Effect of sub-mucosal instrumentation before surgical treatment of moderate/severe peri-implantitis: a multi-center randomized clinical trial

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Sessione Premio HM Goldman 2021 – H.M. Goldman Award 2021 – SIdP 20th International Congress

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Abstract *(English version)*

The present multi-center randomized clinical trial with 12-months follow-up aimed at studying the added effect of sub-mucosal instrumentation before surgical treatment of moderate/severe peri-implantitis.

Forty-two patients were recruited based on the diagnosis of moderate/severe peri-implantitis. After a behavioral intervention phase based on oral hygiene motivation and instructions, patients were randomized to either having supra- and sub-mucosal instrumentation on their affected implants (control group) or only supra-mucosal instrumentation (test group) before receiving surgery.

With the exception of a longer non-surgical treatment time in the control group ($p<0.001$), no other studied outcome demonstrated statistically significant differences between groups.

Smoking status, Vitamin D intake, bone levels and suppuration at baseline, peri-implant phenotype and presence of plaque negatively influenced PPD reduction, while a positive effect was noted for KMH ≥2 mm, deepest PPD at baseline, reason of tooth loss, implant brand and surgical approach.

The presence of suppuration at baseline and of more than 3 sites with a PPD≥6 mm in the mouth other than study implants resulted associated with lower rates of treatment success, while the presence of severe periodontitis and of KMH ≥2 mm were associated with higher rates.

The present findings question the value of non-surgical sub-mucosal instrumentation before surgical treatment of moderate/severe peri-implantitis.

Keywords: peri-implantitis; non-surgical treatment; clinical trial; disease resolution; prognosis.

Abstract *(versione italiana)*
L'obiettivo del presente studio clinico randomizzato multicentrico con follow-up di 12 mesi è stato quello di studiare l'effetto aggiuntivo della strumentazione sotto-mucosa prima del trattamento chirurgico della peri-implantite moderata/severa.
Sono stati inclusi 42 pazienti affetti da peri-implantite moderata/severa. Dopo una fase di intervento comportamentale comprendente istruzioni di igiene orale e prima di ricevere l'intervento chirurgico, i pazienti del gruppo di controllo sono stati sottoposti ad un'accurata strumentazione sopra- e sotto-mucosa degli impianti interessati, mentre i pazienti del gruppo test hanno ricevuto solo quella sopra-mucosa.
Ad eccezione di un tempo di trattamento non chirurgico più lungo nel gruppo di controllo ($p<0,001$), nessun outcome considerato ha mostrato differenze tra i due gruppi.
Il fumo di tabacco, l'assunzione di vitamina D, i livelli ossei e la presenza di suppurazione alla visita iniziale, il fenotipo e presenza di placca hanno influenzato negativamente la riduzione della PPD, mentre è stato osservato un effetto positivo per la presenza di una banda di tessuto cheratinizzato ≥2 mm, PPD più profonde alla visita iniziale, la ragione della perdita del dente, la marca dell'impianto e l'approccio chirurgico utilizzato.
La presenza di suppurazione alla visita iniziale e di più di 3 siti con PPD ≥6 mm in siti differenti dagli impianti di studio sono risultati associati a tassi di successo del trattamento inferiori, mentre la presenza di parodontite severa e di una banda di tessuto cheratinizzato ≥2 mm sono risultate associate a tassi più elevati di successo.
I risultati presentati mettono in dubbio il valore aggiunto della strumentazione sotto-mucosa prima del trattamento chirurgico nei casi di peri-implantite moderata/severa.

Introduction

Peri-implantitis represents an important health complication associated with implant dentistry, due to its high prevalence [1-4] and to its accelerating progression pattern, which may finally lead to the loss of the affected implant and of its restoration [5]. Its management is further complicated by the lack of a clear symptomatology [6] and by the scarce sensitivity of its diagnostic procedures [7,8], which often lead to its late identification when manifested in moderate/severe forms.

A stepwise treatment approach, mirroring the one used in periodontal therapy [9], is also usually employed in the management of peri-implantitis. After a behavioral intervention phase including instructions for self-performed biofilm removal, risk factors control and supra-mucosal instrumentation, the affected implants undergo through a non-surgical sub-mucosal instrumentation phase, generally performed after the removal of the restoration under local anesthesia, with the objective of decontaminating the affected implant surface and supra-structures. A clinical re-evaluation of the peri-implant tissues is then performed to determine whether the endpoints of therapy have been achieved (i.e., disease resolution) or a surgical phase is needed, before introducing the patient in a life-long supportive peri-implant care (SPIC).

