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ORIGINAL ARTICLE

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The effect of timing of orthodontic therapy on the outcomes of regenerative periodontal surgery in patients with stage IV periodontitis: A multicenter randomized trial

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Abstract

Aim: To compare the outcomes after early (4 weeks post surgery) or late (6 months post surgery) orthodontic therapy (OT) following regenerative surgery of intra-bony defects (IDs).

Materials and methods: In a multi-center, parallel-group, randomized clinical trial, 43 patients with stage IV periodontitis were randomized to receive either early ($n = 23$) or late OT ($n = 20$) following regenerative surgery of IDs. Primary outcome was change in clinical attachment level (CAL) in one target ID at 12 months after surgery. Secondary outcomes were changes of probing pocket depth (PPD), bleeding on probing (BOP), and frequency of pocket closure.

Results: No statistically significant differences between groups could be observed for CAL gain (5.4 mm [±2.1 mm] for early; 4.5 mm [±1.7 mm] for late OT). PPD was reduced by 4.2 mm (±1.9 mm) in the early group and by 3.9 mm (±1.5 mm) in the late group ($p > .05$). Pocket closure (PPD ≤ 4 mm) was obtained in 91% of defects in early compared to 85% in late OT.

Conclusion: In the inter-disciplinary treatment of periodontitis stage IV, OT can be initiated already 4 weeks after regenerative surgery of IDs with favourable results, thus reducing the overall treatment time.

KEYWORDS
orthodontic tooth movement, pathologic tooth migration, regenerative periodontal therapy, stage IV periodontitis

Clinical Relevance

Scientific rationale for study: Information on the treatment of patients with stage IV periodontitis with intra-bony defects (IDs) and pathological tooth migration (PTM) in need of orthodontic therapy (OT) is limited. The optimal interval between regenerative periodontal surgery and OT is a matter of ongoing debate.

Principal findings: After 12 months, significant periodontal improvements of similar magnitude were observed following early (after 4 weeks) and late (after 6 months) initiation of OT.
Practical implications: Teeth severely compromised by IDs and PTM can be treated successfully by regenerative surgery followed by early OT with the advantage of an overall reduced treatment time.

1 | INTRODUCTION

The presence of severe periodontal attachment loss, vertical bone loss, and pathological tooth migration (PTM) (Brunsvold, 2005) is a key clinical feature of stage IV periodontitis (Papapanou et al., 2018; Tonetti & Sanz, 2019). An inter-disciplinary approach is required to control the periodontal infection, reconstruct the defects, and realign the migrated teeth (Re et al., 2000; Gkantidis et al., 2010; Cardaropoli et al., 2014; Sanz & Martin, 2015). Such a comprehensive treatment includes the steps 1 and 2 of periodontal therapy followed by step 3 including regenerative periodontal surgery (Sanz et al., 2020) and subsequent orthodontic therapy (OT).

However, only limited data exist on these combined periodontal regenerative and orthodontic approaches (Martin et al., 2021). At present, clinicians have to rely mainly on case reports and prospective as well as retrospective clinical case series. In particular, the optimal time interval between periodontal surgery and the initiation of OT is a matter of ongoing debate. It may be safe to wait until the end point of regenerative therapy has been reached (usually between 6 and 12 months) and not to interfere with periodontal wound-healing (Pini Prato & Chambrone, 2020). Case reports and series with long-term follow-ups have reported favourable periodontal outcomes using such a delayed approach (Ghezzi et al., 2008; Jepsen et al., 2015; Roccuzzo et al., 2018; Aimetti et al., 2020).

Other reports have suggested that OT may be initiated almost immediately or up to 3 months after regenerative surgery (Cardaropoli et al., 2006; Ogihara & Wang, 2010; Attia et al., 2012a, 2019; Ghezzi et al., 2013). No adverse effects were reported, and some authors speculated that early tooth movement could even stimulate periodontal wound-healing. Very recently, a large retrospective case series of patients with stage IV periodontitis, where OT was started 3 months after regenerative surgery, showed substantial improvements after 12 months and could be maintained up to 4 years (Tietmann et al., 2021).

At present, there are no data available from randomized clinical trials (RCTs) that have compared the periodontal outcomes following early versus late initiation of OT in stage IV periodontitis (Martin et al., 2021). As many patients affected by such a condition are interested to seek orthodontic treatment because of the aesthetic and functional changes caused by PTM (Hirschfeld et al., 2019), this question is of high clinical relevance.

The aim of this randomized, multicentre trial was to compare two different protocols of a combined treatment comprising regenerative periodontal surgery and subsequent orthodontic tooth movement in subjects with periodontitis stage IV in order to establish whether one treatment protocol is superior to the other with regard to periodontal outcomes. The two treatment groups differed by the time point of initiation of OT (early: 4 weeks vs. late: 6 months following regenerative periodontal surgery).

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study was designed as a prospective, multicentre, multinational, randomized parallel-group clinical trial with a 12-month follow-up (ClinicalTrials.gov, identifier: NCT 02761668). All investigators attended calibration meetings to standardize case selection by discussion of prospective cases, clinical measurement techniques, and surgical and orthodontic procedures. On-site rules for the compilation of the data collection sheets for appropriate oversight were frequently re-evaluated to ensure the validity of the data. The study was designed to test the hypothesis that one treatment protocol was superior to the other with regard to periodontal outcomes after 12 months. An overview of study procedures and exams is presented in Figure 1.

