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Tooth autotransplantation with adjunctive application of enamel matrix derivatives using a digital workflow: A prospective case series

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ABSTRACT

Objectives: Digital protocols and bioactive materials may reduce complications and improve tooth autotransplantation (ATT) success and survival rates. This prospective study assesses the performance of a fully digital autotransplantation protocol of close-apex molars with the adjunctive application of Enamel Matrix Derivatives (EMD).

Methods: Twelve adult patients with 13 hopeless molar teeth were replaced with autotransplantation of closed apex third molars. Outcomes, including success and survival rates, clinical, endodontic, radiographic, patient-reported outcome measures (PROMs), and digital image assessments, were conducted over a two-year follow-up period.

Results: Survival and success rates were 100% and 91.2%, respectively, with no progressive inflammatory or replacement root resorption (ankylosis) except for one tooth presenting radiographic furcation involvement. A significant probing depth reduction of 2.4 ± 2.58 mm and CAL gains of 2.8 ± 3.03 mm were observed in transplanted teeth compared to the hopeless receptor teeth. Radiographic bone levels remained stable throughout the study period (-0.37 ± 0.66 mm), and digital image assessments showed minimal alveolar ridge width changes (-0.32 to -0.7 mm) and gingival margin changes (-0.95 to -1.27 mm) from baseline to last visit. PROMs indicated very high patient satisfaction.

Conclusion: The use of a digital ATT protocol with adjunctive use of EMD in closed-apex third molars demonstrated promising short-term high success and survival rates. Additionally, this type of therapy adequately preserves the dimensions of the alveolar ridge in the receptor site.

Clinical significance: This is the first prospective clinical study examining the effect of a digital tooth autotransplantation protocol combined with the application of EMD. It demonstrates that this approach is an effective treatment for replacing hopeless teeth and also validates the digital assessment of ATT alveolar ridge preservation at the recipient site.

1. Introduction

Tooth autotransplantation (ATT) is a surgical-restorative treatment aimed to rehabilitate a missing tooth or replace a hopeless tooth immediately after its extraction by repositioning an autologous tooth into either the edentulous site or the fresh alveolar socket. This treatment aims to restore lost oral function and aesthetics with a biologically compatible tooth replacement, avoiding potential post-extraction alveolar ridge resorption typical from traditional prosthesis and late implant placement. Additionally, in young patients, this approach aims to prevent interference with the development of the dentoalveolar complex. Its biological rationale lies in the regenerative potential of the periodontal ligament (PDL) by promoting the re-establishment of the periodontal attachment, preserving at the same time the receptor site phenotype [1].

This treatment concept for tooth replacement has shown successful

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clinical and radiographic outcomes [2], as well as high long-term survival and success rates [3-5]. Recently, given the high incidence of peri-implant diseases associated with the use of dental implants to restore missing teeth [6–8] and the unpredictability of current treatment options [9], tooth autotransplantation has emerged as a valid treatment alternative for replacing missing or hopeless teeth, independently of the root development stage (closed or open apex) of the donor tooth [10, 11]. Furthermore, since successfully transplanted teeth will maintain a vital periodontium, it becomes an ideal treatment option for patients still with active alveolar process growth or those patients with malocclusions where orthodontic movements in the transplanted teeth are indicated [12].

Autotransplantation, however, is not free from technical difficulties and long-term complications, being one of the most frequent inflammatory or replacement root resorption (RRR) [11,13] that usually occurs in areas where the PDL was damaged during the extraction [3,14]. Similar to dental implants, to improve its survival [15] and the feasibility of this therapeutic approach, digital technologies have facilitated the surgical protocols by significantly reducing donor tooth's extraoral time, minimizing surgical trauma during the procedure, and, thus, preserving the integrity of PDL [16]. Furthermore, to reduce the incidence of RRR, the adjunctive use of enamel matrix derivatives (EMD) has been proposed [17,18], based on the well demonstrated EMD's biological activity in regenerating the PDL by promoting the attraction, differentiation, and proliferation of cementoblasts, fibroblasts, and osteoblasts [19,20]. Nevertheless, there are very few reports evaluating the clinical effect of ATT combined with the adjunctive application of EMD [21,22]. It was, therefore, the objective of this prospective clinical study to evaluate the effect of transplanting autologous molar teeth with complete root development (closed-apex), combined with the adjunctive application of EMD, following a fully digital protocol.

2. Material and methods

2.1. Experimental design, setting, and timeframes

This clinical investigation was designed as a single-center, prospective case series and was conducted in compliance with the Preferred Reporting of Case Series in Surgery (PROCESS) guidelines [23]. All the therapeutic and follow-up interventions in this study were carried out in the Specialization Postgraduate Clinic of the Faculty of Odontology at the XX between April 2021 and February 2024.

2.2. Ethical approval

This study was designed in full compliance with the Declaration of Helsinki of 1965 [24], and its protocol was approved by the Ethical Committee from the Hospital Clínico in Madrid (CEIC21/311-E) and registered in ClinicalTrials.gov under code NCT06261255.

2.3. Eligibility criteria

Adult patients were eligible to participate in the study if meeting the following criteria: (1) ≥18 years old capable of reading, participating, and providing informed consent, with at least one hopeless molar tooth (teeth deemed non-restorable or irrational to treat for endo-perio reasons) in need of replacement"; (2) presence of a viable, healthy, periodontally stable, and non-functional tooth (e.g., third molar) suitable for tooth autotransplantation; (3) periodontally healthy individuals or with stable periodontal conditions after periodontal therapy [25].

