019; Pang et al., 2017). Furthermore, the assessment of ISQ (primary and secondary) and other important clinical variables using standard measurement techniques allow future comparability across studies, and the follow-up is comprehensive within the aims of this trial. However, this study was not possible to be carried out in a triple-blinded manner, as the intervention and follow-up phases were carried out by the same clinician, although this shortcoming was minimized because both the patient and data analysts were blinded to the allocation. We employed 2-dimensional X-ray evaluation, and this adds limited information concerning the implant mesial and distal marginal bone loss, and CBCT was only used to appraise radiodensity of the grafted sites during implant planning. Therefore, these results limit definitive conclusions on this particular feature. Notwithstanding, the distribution of implants placed

in molar and anterior sites for both groups was different due to the randomization process which limits also the validity of our conclusions and should be further addressed. Additionally, these specific grinder devices require the use of a cleansing solution onto the autogenous graft turning this material into a medical device with a simple but inherent learning curve.

5 | CONCLUSIONS

Implants placed in sites preserved with MDM had similar implant stability in comparison to xenograft granules. MDM showed a significantly higher quantity of newly formed bone and lower amount of residual graft in histomorphometry results and equal clinical and patient-related outcomes.

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Nothing to declare

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Alexandre Santos: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Validation (lead); Writing-original draft (equal); Writing-review & editing (equal). **Joao Botelho:** Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Writing-original draft (equal); Writing-review & editing (equal). **Vanessa Machado:** Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Writing-original draft (equal); Writing-review & editing (equal). **José João Mendes:** Project administration (supporting); Writing-original draft (equal); Writing-review & editing (equal). **Paulo Mascarenhas:** Conceptualization (supporting); Data curation (supporting); Investigation (supporting); Methodology (supporting); Writing-original draft (equal); Writing-review & editing (equal). **Gil Alcoforado:** Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Writing-original draft (equal); Writing-review & editing (equal).

ETHICAL STATEMENT

This study was approved by an official IRB and followed the CONSORT statement and the Helsinki declaration as revised in 2013.

DATA AVAILABILITY STATEMENT

Data that support these findings are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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