Study participants were consecutively recruited from patients treated by experienced periodontists and orthodontists in Germany (University of Bonn and Private Practice, Aachen), in Italy (Private Practice, Torino), and in Spain (Complutense University of Madrid).

Ethical approval was obtained by the Ethical Committee, University of Bonn (code 034/16) for the centres Bonn and Aachen and by the competent local authorities for the centres Torino (code PROT 04-2017) and Madrid (code 16/492-E). All subjects gave their informed consent after the investigators had provided a thorough explanation of the study procedure and its associated risks and benefits. All study procedures were performed according to the Declaration of Helsinki (1975, revised in 2008) on experimentation involving human subjects.

Individuals presenting severe periodontitis and PTM (stage IV periodontitis; Papapanou et al., 2018) who fulfilled the following inclusion and exclusion criteria were invited to participate:

2.1.1 | Inclusion criteria

- Completed steps 1, 2, and 3 (except for experimental regions) of periodontal therapy;
- Presence of ID(s) (3 mm or deeper) with indication for periodontal regenerative surgery at incisors, canines, or premolars with PTM requiring OT;

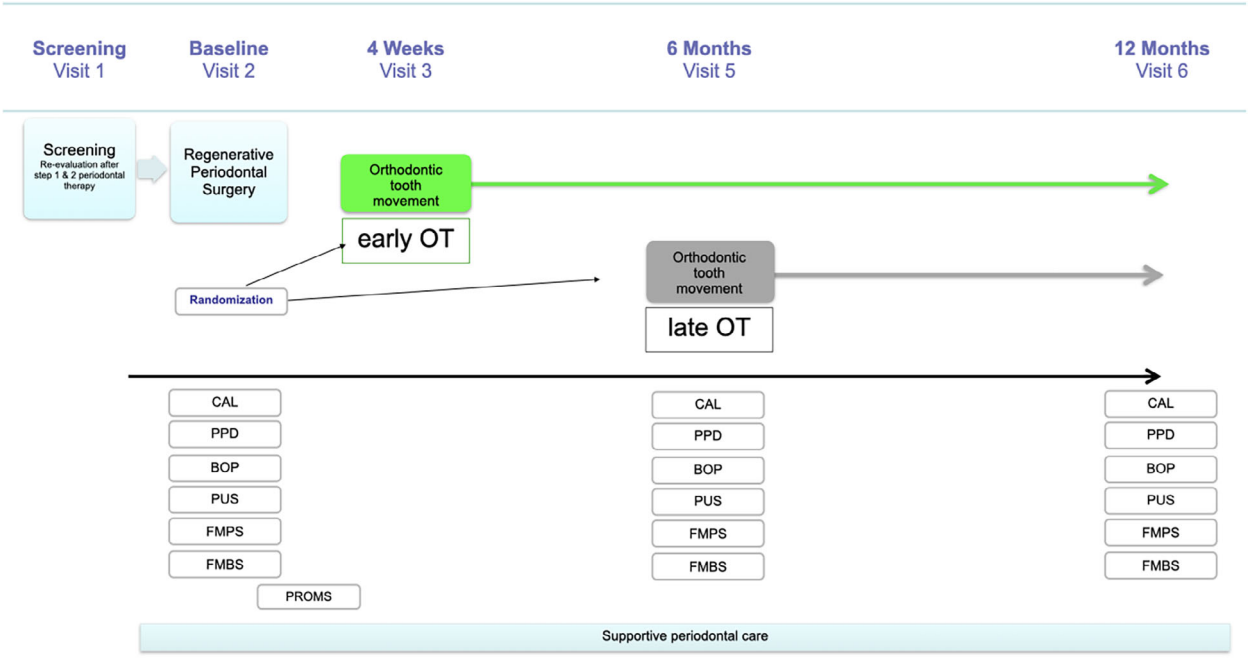

FIGURE 1 Chronological sequence of examinations, periodontal and orthodontic therapy (OT), early OT initiated 4 weeks after, and late OT initiated 6 months after regenerative periodontal surgery

- Adequate oral hygiene and control of inflammation in the whole dentition as demonstrated by a full-mouth plaque score (FMPS) of <25% and a full-mouth bleeding score (FMBS) of <25%.

2.1.2 | Exclusion criteria

- Furcation involvement of the teeth to be treated;
- Smoking exceeding five cigarettes per day or pipe or cigar smoking;
- Uncontrolled metabolic disorders;
- Presence of medical contraindications for oral surgical procedures;
- Known sensitization to collagen-based medical products.

In patients with more than one ID meeting the inclusion criteria, only one tooth was defined as the target tooth and the most severe defect as the target site.