The exclusion criteria were as follows: (1) clinical attachment loss (CAL) of the donor's tooth >6 mm; (2) compromised general health (ASA III-VI patients) or patients with systemic diseases that could influence the therapeutical outcome (e.g., uncontrolled diabetes mellitus, bone disorders); (3) pregnant or nursing women; (4) chronic use of corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or immune-modulator drugs; (5) patients requiring medications that affect bone metabolism (bisphosphonates); (6) chronic oral mucosa diseases; (7) evident signs of severe bruxism or clenching habits; (8) smokers of more than 10 cigarettes per day; (9) non-compliant patients with >25% plaque index [26] at the time of re-evaluation after non-surgical periodontal therapy and oral hygiene instructions; and (10) patients unable to attend study-related procedures and follow-up visits.

2.4. Interventions

2.4.1. Pre-study phase

Potential eligible participants received oral hygiene instructions (OHI) and cause-related periodontal therapy as needed. Smokers (< 10 cigarettes/day) were encouraged to quit or at least limit their smoking.

2.4.2. Digital planning

Before the baseline surgical intervention, intraoral scans (IOs) and cone-beam computed tomography (CBCT) were acquired for each patient [27]. Digital planning involved a three-dimensional (3D) analysis to identify the compatible donor tooth by segmenting the DICOM files into a Standard Tessellation Language (STL) file. This planning considered the tooth dimensions and morphology of the potential donor molar, its volume compatibility with the tooth planned for extraction, and the receptor site (extraction socket), as well as the foreseen complexity of extracting the donor tooth and potential associated hazards when adjacent vital anatomical structures were present. (Fig. 1)

Once the donor tooth was selected, a tooth replica made of biocompatible resin (Formlabs 3, Formlabs Inc.) was created using computer-aided rapid prototyping (CARP) [28] and a stereolithography (SLA) 3D printer (Formlabs 3, Formlabs Inc.), following the manufacturer's recommendations. Then, a surgical stent designed for a multi-drilling axis guide [29] was created for each patient. Both appliances were disinfected by soaking them in 0.12% CHX + 0.05% CPC (Perio-aid treatment®) for 20 mins.

2.4.3. Surgical procedure

All surgical treatments were performed by two experienced periodontists (IP, ISS). After administration of local infiltration (Septanest ® 40 mg/ml + 10 micrograms/ml), extraction of the hopeless tooth was carried out by tooth sectioning with fissure carbide burs, and careful extraction of the fragments with minimal trauma to the fresh extraction socket walls. With the use of the 3D planned customized multidrilling-axis tooth-supported surgical guide, [29] the recipient site was prepared, and the CARP model was tried on. If necessary, additional alveoloplasty was performed with round diamond burs. No antibiotic solution was used in the receptor site. If the receptor site presented a bone dehiscence, no grafting material was used in any case. The donor tooth was extracted as less traumatic as possible, utilizing a piezoelectric surgical instrument if osteotomy was required, avoiding the use of elevators or forceps over the root surface. Once extracted, EMD (Emdogain gel, Straumann, Basel, Switzerland) was directly applied to the root surface of the donor tooth. No prior conditioning with EDTA (PrefGel®, Straumann, Basel, Switzerland), saline, or antibiotic solution was used. (Fig. 2)

Once the donor tooth was positioned and stabilized into the surgically created recipient bed, a semi-rigid orthodontic wire was used to splint the tooth to the mesio-buccal and disto-buccal aspects of the adjacent teeth. If the autotransplanted tooth was the last molar in the arch, buccal and lingual splints were used for splinting to the mesial tooth. Then, the mucosal margins were closely adapted around the autotransplanted tooth with non-resorbable sutures. Occlusal contacts were adjusted if necessary to assure 1 mm infra-occlusion. Alternatively, orthodontic composite bite stops were placed on the adjacent teeth to temporarily alleviate the donor tooth of occlusal contacts during the healing phase. Fig. 3 depicts a clinical example of the step-by-step surgical approach. Immediately after the surgical intervention, a periapical

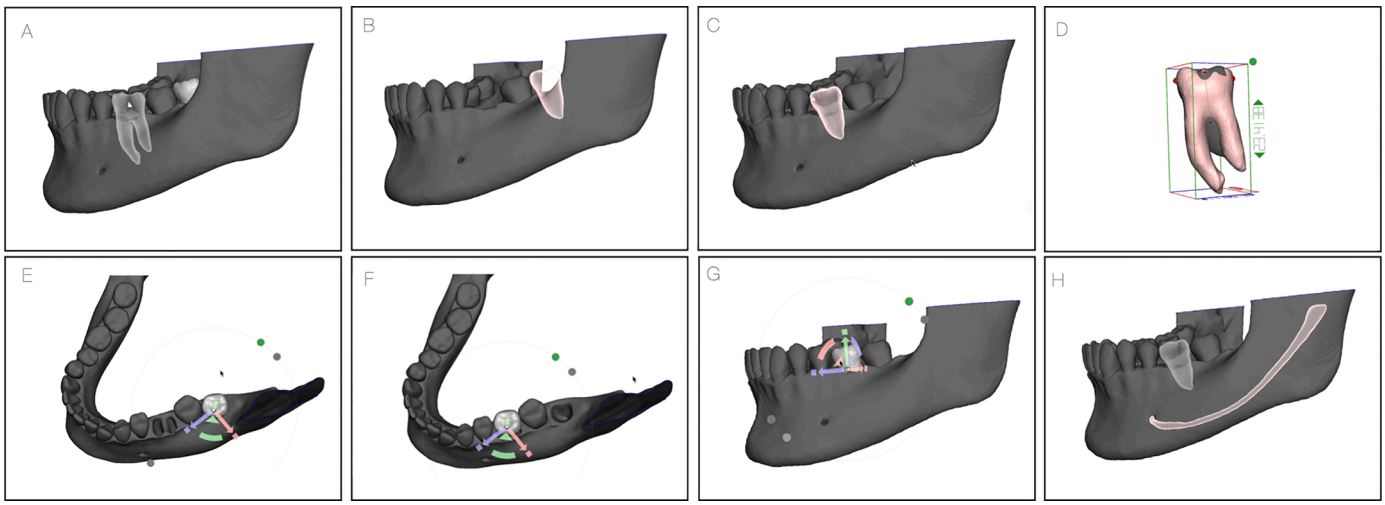

Fig. 1. Digital planning using DICOM files data segmentation.