In the management of periodontitis, this stepwise therapeutic approach is widely justified since sub-gingival instrumentation frequently achieves the pre-determined endpoints of therapy [10], thus reducing the need for periodontal surgery to a minority of selected advanced cases. However, in the case of peri-implantitis, disease resolution represents only seldom the outcome of sub-mucosal instrumentation [11-13], what makes the surgical therapy the gold standard approach in its moderate/severe forms. As a consequence, the sub-mucosal instrumentation phase has become more a preparatory phase towards surgery than a definite treatment procedure and hence some authors have questioned the validity of this therapeutic intervention. In fact, several studies have only employed a supra-mucosal instrumentation before the surgical treatment of peri-implantitis [14,15]. There is, therefore, a need for evidence demonstrating the added effect of sub-mucosal instrumentation before the surgical treatment of peri-implantitis, since this intermediary intervention involves longer treatment times, higher costs and increased discomfort for patients.

The present manuscript reports the 1-year outcomes from a multi-center randomized clinical trial designed to evaluate the added effect of the non-surgical sub-gingival instrumentation prior to the surgical treatment of moderate/severe peri-implantitis cases.

Materials and Methods

This manuscript is reported following the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [16]. The protocol of the study was registered in Clinicaltrials.gov (NCT03620331) and approved by

the respective ethical committees in each of the participating centers (Rome: Prot. n. 24/17; Madrid: 18/041-E; Turin: CS2/676). All the participants were informed in detail about the study aims and procedures, and provided a written informed consent before their inclusion in the trial.

Trial design

The present study was designed as a randomized, surgeons- outcome assessors- and statistician-blinded, multi-center, superiority trial with two parallel groups and with a 1:1 allocation ratio.

Participants

The following 3 centers equally contributed in providing participants between January 2018 and September 2019: 1) Section of Post-Graduate Periodontology, Faculty of Odontology, Complutense University (Madrid, Spain), 2) Department of Periodontology and Prosthodontics, "George Eastman" Dental Hospital, University Policlinic "Umberto I" (Rome, Italy) and 3) Section of Periodontology, C.I.R. Dental School, University of Turin (Turin, Italy).

Any patient having at least one implant affected by moderate/severe peri-implantitis, being at least 18 years old and able to sign an informed consent form was potentially eligible for this trial. Moderate/severe peri-implantitis was defined as the presence of a peri-implant probing pocket depth (PPD) ≥6 mm, bleeding and/or suppuration on probing (BoP and/or SoP) and radiographically documented marginal bone loss >3 mm on implants in function by at least 1 year [14]. In the absence of baseline radiographs, implants had to present a bone level >3 mm [8].

Primary exclusion criteria were: compromised general health, inability to attend the study-related procedures, pregnancy or lactation, chronic use of anti-inflammatory, immune-suppressive or affecting bone/mucosa drugs, previous peri-implantitis treatment, implant mobility.

Before their inclusion in the trial, all potentially eligible patients received oral hygiene instructions (OHI) and their restorations were corrected whenever needed. Periodontitis patients also received periodontal therapy on their residual dentition, without involving study implants. Smokers were motivated to limit and possibly quit smoking. Two weeks after completing this preparatory phase, only patients with a full-mouth plaque score <25% (secondary inclusion criteria) were finally included in the trial and consecutively assigned to an envelope for their random allocation to one of the following study groups:

- Control group (NS + S): supra- and sub-mucosal instrumentation, followed by surgical therapy 6 weeks after;
- Test group (S): supra-mucosal instrumentation only, followed by surgical therapy 2 weeks after.

Study groups specific interventions

An unblinded center-specific non-surgical operator (AL, GB, IP) performed in both groups (NS+S and S) a full-mouth supra-mucosal and supra-gingival instrumentation through the use of both ultrasonic and hand instruments, followed by the use of rubber cups and polishing paste. In the same appointment, only patients of the control group (NS+S) also received, under local anesthesia, a complete non-surgical submucosal instrumentation. In brief, after removing the screw-retained supra-constructions, overdentures and, when possible, cement-retained implant restorations, the study implants underwent through a deep sub-mucosal instrumentation by means of titanium curettes (Hu-Friedy, Chicago, USA) followed by three irrigations of the peri-implant pockets with 0.12% chlorhexidine (CHX) + 0.05% cetylpyridinium chloride (CPC) solution (DentAid, Barcelona, Spain) and the sub-mucosal application of the same active principles in gel formulation (DentAid, Barcelona, Spain), before reconnecting the removed restorations. Thereafter, implants of the control group (NS+S) received surgical therapy 6 weeks after supra- and sub-mucosal instrumentation, while the ones of the test group (S) received the surgical therapy 2 weeks after the supra-mucosal instrumentation.