2.2 | Interventions

2.2.1 | Regenerative periodontal surgery

Selected areas for surgery were anaesthetized by block and/or infiltration. The surgical procedures were adapted to the treatment algorithm introduced by Cortellini and Tonetti (2015). Minimally invasive microsurgical approaches including access by papilla preservation flaps were used. Depending on the defect configuration and/or prevention of soft tissue collapse into the defect, a bone filler (DBBMc, Bio Oss® Collagen; Geistlich, Wolhusen, Switzerland) was used. If the graft material was at risk for dislocation in non-contained defects, a collagen membrane (Bio Gide®Perio; Geistlich, Wolhusen, Switzerland) was applied without pin or suture fixation. Enamel matrix derivative (EMD, Emdogain®; Straumann, Basel, Switzerland) was applied as an adjunct to the root surface after debridement for contained defects. In some cases, a periosteal fenestration at the base of the flap was used to facilitate coronal repositioning of the soft tissue. Suturing techniques using non-resorbable 6–0 and 7–0 monofilament sutures (e-PTFE, W.L. Gore, Phoenix, AZ) included internal offset vertical mattress suture, interrupted single suture, double sling suture, or a combination of these. Primary closure of the surgical site was confirmed with magnification (3.5- to 4.4-fold) at the end of surgery. In all centres, one single experienced periodontal surgeon performed all procedures (Karin Jepsen, Christina Tietmann, Daniele Cardaropoli, Ignacio Sanz Sanchez).

A stringent anti-infective regimen was enforced post operation, including the use of a chlorhexidine mouth rinse (0.2%) three times daily for the first 4 weeks. Pain control consisted of 600 mg ibuprofen or 500 mg paracetamol; patients were instructed to take one tablet at the end of the procedure and one 6 h later, and to continue as needed in case of pain. Antibiotics were prescribed at the discretion of the surgeon. After 10–14 days, sutures were removed. Regular tooth brushing was resumed 4 weeks post surgery.

2.2.2 | Orthodontic therapy

For each subject individual, the treatment objectives were defined and visualized with manual or virtual set-ups. Prior to periodontal therapy, passive fixed appliances were inserted for stabilization in cases of increased tooth mobility (>grade 1). Initiation of active OT

was commenced at 4 weeks (early) or 6 months (late) after periodontal surgery according to randomization, involving fixed orthodontic appliances and individualized segmented arch mechanics. Maximum emphasis was on applying low forces and moments. Bone-borne temporary anchorage devices, splints, as well as trans-palatal and lingual arches served for anchorage reinforcement. After the pre-defined tooth positions were accomplished, orthodontic appliances were removed and teeth were stabilized with a combination of splints for the night and bonded retainers or fibre-reinforced restorations.

2.2.3 | Supportive periodontal therapy

Following periodontal surgery, recall visits were scheduled at 2 days, 2 weeks, and 4 weeks; thereafter, all subjects received regular supportive care every 2 months for the whole duration of the study. In case of recurrence of signs of inflammation, OT would be discontinued until controlled by gentle professional tooth cleaning and oral hygiene reinforcement.

2.3 | Outcomes

The primary outcome measure was the change in clinical attachment level (CAL) on the pre-determined tooth site (target site) after 12 months. During surgery, the tooth site with the most advanced bone loss (cemento-enamel junction [CEJ] to bottom of the defect) was determined and became the target site. Secondary outcomes were probing pocket depth (PPD), recession (REC), bleeding on probing (BOP), suppuration, pocket closure (PPD ≤4 mm; PPD ≤4 mm; no BOP), wound-healing, and patient-reported outcomes with respect to pain.

Prior to initiation of the study, all investigators participated in a calibration meeting. Intra-examiner agreement level for CAL/PPD within 1 mm (±1 mm) was set at 97%.