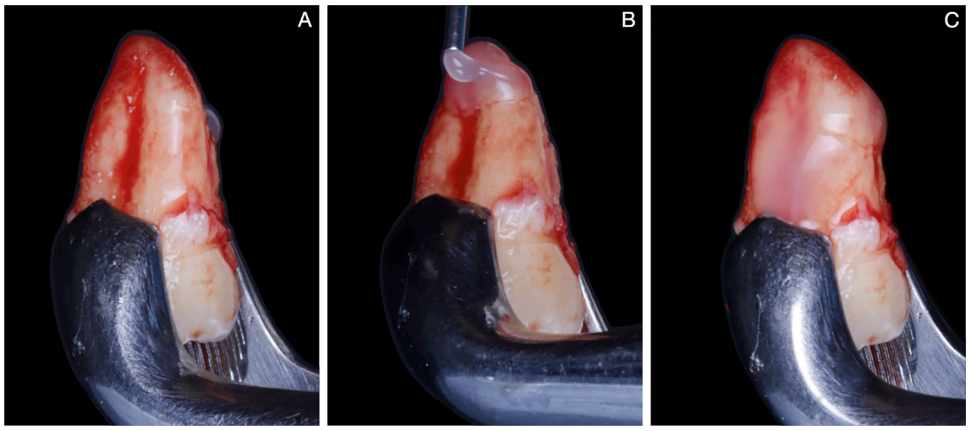

Fig. 2. A. Donor tooth extracted (note remnants of PDL over the root surface); B. Application of EMD over root surface; C. Donor tooth with root coverage with EMD ready to be placed in the receptor site.

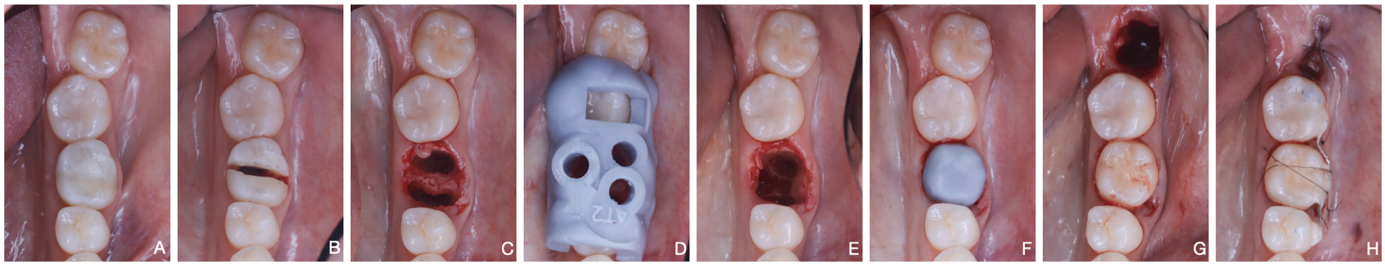

Fig. 3. Surgical procedure. A. Baseline situation; B. Tooth sectioning of hopeless tooth; C. Receptor site after extraction; D. Multidrilling axis surgical guide in place; E. Receptor site modified to receive donor tooth; F. Donor tooth 3D replica in receptor site to check proper adaptation; G. Donor tooth extracted and placed in receptor site; H. Immediate postoperative situation.

radiograph was taken.

2.4.4. Postoperative care

All patients were instructed to rinse with 0.12% CHX + 0.05% CPC (Perio-aid treatment®) for 1 min, three times a day, for 2 weeks. Additionally, a 7-day antibiotic regimen [30] (amoxicillin 500 mg every 8 h, three times a day) due to a long-duration surgery for educational and recording purposes. An analgesic regimen (Ibuprofen 600 mg, three times per day, as required) was recommended. Patients were advised to avoid any mechanical trauma, including toothbrushing in the surgical area, and were instructed to follow a 2-week soft diet. Sutures and the semi-rigid splint were removed after 2–4 weeks. To standardize the protocol, root canal therapy of the transplanted tooth was performed by a specialist within 2 to 4 weeks postoperatively. This time allowed for initial soft tissue healing and facilitated rubber dam isolation [5,30,31]. Normal function (occlusion) was allowed after splint removal. Patients were scheduled for follow-up visits at 1, 3, 12, and 24 months, where besides the study outcome data collection, their OHI was reinforced, and professional supragingival plaque control was implemented if needed.

2.5. Data collection

During the pre-study phase, sociodemographic data (i.e., age, sex, smoking habits), medical information (i.e., systemic diseases, medications), and dental history (i.e., history of periodontal treatment) were collected.

2.5.1. Clinical variables

Clinical outcome variables were collected in the hopeless tooth before its extraction and subsequently in the donor tooth and in the mesial and distal adjacent teeth. The following outcomes were recorded using a periodontal probe (PCP UNC 15, Hu-Friedy, Chicago, IL) at baseline (before autotransplantation), 3, 12, and 24 months study visits at six sites per tooth: probing depth (PD), gingival recession, clinical attachment loss (CAL), bleeding on probing (BoP), and plaque Index [26]. Additionally, the tooth mobility and the periodontal status of the autotransplanted tooth were diagnosed using the criteria from the 2018 Classification of Periodontal Diseases and Conditions [32].