Surgical therapy

Surgical interventions were carried out in both groups by operators blinded to the patient allocation, using the same surgical instruments (Hu-Friedy, Chicago, USA). The surgeons were left free to choose the most appropriate surgical approach (access, resective, regenerative, combination) according to the individual case characteristics. As a general rule, intra-bony circumferential defects were meant to be treated through regenerative surgery, by means of a bone substitute material (BioOss spongiosa granules, Geistlich AG, Wolhusen, Switzerland) and a resorbable membrane (BioGide Perio, Geistlich AG, Wolhusen, Switzerland). Supra-bony defects and non-circumferential intra-bony defects were meant to be treated by means of resective surgery with implantoplasty. Finally, combined defects were meant to be treated by means of a combined

approach. Decontamination of the implant surfaces always included at least the use of titanium curettes (Hu-Friedy, Chicago, USA). Flaps were sutured in order to allow for a non-submerged healing. Implant restorations were reconnected either just after the surgery or at the 2-weeks follow-up examination, according to the specific clinical situation. Post-operative care is reported in the Appendix.

Study outcomes and covariates

Details about collection and calibration methods of clinical, radiographic and exploratory outcomes, as well as of co-variates, are reported in detail in the Appendix. Briefly, clinical variables were collected by a center-specific outcome-assessor (MR, LP, FF), blinded to the patient allocation, at the following time-points: baseline, just before surgery, and at 6- and 12-months after surgery. The three outcome-assessors were calibrated before the start of the trial to apply the same examination criteria.

Digital standardized long cone intra-oral radiographs were obtained at baseline and at 2-weeks, 6- and 12-months after surgery. One previously calibrated and blinded investigator (CL) measured in each radiograph the marginal bone level from the implant shoulder to the first bone-implant contact, using a software program (Autocad 2016 TM, AutoDesk Inc.), following a well-established protocol [4,17]. Several covariates including demographic, medical and dental history data, as well as intra-oral variables were also collected to test them in prediction models.

Five different combinations of clinical and radiographic data were used as composite outcomes of therapy (treatment success). Probing pocket depth reduction with respect to baseline and treatment success criteria n.1 (no implant loss, no bone loss >0.5 mm, BoP/SoP- and PPD≤5 mm [14]) at the 12-months examination were regarded as the primary outcomes of the trial.

Sample size calculation

The sample size calculation was based on having 80% power to detect clinically relevant differences of 1.0 mm in the reduction of the deepest PPD (34 patients) and of 35% in treatment success criteria n.1 (number need to treat - NNT=3 – 42 patients) between groups at the 12-months follow-up examination, using two-sided hypothesis tests and critical levels of significance of 0.05. It was assumed that the standard deviation (SD) of PPD reduction in each group was the same and equal to 1.0 mm. A total sample size of 42 participants (21 in each treatment arm), 14 for each center, was then required.

Randomization and blinding procedures

Randomization and blinding procedures are reported in detail in the Appendix. Briefly, a random permuted blocks randomization list stratified by study center with a 1:1 allocation ratio was generated by an independent researcher. Notes with the assigned randomized group (blinded: A or B) were enclosed in sequentially numbered, identical, opaque and sealed envelopes.

The outcome assessors were blinded, as well as the surgeons, the investigators involved in the selection and inclusion of the patients, and the statistician. Due to the nature of the interventions, neither patients nor the center non-surgical treatment operator could be blinded to allocation, but they were strongly inculcated to not disclose the allocation status at the surgical appointment and at follow-up assessments.

Data analysis

Data analysis was performed by a blinded statistician using STATA version 13.1 software (StataCorp LLC, Texas, USA) and applying the intention-to-treat principle.

Descriptive key characteristics of the study participants and implants were summarized: continuous variables were expressed as mean (SD), while categorical ones as number (%).

Differences between groups were analyzed for implant-level variables through multilevel multivariate logistic (binary) or linear (continuous) regression analyses adjusting for clustering. More than 150 covariates (including center) were tested as possible confounders of the effect of the allocated group on the two primary outcomes. Possible interactions between the employed surgical approach (involving or not regenerative procedures) and all the primary/secondary implant-level outcomes were also tested, by adding interaction terms in the multilevel analyses. Patient-level variables were compared between groups applying the $\chi 2$ test for binary variables and unpaired Student t-test for continuous ones. Comparisons between groups were carried out using 2-sided hypothesis and an alpha <0.05 level of significance. Treatment times variables, which were expected to be possibly indicative of group allocation, were analyzed at the end of data analysis in order to preserve the statistician blinding.