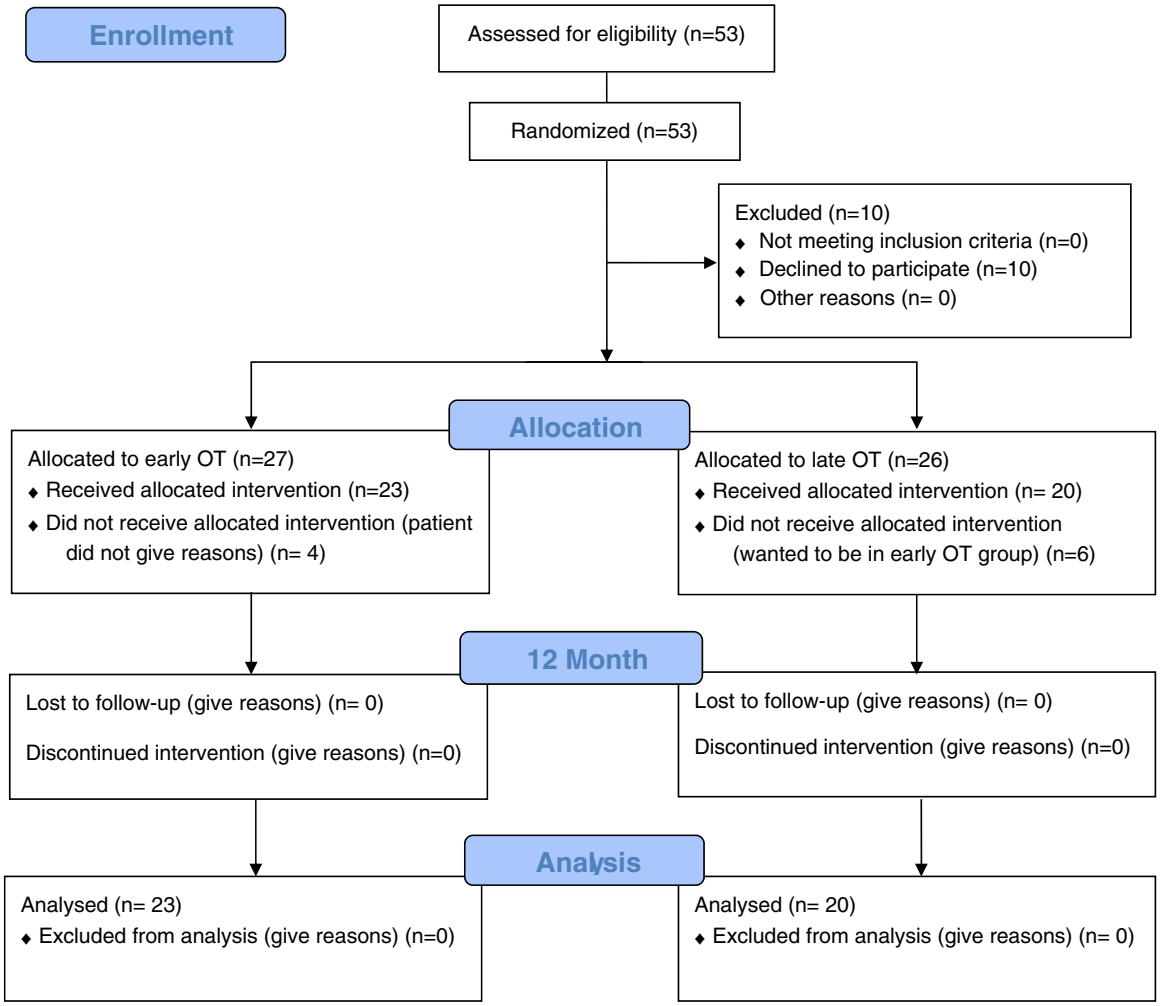

FIGURE 2 Study flowchart following CONSORT guidelines for clinical trials. Fifty-three patients met the inclusion criteria, and 26 patients were allocated to the group with late orthodontic therapy (OT) after regenerative periodontal surgery and 27 to the group with early OT after regenerative periodontal surgery. Ten patients withdrew from the study: six expected to be part of the early and withdrew after allocation to the late treatment group, and four (allocated to the test group) did not want to continue the study without giving any reason

2.3.1 | Clinical measurements

Three to six months after completion of steps 1, 2, and 3 (except for study regions) of periodontal therapy, baseline clinical parameters were recorded. All measurements were repeated 6 and 12 months after regenerative periodontal surgery (Figure 1).

The measurements of CAL and PPD were obtained with a pressure-sensitive probe (Click-Probe, Kerr, Switzerland; or Florida Probe, Gainesville, FL) to the nearest millimetre at six sites per tooth. BOP and suppuration were assessed dichotomously (as present or absent); BOP was positive if it occurred within 15 s after periodontal probing. Bleeding scores were recorded at six sites (mesio-buccal, buccal, disto-buccal and mesio-oral, oral, and disto-oral). FMBS were then calculated. FMPS were recorded at four sites (mesial, buccal, distal, and oral) of each tooth present and calculated as the percentage of the total surfaces exhibiting plaque (O'Leary et al., 1972).

2.3.2 | Clinical characterization of intra-bony defects during surgery

Using intra-operative exploration, defects were described as one-, two- and three-wall defects (Papapanou & Tonetti, 2000). The distance from the CEJ to the bottom of the defect was measured, and the depth of the intra-bony component was recorded as the distance between the marginal bone crest and the deepest location of the osseous defect.

The site with the most advanced bone loss, as measured from CEJ to the bottom of the defect, was determined and became the target site.

2.3.3 | Assessment of wound-healing and pain

Complete flap closure of the surgical site was confirmed with magnification at the end of surgery and then re-evaluated at the 2- and 4-week follow-up appointment. The presence of any dehiscence in the soft tissues was noted. Local adverse events such as hematoma, oedema, or signs of inflammation at the treated site were recorded. Patient perceptions of pain were rated using a 100-mm visual analogue scale (VAS) in a questionnaire given to the patient.

2.4 | Sample size

2.4.1 | Sample size calculation

The calculation of the number of patients to be treated was based on the primary objective of detecting a true mean difference of at least 1 mm difference in CAL change after 12 months between both groups (early vs. late). Assuming a standard deviation of 1.71 mm for the CAL change (Ghezzi et al., 2013), the intended sample size of 20 patients per treatment group was calculated to be sufficient to detect the established CAL difference between groups with a power of 80%.

2.5 | Randomization and blinding

Study registration and treatment assignment procedures were done by the clinical research centre at the University Bonn, Germany. Subjects were randomized to early or late OT based on computer-generated random codes using random permuted blocks. Allocation was concealed to the surgeon by sealed opaque envelopes. The calibrated examiner in each centre was blinded to the treatment assignment. Study nurses administering questionnaires were masked with respect to treatment allocation.