2.5.2. Digital imaging assessments

An independent and calibrated examiner (E.C.Q) performed all the linear measurements from high-resolution STL files obtained with an intraoral scanner (3Shape Trios, Copenhagen, Denmark). Calibration was achieved from repeated measurements after achieving an inter-class correlation coefficient of $\geq$ 0.9. Digital data were analyzed at baseline and 24 months. (Appendix)

2.5.3. Baseline bone and soft tissue linear measurements

At baseline, a sagittal section was made from the CBCT at the middle of each tooth on the receptor site. Mid-facial and mid-lingual bone thickness was measured at 1 mm apical to the alveolar bone crest. Mid-facial and mid-lingual soft tissue thickness was measured at 1 mm apical to the gingival margin.

2.5.4. Position of the gingival margin and alveolar ridge linear measurements

To assess the changes in the position of the gingival margin between baseline and the final follow-up visit, STL files were analyzed using a specialized software package (Geomagic Control X, 3D Systems, Rock Hill, SC, USA). Changes in the linear distance between the gingival margin and alveolar ridge were measured at both buccal and lingual aspects in mesial, mid, and distal sites. Furthermore, reference at intervals of 1, 3, and 5 mm below the alveolar crest, quantified linear changes in ridge width (Appendix) (Fig. 4)

2.5.5. Radiographic variables

Standardized periapical digital radiographs taken 3 months after the autotransplantation and at the two-year visit were compared. Standardization was achieved by using custom-made bite blocks mounted on a film holder-beam aiming device (i.e., Rinn System [Dentsply International, York, PA, USA]) for each patient.

A calibrated outcome assessor (I.S.S) performed the radiographic evaluation at both time points to assess bone level changes at the autotransplanted site. Linear measurements from the CBCT were used to obtain a reference value and calibrate it with the autotransplanted tooth. The length from the cuspid to the apex of the adjacent tooth was measured and used as a reference for calibration. Before this assessment, a calibration process was conducted, achieving an intra-examiner reproducibility of at least 0.85.

2.5.6. Patient reported outcomes measures (PROMS)

At the study's completion, each patient received standardized questionnaires from a member not involved in the research project to evaluate the following aspects related to the autotransplantation treatment: comfort, aesthetics, masticatory function, and general satisfaction. Each category was assessed on a Likert scale from 1 to 5 (from 'very unsatisfied' to 'very satisfied').

2.5.7. Definition of survival and success

Survival was defined as the presence of an autotransplanted tooth in the oral cavity, with no indications for extraction at the time of the last clinical and radiographic evaluation [16].

Success was defined as the fulfillment of specific clinical and radiographic conditions, including:

1. Normal masticatory function and physiologic tooth mobility in the absence of pain or discomfort during palpation and percussion.
2. Stable periodontal attachment apparatus, as defined by the absence of PD $>$ 4 mm and CAL of $\leq$5 mm.
3. Radiographic images compatible with the presence of periodontal ligament around the transplanted tooth, absence of progressive root resorption, periapical radiolucency, furcation involvement, or radiographic bone loss $\geq$25%.

2.6. Statistics

Statistical analyses were performed using each autotransplanted tooth as the statistical unit. The descriptive analysis presented continuous variables as means (SD) and confidence intervals of 95%, while categorical variables as a percentage (%). Data normality was calculated utilizing a Shapiro-Wilk test.

The primary outcome variable was the CAL level changes on the donor tooth between the baseline situation and the last two-year follow-up visit. These differences were evaluated using a paired sample Student's *t*-test using 2-sided p-values with alpha $<$0.05 level of significance. If the data samples did not meet normality criteria, a Wilcoxon signed-rank test was used. Binary categorical values were evaluated through a Chi-squared test.

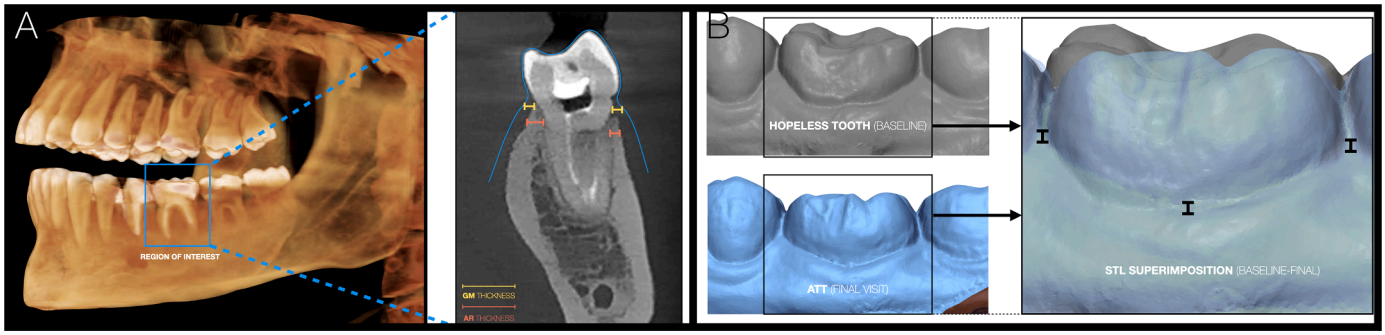

Fig. 4. A. Sagittal radiographic section showing the method followed to make baseline linear measurements of the facial gingival (yellow line), and bone (orange line); B. Example of linear measurements comparison of the position of the gingival margin at baseline and the last follow-up visit in three sites (mesial, facial distal) of the buccal aspect; C. Example of alveolar ridge width changes assessment at both buccal and lingual aspects (reference points at 1, 3, 5 mm).

Secondary outcomes included tooth survival, success rate, PD, recession, BoP, plaque index, mobility, radiographic bone levels, gingival margin levels, and tooth loss. Within-patient changes were compared for continuous variables using paired Student *t*-test or Wilcoxon signed-rank test depending on the normality of data, while for dichotomous categorical variables, they were compared using Chi-squared tests.). All data analyses were performed with SPSS version 21.0 software (Chicago, IL, USA).

3. Results

3.1. Patient demographics

Fourteen subjects were screened, and 12 patients fulfilled the criteria, providing a total of 13 autotransplanted teeth. This study population included 8 males (66.7%) and 4 females (33.3%) with a mean age of 35.6 ± 2.9 years (ranging from 23 to 58 years). At the screening visit 54% of the subjects were periodontal healthy, 23% presented generalized gingivitis, and 23% had generalized stage III grade B periodontitis.

The most frequently transplanted tooth was the mandibular third molar (92% of teeth), followed by the maxillary third molar (8%). The most frequent recipient site was the mandibular first molar (66.7%), followed by the mandibular second molar (33.3%). Among the donor teeth, 11 were fully erupted, 1 was partially erupted, and 1 was completely retained before the surgical procedure. At the recipient site, 4 out of 13 cases (30.7%) exhibited a partially damaged socket with buccal dehiscence, and 3 teeth (23%) depicted a radiographic periapical lesion. (Table 1)

3.2. Survival and success

Survival and success rates were 100% and 91.2%, respectively, after a two-year follow-up period. In one transplanted tooth, PD was 6 mm, and the radiographic image was compatible with furcation involvement; this case was categorized as survival but not as successful, since its extraction was not indicated. (Fig. 5)

3.3. Clinical outcomes

The mean PD of the hopeless teeth at baseline was 4.74 ± 2.38 mm, whereas the mean PD of the transplanted teeth at the two-year visit was 2.42 ± 0.56 mm. This PD reduction (−2.4 ± 2.58 mm) was statistically significant ($p = 0.024$). Similarly, CAL showed a statistically significant gain of 2.82 ± 3.03 mm ($p = 0.023$). The position of the gingival margin remained stable from baseline to the last follow-up, with no gingival recession observed (0.29 + 0.40 mm; $p = 0.180$). The autotransplanted teeth showed a reduction in BoP as compared to the baseline hopeless tooth, and there were no significant differences in plaque levels during the study. All the autotransplanted teeth yielded physiologic mobility.

No differences were observed in any of the clinical parameters (including tooth mobility) at the autotransplanted teeth during the different follow-up study visits. These results demonstrated periodontal health stability after the surgical procedure. Similarly, no changes were found when assessing the clinical variables of the donor tooth in its baseline third molar position to its new transplanted position at the final evaluation of the study. (Table 3)

Table 1
Demographic characteristics of the sample. Abbreviations: M: Male; F: Female; (+) presence/positive.

Sex (M/F)	8/4
Age	35.6 ± 2.9 years
Periodontal status	6 periodontal health 3 generalized gingivitis 3 periodontitis stage III grade B
Smoking status (Yes/No)	1 /11
Donor tooth	Mandibular third molars (92%) Maxillary third molars (8%)
Eruption status	11 fully erupted teeth 1 non-erupted 1 partially erupted
Recipient site	Mandibular first molar (66.7%) Mandibular second molar (33.3%)
Buccal Bone Dehiscences (+)	4/13 teeth
Baseline Periapical lesions (+)	3/13 teeth
Buccal bone thickness (mean)	0.81 mm
Lingual bone thickness (mean)	1.55 mm
Buccal soft tissue thickness (mean)	1.48 mm
Lingual soft tissue thickness (mean)	1.84 mm

3.4. Endodontic outcomes

No signs of progressive inflammatory or RRR (ankylosis) were observed in any autotransplanted teeth in the final evaluation after receiving all of them prophylactic root canal treatment between 2 and 4 weeks after the surgical procedure.

3.5. Radiographic outcomes

The radiographic bone level change at the transplanted teeth between 3 months and the last follow-up visit showed a non-significant bone loss (−0.37 ± 0.66 mm, $p = 0.065$). One transplanted tooth showed an image compatible with furcation involvement, which had a complex surgical extraction due to its retained situation and curved root anatomy.

3.6. Digital imaging assessments

Linear measurements using CBCT to compare the donor tooth and the receptor site were assessed at three distinct reference points. The coronal reference point exhibited no statistically significant differences (−0.93 ± 2.60 mm, $p = 0.21$) between the transplanted tooth and the alveolar ridge in the coronal third. However, a statistically significant discrepancy was observed in the middle (−4.53 ± 2.50 mm, $p < 0.001$) and apical thirds (−7.22 ± 1.68 mm, $p < 0.001$).

At baseline, the mean buccal and lingual bone thickness at the receptor site was 0.99 + 0.34 mm and 1.55 + 0.68 mm, respectively, and the mean buccal and lingual soft tissue thickness was 1.47 + 0.72 mm and 1.84 + 0.67 mm, respectively (Table 1). Alveolar ridge dimensions at the recipient site showed minimal changes after tooth autotransplantation in the different sites and landmarks measured, as reported in Table 2. Similarly, the position of the gingival margin remained stable over time, both at buccal and lingual sites, as well as at the mesial, mid, and distal regions. (Table 2)

3.7. Patient-Reported outcomes measures

Patient satisfaction was high, with 100% of the study participants being “very satisfied” in the overall satisfaction category at the end of the study period. Satisfaction scores were 96% for the masticatory function, 95% for the esthetic perception, and 95% for comfort. Individual observations include one patient who perceived the transplanted tooth smaller than adjacent teeth and one patient who reported facing challenges in maintaining oral hygiene around the transplanted tooth.