2.6 | Statistical analysis

Computerized chairside data entry into a periodontal electronic database (Parostatus, Berlin, Germany or Florida Probe database) allowed export via Excel into the statistical software program. Descriptive statistics were summarized as means and standard deviations for quantitative data and frequencies and percentages for qualitative data. Means for each treatment group and differences between treatment groups were presented, along with the associated 95% confidence intervals as well as *p*-values for differences within treatment groups. The primary comparison of CAL change after 12 months between treatment groups was based on a two-sided (95% confidence limits) two-sample *t*-test, at the 5% level of significance.

TABLE 1 Patient, tooth, and defect characteristics at baseline

	Early OT, $n = 23$	Late OT, $n = 20$
Age (years)	45.4 ± 11.9	52.0 ± 9.4
Gender (female/male)	17/6	9/11
Smoking status		
Current (<5 cigarettes)	3	3
Former	1	0
Never	19	17
FMPS	12.9 ± 4.9	15.2 ± 6.2
FMBS	10.5 ± 4.8	12.7 ± 6.9
Tooth		
Incisor/canine/premolar	21/2/0	13/6/1
PPD (mm)	7.3 ± 1.6	7.1 ± 1.7
CAL (mm)	9.8 ± 2.5	9.2 ± 2.5
Defect characteristics		
CEJ–bottom of defect (mm)	11.2 ± 2.6	10.0 ± 3.5
Depth intra-bony component (mm)	5.9 ± 2.7	5.2 ± 1.8
Three walls	11	13
Two to three walls	6	4
Two walls	6	3

Abbreviations: CAL, clinical attachment level; CEJ, cemento-enamel junction; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; OT, orthodontic treatment; PPD, probing pocket depth.

The effect of centres on the primary outcome was checked with a two-factorial analysis of variance for the factor treatment and centre including treatment by centre interaction. Since no evidence for interaction was found, the centre-controlled treatment effect was estimated from a second model, dropping the interaction term.

Statistical analysis of the clinical data was performed by an independent biostatistician (Rolf Fimmers) using the software SAS version 9.2 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Patient and defect characteristics

Between July 2016 and July 2019, a total of 53 patients were consecutively recruited and screened at the four study centres (7–26 per centre). All screened and potentially to be included subjects had received steps 1, 2, and 3 (except for study regions) of periodontal therapy (Sanz et al., 2020). Following the screening visit 3–6 months after therapy,

FIGURE 3 A 25-year-old patient diagnosed with periodontitis stage IV with pathological tooth migration (spacing and flaring). (a) Clinical situation after steps 1 and 2 of periodontal therapy, flaring teeth 12, 11 and 21, 22 with advanced attachment loss, labially displaced and elongated. Target site 21b, with CAL = 7 mm and PPD = 7 mm. (b) Regenerative surgical procedure for an intra-bony two-wall defect, 6 mm deep; follow-up 1 week and 2 weeks. (c) Clinical situation 12 months after regenerative surgery (early OT group): Target site 21b, with CAL = 2 mm and PPD = 3 mm. (d) Radiographic situation at baseline (left) and 12 months after (right) regenerative surgery

subjects were included in the study if the inclusion/exclusion criteria were met. A total 10 patients withdrew from the study: 6 expected to be part of the early treatment group and withdrew after allocation to the late treatment group, and 4 dropped out without giving any reason. After surgery, 43 patients remained in the study (early = 23; late = 20). The 12-month follow-up was completed by July 2020. A study flowchart is presented in Figure 2. Baseline patient and defect characteristics showed to be well balanced for the two study groups and are displayed in Table 1. All 43 patients had been diagnosed with periodontitis stage IV and—based on a calculation of percent bone loss/age at baseline—with grade C, except for 6 patients with grade B (2 in early and 4 in late OT). A combination therapy of EMD + DBBM was used in 35 defects (17 in early and 18 in late OT), and a combination of collagen membrane and DBBM in 4 defects (2 in early and 2 I late OT); 4 defects in the early OT group received EMD alone because these patients had not consented to the application of a bovine-derived graft. A representative example of a treated patient included in the present analysis is displayed in Figure 3 and in Figure S1.

3.2 | Outcomes

The analysis for the primary outcome—namely CAL change after 12 months—revealed a difference in CAL gain of 0.89 mm (95% confidence interval: [−0.36 to 2.15], $p = .159$) in favour of the early treatment group, formally not rejecting the null hypothesis of no difference in treatment effects between both groups (Table 2).

Clinical findings at baseline and at 6 and 12 months after regenerative surgery are presented as group means for the target sites (Table 3). Both groups were well balanced at baseline with regard to CAL and PPD and showed statistically significant improved outcomes after 12 months ($p < .0001$). After 12 months, in groups with early and with late initiation of OT, the percentage of target sites showing pocket closure (PPD ≤ 4 mm) was similar (91% vs. 85%). Pocket closure in combination with the absence of BOP was seen in 69% of the target sites in the group with early OT compared to 75% in the group with late OT (Table 3).