4. Discussion

This prospective case series was aimed to assess the performance of a digitally guided tooth autotransplantation protocol combined with the adjunctive use of EMD to replace hopeless molars with closed-apex third molars. The results from this clinical report show the predictability of successful outcomes, with a success rate of 91.2% and a survival rate of 100% after a two-year follow-up of 13 autotransplanted teeth. Only one

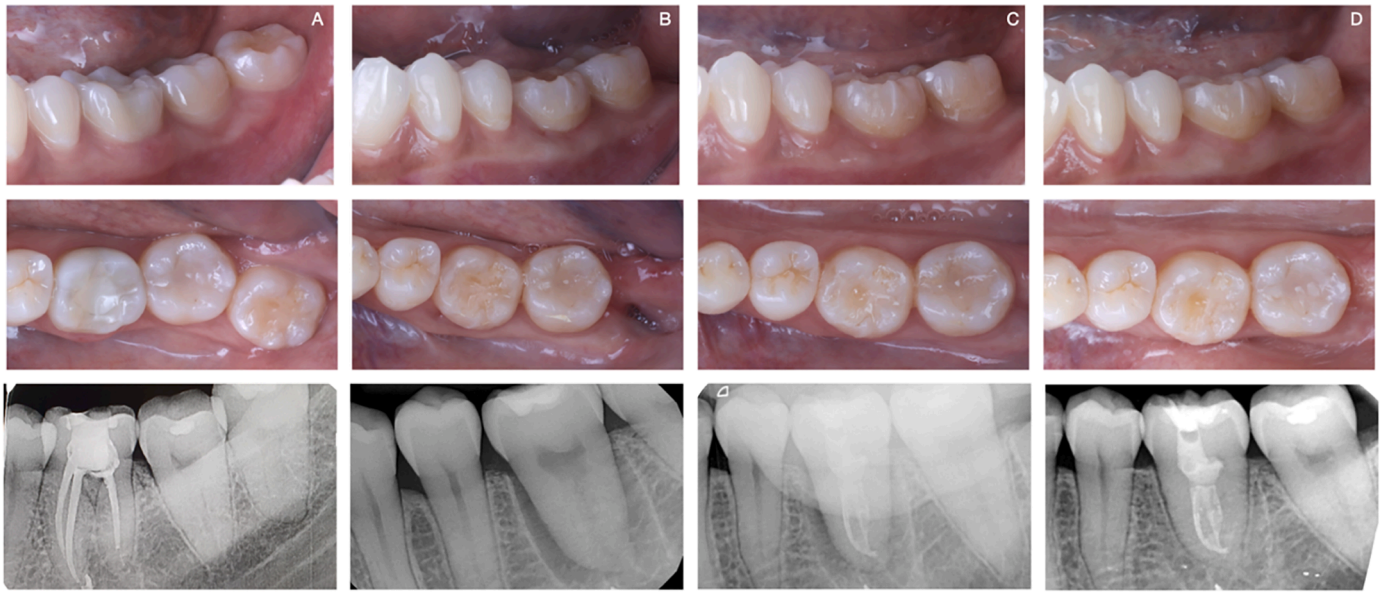

Fig. 5. Clinical and radiographic evolution of a study case.

Table 2
Hard and soft tissue changes between baseline and the final evaluation. ST: Soft tissue; AR: Alveolar ridge; GM: gingival margin; SD: Standard deviation.

Alveolar ridge (AR) changes between baseline and final evaluation (mm)					
	mean	SD		mean	SD
Baseline buccal bone thickness	0.99	0.34	Baseline lingual bone thickness	1.55	0.68
Buccal AR changes - mesial 1 mm	−0.32	±0.33	Lingual AR changes - mesial 1 mm	−0.70	±0.61
Buccal AR changes - mesial 3 mm	−0.34	±0.27	Lingual AR changes - mesial 3 mm	−0.54	±0.63
Buccal AR changes - mesial 5 mm	−0.34	±0.30	Lingual AR changes - mesial 5 mm	−0.35	± 0.30
Buccal AR changes - mid 1 mm	−0.34	±0.73	Lingual AR changes - mid 1 mm	−0.36	±0.25
Buccal AR changes - mid 3 mm	−0.46	±0.46	Lingual AR changes - mid 3 mm	−0.37	± 0.09
Buccal AR changes - mid 5 mm	−0.46	±0.74	Lingual AR changes - mid 5 mm	−0.36	±0.32
Buccal AR changes - distal 1 mm	−0.55	±0.44	Lingual AR changes - distal 1 mm	−0.48	±0.33
Buccal AR changes - distal 3 mm	−0.66	±0.56	Lingual AR changes - distal 3 mm	−0.56	±0.56
Buccal AR changes - distal 5 mm	−0.57	±0.50	Lingual AR changes - distal 5 mm	−0.44	±0.65
Linear soft tissue (ST) changes between baseline and final evaluation (mm)					
	mean	SD		mean	SD
Baseline buccal ST thickness	1.47	0.72	Baseline lingual ST thickness	1.84	0.67
Buccal GM changes - mesial	−0.97	0.61	Lingual GM changes - mesial	−1.14	0.90
Buccal GM changes - mid	−1.27	0.62	Lingual GM changes - mid	−1.23	0.98
Buccal GM changes - distal	−1.13	0.98	Lingual GM changes - distal	−0.95	0.77

Table 3
Mean probing depths (PD), Clinical attachment level (CAL), Plaque index (PI), Bleeding on probing (BoP), and gingival recession (Rec) values at each tooth and each time-point. Comparisons between the hopeless and donor teeth are presented.