Low baseline FMPS of 12.9 ± 4.9% versus 15.2 ± 6.2% (early vs. late) were well maintained over the study period with values of 15.0 ± 5.8% versus 15.0 ± 7.0% at 6 months and 16.9 ± 10.1% versus 17.0 ± 8.6% at 12 months. These scores were accompanied by low FMBS of 10.5 ± 4.8% versus 12.7 ± 6.8% at baseline, 10.6 ± 4.9% versus 7.7 ± 4.9% at 6 months, and 14.7 ± 13.1% versus 11.3 ± 9.1% at 12 months.

Surgeries and post-operative sequelae were uneventful, and no patient in any group developed major complications. Patient perceptions after surgery and wound-healing scores were very similar in both

TABLE 2 Changes in clinical parameters clinical attachment level (CAL) and probing pocket depth (PPD) compared to baseline at 6 and 12 months (mean ± standard deviation [SD]) for target sites in early and late treatment group and differences between both groups in CAL change after 12 months (primary outcome)

		Early OT $n = 23$, BL—6 months	BL—12 months	Late OT $n = 20$, BL—6 months	BL—12 months	Early versus late OT, Δchange BL—12 months	
ΔCAL (mean ± SD)	mm	4.69 ± 1.7	5.39 ± 2.2	4.05 ± 2.0	4.45 ± 1.7	0.89	$p = .16$
Estimate	95% CI	5.4–3.9	6.3–4.4	4.9–3.1	5.3–3.6	2.2 to −0.3	
ΔPPD (mean ± SD)	mm	4.34 ± 1.7	4.21 ± 1.9	3.80 ± 1.3	3.90 ± 1.5	0.31	$p = .51$
Estimate	95% CI	5.1–3.6	5.0–3.4	4.4–3.2	4.6–3.2	1.3 to −0.6	

Abbreviations: BL, baseline; CI, confidence interval; OT, orthodontic treatment.

TABLE 3 Clinical parameters (mean ± standard deviation [SD]) for target sites in early and late orthodontic treatment (OT) group at baseline, 6 months, and 12 months

Variable		Early OT baseline	$n = 23$, 6 months	12 months	BL versus 12 months	Late OT baseline	$n = 20$, 6 months	12 months	BL versus 12 months
CAL (mean ± SD)	mm	9.8 ± 2.5	5.1 ± 1.9	4.4 ± 1.7	$p < .0001$	9.2 ± 2.5	5.1 ± 2.1	4.7 ± 2.4	$p < .0001$
Estimate	95% CI	8.8– 10.9	4.3–5.9	3.7–5.2		8.0–10.4	4.1–6.1	3.6–5.8	
PPD (mean ± SD)	mm	7.3 ± 1.6	3.0 ± 0.9	3.1 ± 0.9	$p < .0001$	7.1 ± 1.7	3.2 ± 0.9	3.2 ± 1.1	$p < .0001$
Estimate	95% CI	6.6–8.0	2.6–3.4	2.7–3.5		6.3–7.9	2.7–3.6	2.7–3.7	
Plaque (+)	*n* (%)	4 (17%)	3 (13%)	3 (13%)		1 (5%)	1 (5%)	2 (10%)	
BOP (+)	*n* (%)	13 (53%)	6 (26%)	7 (30%)		9 (45%)	4 (20%)	3 (15%)	
PUS (+)	n (%)	1	0	0		2	0	0	
Pocket closure (PPD ≤ 4 mm)	*n* (%)	n/a	22 (95%)	21 (91%)		n/a	17 (85%)	17 (85%)	
Pocket closure (PPD ≤ 4 mm, no BOP)	*n* (%)	n/a	16 (69%)	16 (69%)		n/a	15 (75%)	15 (75%)	

Abbreviations: BL, baseline; BOP, bleeding on probing; CAL, clinical attachment level; CI, confidence interval; PPD, probing pocket depth; PUS, suppuration.

groups. Two weeks after surgery, 7/23 patients (early OT) and 6/20 patients (late OT) reported having experienced some pain (VAS ranges: 4–49, 9–50). None of the patients presented with signs of swelling or complications at the second and fourth week visit. At these time points, primary closure was noted in 21/23 defects of the early OT group, with 2 defects showing a slight dehiscence. All defects in the late OT group healed with primary closure. No patients showed recurrence of signs of inflammation.

A subsequent additional analysis with the intention to assess possible effects due to the centre revealed a significant difference of CAL change between centres ($p = .030$), without evidence for a treatment–centre interaction ($p = .635$). An estimation of the treatment effect controlling for centres revealed a difference in CAL change after 12 months of 1.30 mm ([0.12–2.47], $p = .032$) between the groups in favour of the early treatment group (Figure S2).

4 | DISCUSSION

The present multicentre, randomized trial was designed to test the hypothesis that one protocol for a combined perio-regenerative/OT (early or late OT after regenerative surgery) would be superior to the other. Our results did not provide evidence for superiority of one over the other treatment approach with regard to the primary outcome of CAL after 12 months. Even though in the group with early OT, on average, 0.9 mm more CAL gain was observed, this difference failed to reach statistical significance. Both treatment modalities led to significant periodontal improvements, as demonstrated by mean CAL gains of 5.4 and 4.5 mm, respectively, as well as pocket closure (PPD ≤ 4 mm) in the vast majority of the treated defects. An additional analysis, taking any centre effect into account, pointed to a significant advantage of early OT. Taken together, these findings show for the first time in a large randomized trial that in the interdisciplinary treatment of periodontitis stage IV with PTM and IDs, OT can be initiated already 4 weeks after regenerative surgery with favourable results, thus reducing the overall treatment time for the patients.