Clinical outcomes: Mean ± SD					
Mean data per group					
	PD	CAL	PI	BoP	Rec
Donor tooth baseline	2.85 ± 0.23 mm	2.85 ± 0.23 mm	0.85 ± 0.17	0.82 ± 0.35	0.00 ± 0 mm
Hopeless (receptor) tooth baseline	4.74 ± 2.38 mm	5.25 ± 2.70 mm	0.51 ± 0.33	0.76 ± 0.35	0.58 ± 0.44 mm
ATT 3 months	2.25 ± 0.60 mm	2.00 ± 0.71 mm	0.10 ± 0.15	0.04 ± 0.08	0.10 ± 0.18 mm
ATT 12 months	2.46 ± 0.63 mm	2.69 ± 0.70 mm	0.26 ± 0.23	0.12 ± 0.21	0.23 ± 0.30 mm
ATT 24 months	2.42 ± 0.57 mm	2.61 ± 1.01 mm	0.26 ± 0.28	0.19 ± 0.25	0.29 ± 0.40 mm
Comparisons between hopeless and donor teeth					
	PD	CAL	PI	BoP	Rec
Donor - hopeless tooth (baseline)	−0.95 ± 0.96 mm (p = 0.144)	−1.26 ± 1.26 mm (p = 0.138)	−1.342 (p = 0.180)	0.0 (p = 1.0)	−1.41 (p = 0.157)
ATT 24 months - Hopeless tooth (baseline)	−2.4 ± 2.58 mm **(p = 0.024)**	−2.82 ± 3.03 mm **(p = 0.023)**	−1.272 (p = 0.203)	−2.084 **(p = 0.037)**	−1.47 (p = 0.141)
Donor tooth baseline -ATT 24 months	−0.39 ± 0.52 mm (p = 0.235)	−0.51 ± 1.44 (p = 0.526)	−1.461 (p = 0.144)	−1.473 (p = 0.141)	−1.342 (p = 0.180)
ATT 3 months - ATT 24 months	−0.20 ± 0.63 (p = 0.352)	−0.69 ± 1.22 (p = 0.126)	−2.032 **(p = 0.042)**	−1.604 (p = 0.109)	−1.604 (p = 0.109)

* Represent statistically significant values ($p < 0.05$). Abbreviation: F-up = follow-up. Note: "Hopeless tooth" refers to the receptor tooth to be replaced.
** Physiological tooth mobility was present in all teeth.

tooth was not considered successful due to deep probing depths and a radiographic image compatible with furcation involvement.

These results are encouraging compared with several retrospective studies where, however, some methodological differences should be highlighted (i.e. the absence of digital workflows or adjunctive EMD. Tsukiboshi et al. reported survival rates of 94.6% and success rates of 85.3% in a sample of 129 teeth after a mean follow-up period of 10.2 years [33]. Similarly, Boschini et al. [34] reported survival rates of 95% and success rates of 80%. Barendregt et al. demonstrated a success rate of 83.3% in adult patients within a sample of 1654 premolars followed up to 10 years [5]. However, these long-term retrospective studies with

larger sample sizes did not use a digital workflow nor the adjunctive use of EMD, which might have influenced the results. On the other hand, a retrospective study on third molar autotransplantation, using an identical digital protocol, reported a survival rate of 97.2% and a success rate of 91.7%, but they included open and closed-apex molars [16]. The current scientific evidence indicates that autotransplantation of open-apex teeth and young patients has a higher predictability in terms of survival and success rates [4,11]. The presented prospective case series, however, exclusively utilized as donor teeth, closed-apex teeth, and still demonstrated similarly elevated survival and success rates, which may generate the hypothesis that the adjunctive use of EMD may somehow, compensate for the absence of Hertwig's epithelial root sheath and the higher regenerative capacity of the PDL cells found in open-apex teeth. However, this hypothesis needs to be confirmed further in prospective long-term randomized control clinical trials since the presented results may be a consequence of the combination of other factors, such as the use of digital protocols, which led to reduced extraoral times, or the atraumatic extractions.

The present digital protocol with the adjunctive use of EMD led to a mean PD reduction of 2.42 ± 0.15 mm and CAL gains of 2.82 ± 3.03 mm when comparing the hopeless tooth before extraction at the recipient site and the transplanted teeth in its new position. The only available scientific report on this combined therapy comes from a case report of 2 closed apex teeth, which yielded a similar PD reduction of 2.4 mm and 2.35 mm CAL gain [17]. A similar comparison between the hopeless tooth and the transplanted one was made in a retrospective study without the adjunctive use of EMD [16], also reporting a mean PD reduction of 2.71 ± 0.48 mm and a mean CAL gain of 0.626 mm. Despite the cemento-enamel-junction (CEJ) position of the transplanted teeth at the receptor site may have an impact on PD and CAL values, a re-establishment of the physiological supra crestal tissue attachment was indeed obtained.

Early bone remodeling around the transplanted tooth may be expected due to trauma during the extraction and to the re-establishment of the supracrestal tissue attachment. This was the reason why the baseline radiograph in the present study was taken 3 months after ATT. Radiographic bone levels remained stable during the study period, which may be attributed to the preservation of the transplanted tooth's PDL and the use of EMD. At the same time, this bone stability could explain the reported soft tissue stability, contributing to long-term stability and aesthetics. CBCT linear measurements at the coronal level comparing the donor tooth and the receptor site dimensions revealed no significant differences, indicating that the donor's teeth were compatible in size in most cases. These results recognize the utilization of third molars as potential replacements for hopeless molars and emphasize the importance of CBCT tooth segmentation and virtual planning to select the most suitable and compatible donor tooth.

No signs of progressive inflammatory or RRR were observed in the present case series. This could be attributed in part to the digital workflow used, as it enabled us to select an ideal donor tooth, minimize its extraoral time, and reduce iatrogenic damage to the donor tooth's periodontal ligament (PDL). The digital workflow allowed for precise guided socket preparation and the use of a 3D-printed replica for donor tooth selection before extracting the donor molar. Furthermore, the adjunctive use of EMD could maximize the PDL regenerative potential in case the trauma inherent to any tooth extraction caused large PDL lesions (9–16 mm^2) that surpass the limit of auto-regeneration [14]. However, histological samples would be needed to confirm these statements. The results from this study have reported a minimum number of complications and high percentages of successful outcomes, which may indicate that this treatment option is an appropriate alternative to dental implants.