The question addressed in this study is of high relevance for clinicians and for patients, as, so far, the available information to guide the decision making on the treatment of stage IV periodontitis patients in need of OT is scarce (Martin et al., 2021). Based on the outcomes of the present study, the clinician together with the patient can select the treatment protocol that will best suit the individual needs of the patient. The selected study design—a randomized trial—is the only way to answer the study question. The trial was based on an adequate sample size calculation and had sufficient statistical power. The multicentre approach enabled recruitment of sufficient suitable participants in a reasonable period of time and, together with the multi-national distribution of the centers, added to the generalizability of our findings. Both patient groups were well matched with regard to their baseline characteristics. Furthermore, all patients were treated by experienced, calibrated, and blinded surgeons and examined by experienced, calibrated, and blinded assessors using pressure-sensitive periodontal probes. Importantly, the study was conducted independently of industry and employed a variety of biomaterials from different manufacturers. The selection of these biomaterials was well justified based on the recommendations of a recent clinical guideline workshop for the regenerative treatment of IDs (Nibali et al., 2020; Sanz et al., 2020). That in most defects a combination approach of either DBBM + EMD or DBMM + collagen membrane was used is supported by current evidence that such combination therapies yield the most favourable results (Stavropoulos et al., 2020; Tsai et al., 2020). Finally, the data analysis was conducted by an independent expert statistician who was not involved in the clinical phases of the trial.

Interestingly, the direction and magnitude of the between-group effect (favouring early vs. late OT) on the primary outcome was very similar in three of the four centers, whereas no obvious differences were observed in one center. The size of the within-group treatment effect in the four centers could have been affected by the respective patient, by the case/defect selection, and also by slight variations in treatment, such as directions of tooth movements and others.

However, the present study has also some limitations, which are inherent to the study design. It was not possible to blind the examiners for the 6 months' evaluation because at this time point one group of patients (early OT) presented with orthodontic appliances, whereas the other (late OT) group did not. Likewise, a blinding of the orthodontists was not always possible. Furthermore, probing measurements at all six tooth sites were sometimes impaired by the orthodontic appliances. The use of a stent with grooves for guiding the probe at the "target sites" was not possible, because teeth would change their position over time. This also precluded the use of reproducible radiographs for the analysis of radiographic bone changes. Altogether, these limitations illustrate the challenges faced during the design and conduct of studies on combined perio-regenerative-orthodontic therapies.

Because of the differences in study protocols with regard to patient and defect selection, regenerative procedures, choice of outcome measures, intervals between periodontal and OT, and lengths of follow-up, the present results cannot be easily compared with those of previously published studies. Only one earlier study has evaluated in a comparative non-randomized fashion the effectiveness of different time points of initiating active orthodontic tooth movement on the regenerative potential of IDs (Attia et al., 2012a). Using a split-mouth design, the authors compared in 15 patients with malocclusion, each contributing three IDs, three protocols: regenerative therapy with bioactive glass and a collagen membrane followed by (1) immediate OT, (2) OT starting after 2 months, and (3) no OT. In defects treated according to modality (1) CAL gains of 5.1 ± 1.4 mm and PPD reductions of 4.0 ± 0.8 mm were found after 12 months as compared to 4.3 ± 0.6 mm and 3.7 ± 0.9 mm in group 2. However, these differences between immediate and delayed OT were not statistically significant. Owing to lack of a sample size calculation, no randomization, and information on treatment allocation and blinding, the study has obviously a high risk of bias as judged by current standards. Still, the authors are to be commended to have addressed the question of

timing and early orthodontic treatment for the first time. It is of interest to note that their results are comparable in magnitude with the outcomes of the present large multicentre trial. With regard to the primary outcome, that is, CAL change after 12 months, the mean CAL gains after early and late OT obtained in our study amounted to 5.4 and 4.5 mm, respectively. Previous studies had reported mean values of 5.8 mm (Ghezzi et al., 2008), 4.4 mm (Ghezzi et al., 2013), 3.7 mm (Ogihara & Wang, 2010), and 3.1 mm (Attia et al., 2019). As indicated above, there is an ongoing debate whether the application of orthodontic forces during the healing after regenerative surgery may be detrimental or rather beneficial for the periodontal outcomes.

In order to put the magnitude of CAL gains into perspective, a comparison with reported CAL changes following regenerative procedures in IDs in stage III periodontitis are of interest. Here, in a recent systematic review which included 79 RCTs and various regenerative techniques, CAL gains between 1.3 and 4.8 mm were reported (Nibali et al., 2020). Thus, the measured CAL gains in the present study following combined perio-regenerative/orthodontic treatment are on the higher end of the scale. This can be due to differences in initial defect selection and in particular baseline defect morphology in the different studies, as shown by Nibali et al. (2021). However, this comparison may also indicate an enhancement of healing due to the applied biomechanical forces and the resulting occlusal equilibration when regenerative procedures are combined with OT.