Given the complete root development stage in the sample, root canal therapy was necessary due to the inability of pulp revascularization [10]. In the present study, early root canal therapy was performed between 2 and 4 weeks after ATT [5] to minimize confounding factors, standardize the sample and prevent inflammatory root resorption as demonstrated in the results. However, the ideal timing for root canal therapy may be controversial. Performing it prior to ATT may have the advantage of doing it in a vital pulp instead of a necrotic one [35], and overcome during the surgical procedure via retrograde access some of the complications that may occur, such as perforation or instrument fracture. It also *avoids additional manipulation and microtrauma caused by the endodontic instrumentation of the auto-transplanted tooth during the initial healing phase.* Nonetheless, the feasibility of accessing third molars for endodontic treatment varies based on tooth position, clinician dexterity, patient mouth opening, and possible inclusion/impaction.

Analysis of linear alveolar bone and soft tissues at the recipient site exhibited minimal changes following ATT. A comparison of this data with the physiological dimensional changes observed in the alveolar ridge after unassisted socket healing or alveolar ridge preservation [36] suggests that ATT could be used as an alternative therapeutic option to preserve ridge dimensions. Moreover, the gingival margin remains stable (no recession), although its final level may be influenced by the apico-coronal position of the donor's tooth in the recipient site.

PROMs showed that all the participants were very satisfied with the treatment, indicating that ATT may be a good alternative to dental implants with very good acceptance. Nevertheless, further studies are needed to evaluate the balance between costs, risks, benefits, and complexity to understand which treatment alternative could be more appropriate. Also, analysis of post-operative PROMs should be considered for future studies.

This case series represents the first prospective clinical study examining the efficacy of EMD and digital tooth autotransplantation. However, some limitations should be acknowledged. Digital evaluation of the periodontal phenotype could be considered a limitation. However, a recent study has demonstrated that a CBCT scan is a viable method to assess the hard and soft tissue dimensions of the around teeth [37]. The absence of a control group, a blinded surgeon, and a longer follow-up period hinders the comprehensive assessment of the added effects of EMD. Due to the study design and the reduced sample size, this pilot prospective study serves only as a hypothesis generator. However, it provides a foundation for future randomized clinical trials with larger sample sizes and longer follow-ups, to further confirm the effect of EMD on the incidence of complications and long-term survival and success rates. Furthermore, a unique aspect of this study is the introduction of digital comparisons before and after the treatment to evaluate phenotype and ridge dimensional changes.

Within the limitation of this study, it can be concluded that the proposed digitally guided autotransplantation protocol with adjunctive use of EMD is an effective treatment for the replacement of hopeless molars, with high short-term success and survival rates in 13 autotransplanted teeth, and a good capacity to preserve alveolar ridge dimensions.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethics approval statement

This study was approved by the committee of Hospital Clínico de Madrid, Spain. Ethical Committee (CEIC21/311-E)

CRediT authorship contribution statement

Ignacio Pedrinaci: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Javier Calatrava:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis. **Emilio Couso-Queiruga:** Writing – review & editing,

Visualization, Validation, Software, Formal analysis, Data curation. **Juan del Rosal Bethencourt:** Writing – review & editing, Investigation, Data curation. **Ignacio Sanz-Sanchez:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **German O. Gallucci:** Writing – review & editing, Visualization, Validation, Supervision. **Mariano Sanz:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Formal analysis, Data curation.

Declaration of competing interest

The authors have no conflicts of interest to report pertaining to the conduction of this study.

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Appendix

2.5.2. Digital imaging assessments

An independent and calibrated examiner (E.C.Q) performed linear measurements for all patients with a baseline and final intraoral scan, ensuring an inter-class correlation coefficient of at least 0.9 before commencing data collection. High-resolution STL files acquired using an intraoral scanner (3Shape Trios, Copenhagen, Denmark) were analyzed at baseline and the last follow-up visit.

2.5.3. Baseline bone and soft tissue linear measurements

The baseline STL and DICOM files were imported to a software package (Romexis, Planmeca v.5.2.1., Hoffman Estates, IL, USA) and superimposed by matching at least 8 points from anatomical landmarks to allow the visualization of soft and hard tissue structures beneath the overlying surface, as described elsewhere [27, 28]. At baseline, a sagittal section was made from the CBCT at the middle of each tooth on the receptor site. Mid-facial and mid-lingual bone thickness was measured at 1 mm apical to the alveolar bone crest. Mid-facial and mid-lingual soft tissue thickness was measured at 1 mm apical to the gingival margin.

2.5.4. Position of the gingival margin and alveolar ridge linear measurements

To assess the changes in the position of the gingival margin between baseline and the final follow-up visit, STL files were analyzed using a specialized software package (Geomagic Control X, 3D Systems, Rock Hill, SC, USA). For each patient, the baseline, and the last follow-up visit STL files were superimposed for best-fit alignment. The average error between STL files was established at ±0.15 mm. To quantify the linear difference in the position of the gingival margin in mm at the buccal and lingual mesial, mid, and distal sites, the zenith of the gingival margin in the baseline STL file was taken as a reference. The alveolar ridge width changes were also evaluated at the buccal and lingual mesial, mid, and distal sites. A sagittal section at each area of interest was made. Horizontal alveolar ridge width linear changes were quantified in mm at three predetermined reference points established at 1, 3, and 5 mm from the baseline gingival margin.

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