Up to now, only one RCT has compared regenerative surgery without or with "limited" orthodontics after 4 weeks (Ogihara & Wang, 2010). The authors assessed periodontal outcomes after the application of slight extrusive forces 4 weeks after regenerative surgery of IDs mainly in molar teeth. At 12 months, no significant differences in CAL gains and PPD reduction could be found between the groups. Data of the 6-month follow-up from the present randomized multicentre trial also allowed a direct comparison between the clinical healing of IDs with or without the influence of OT. The CAL gain after 6 months in the early OT group (under the influence of 5 months of active orthodontic tooth movement) amounted to 4.7 mm, whereas in the late OT group (no orthodontic tooth movement), 4.1 mm of CAL gain was obtained. Even though the present RCT was not primarily designed for this comparison because the predetermined study end point was at 12 months, these observations can be cautiously interpreted as OT having no detrimental but perhaps a slight beneficial effect on the periodontal outcome after 6 months.

These findings are in line with indirect evidence that was put forward and discussed in a previous publication (Tietmann et al., 2021). The authors compared data from two independent retrospective cohort studies; in both of them patients with IDs with similar baseline characteristics with regard to mean bone level and PPD were treated in the same practice with the same protocol, including the regenerative surgical procedure, outcome measures, and follow-up. In one of the cohorts, there was no need for orthodontic tooth movement (Bröseler et al., 2017), whereas in the other cohort the necessary OT was initiated 3 months after regenerative surgery (Tietmann et al., 2021). Within all limitations of such an indirect comparison using a "historical control group", it was interesting to observe that the improvements with regard to mean radiographic bone level gain in the cohort with combined perio/orthodontic therapy were higher (4.6 mm) than in the cohort, where patients did not undergo OT (3.9 mm). Even though in these studies the mean radiographic bone level gain was the primary outcome as compared to the CAL gain in the present RCT, the magnitude of differences in outcome between groups with and without OT was quite similar. Moreover, in the cohort studies (Bröseler et al., 2017; Tietmann et al., 2021) the selection of biomaterials was very similar to that in the present RCT.

Taken together, these findings seem to indicate a possible "stimulating" effect of orthodontic tooth movement in the early healing phase on the regenerative outcomes, as previously suggested (Vardimon et al., 2001; Diedrich et al., 2003; Nemcovsky et al., 2004; Attia et al., 2012b). However, as stated above, these observations should be interpreted with great caution. Further well-controlled, pre-clinical experiments are needed to elucidate the effects of mechanical loading on the early and late healing events after regenerative procedures.

With regard to secondary outcomes, the mean PPD reduction we observed following early and late OT of 4.2 and 3.9 mm, respectively, are in agreement with the mean PPD reduction ranging from 3.2 to 5.5 mm in previous studies (Ghezzi et al., 2008; Ogihara & Wang, 2010; Attia et al., 2012a; Ghezzi et al., 2013; Roccuzzo et al., 2018). The frequency of pocket closure (PPD ≤ 4 mm) in the present study was 91% and 85%, respectively. These values compare well to the 84% observed by Tietmann et al. (2021) and are also in agreement with a reported frequency of 17% of pockets with residual PPD >4 mm after 10 years, by Roccuzzo et al. (2018).

According to a recently published commentary, the lack of an accurate "gold standard", a research-based moment for initiating orthodontic tooth movement after periodontal therapy, would demonstrate that a "grey zone" of evidence remains and knowledge on periodontal wound-healing dynamics may be considered the best "biologic starting point" of orthodontic treatment for treated periodontitis patients (Pini Prato & Chambrone, 2020). The authors proposed a personalized periodontal algorithm and postulated that OT should be initiated 1 year after regenerative treatment. In view of the present new evidence, such a cautious approach should be revisited. OT may be initiated much earlier with no detrimental effects on the healing outcomes and with the prospect of a shortened overall treatment time for the patient.

5 | CONCLUSION

The findings of the present randomized trial have demonstrated that in stage IV periodontitis, teeth with IDs and in need of orthodontic tooth movement, in patients who adhered well to regular SPT and maintained a high level of oral hygiene, OT can be initiated as early as 4 weeks after regenerative surgery with favourable periodontal outcomes that are at least as good as those obtained after delayed OT.

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ETHICS STATEMENT

Ethical approval was obtained by the Ethical Committee, University of Bonn (code 034/16) for the centres Bonn and Aachen and by the competent local authorities for the centres Torino (code PROT 04-2017) and Madrid (code 16/492-E).

CONFLICT OF INTEREST

The authors declare no conflict of interest with regard to this study, that was partially funded by an Advanced Researcher Grant (15-249) of the Osteology Foundation to KJ and S.

AUTHOR CONTRIBUTIONS

Karin Jepsen and Søren Jepsen contributed to the conception and design of the study; Karin Jepsen, Christina Tietmann, Eric Kutschera, Peter Wüllenweber, Daniele Cardaropoli, Lorena Gaveglio, Ignacio Sanz Sanchez, and Conchita Martin contributed to the clinical phases of the study and collected the data; Rolf Fimmers contributed to the statistical analysis; Karin Jepsen and Søren Jepsen contributed to interpretation of the data and drafted and finalized the manuscript. All authors critically reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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