All the collected covariates were also tested as possible predictors of the two primary outcomes, through multilevel multivariate logistic/linear regression analyses. Due to the paucity of data in the literature, an

exploratory approach was employed [17]. Each potential predictor was tested individually by adding it to an empty model having as dependent variable the studied primary outcome. All variables that were significant at the 0.10 level were included in an intermediate multilevel multivariate model, and non-significant variables were then sequentially removed. On that model which included all factors that remained significant ($p < 0.05$), the non-significant indicators were tested again and the significant ones ($p<0.05$) were retained in the final model.

Results

After screening 90 patients for eligibility, 42 of them (53 implants) were included in the trial, 21 in each of the treatment groups (study flowchart reported in the Appendix). The study population consisted mainly of female patients (26 - 61.9%), and had a mean age at baseline of 61.36 (± 12.27) years (Table 1).

Table 1. General characteristics of the study patients (N=42) and implants (N=53).

Patient-level characteristics	**Overall** (N=42)	**Control group (NS+S)** (N=21)	**Test group (S)** (N=21)
Age (years), mean (±SD)	61.36 (±12.27)	63.62 (±11.14)	59.10 (±13.18)
Gender, N (%)			
Male	16 (38.10)	7 (33.33)	9 (42.86)
Female	26 (61.90)	14 (66.67)	12 (57.14)
Smoking Status, N (%)			
Non-smokers	20 (47.62)	12 (57.14)	8 (38.10)
Former smokers	15 (35.71)	8 (38.10)	7 (33.33)
Current smokers	7 (16.67)	1 (4.76)	6 (28.57)
Diabetes Status, N (%)			
No diabetes	38 (90.48)	19 (90.48)	19 (90.48)
Diabetes	4 (9.52)	2 (9.52)	2 (9.52)
Periodontal Status (AAP), N (%)			
No/Mild/Moderate Periodontitis	9 (21.43)	5 (23.81)	4 (19.05)
Severe Periodontitis	28 (66.67)	14 (66.67)	14 (66.67)
Edentulous	5 (11.90)	2 (9.52)	3 (14.29)
Implant-level characteristics	**Overall** (N=53)	**Control group (NS+S)** (N=29)	**Test group (S)** (N=24)
Jaw, N (%)			
Maxilla	28 (52.83)	14 (48.28)	14 (58.33)
Mandible	25 (47.17)	15 (51.72)	10 (41.67)
Location, N (%)			
Anterior (incisors/canines)	11 (20.75)	7 (24.14)	4 (16.67)
Posterior (premolars/molars)	42 (79.25)	22 (75.86)	20 (83.33)
Implant Brand, N (%)			
N	18 (33.96)	11 (37.93)	7 (29.17)

S	17 (32.08)	11 (37.93)	6 (25.00)
Other	9 (16.98)	3 (10.34)	6 (25.00)
Unknown	9 (16.98)	4 (13.79)	5 (20.83)
Implant Surface, N (%)			
Non-modified	2 (3.77)	0 (0.00)	2 (8.33)
Modified	42 (79.25)	25 (86.21)	17 (70.83)
Unknown	9 (16.98)	4 (13.79)	5 (20.83)
Function time (years), mean (SD)	8.32 (±4.05)	8.09 (±3.91)	8.60 (±4.28)
Surgical Approach, N (%)			
Resective	17 (32.08)	12 (41.38)	5 (20.83)
Combined (resective+regenerative)	15 (28.30)	7 (24.14)	8 (33.33)
Regenerative	18 (33.96)	8 (27.59)	10 (41.67)
Open flap debridement	3 (5.66)	2 (6.90)	1 (4.17)

Footnote:
NS, non-surgical; S, surgical; N, number; SD, standard deviation; %, percentage. Implant brands: S, Straumann; N, Nobel Biocare; Other included the following brands: Euroteknica, Sweden & Martina, Astra, Biomet 3i and Prodent.

All patients received the allocated interventions (including surgery), without protocol deviations. In one patient from the test group one implant was removed during the surgical intervention due to implant fracture. All patients attended the 2-weeks examination, but one patient from the control group did not attend both the 6- and 12-months examinations.

Clinical and radiographic outcomes

Table 2 reports the clinical and radiographic outcomes of the included implants, revealing that no statistically significant differences were found in any outcome measurement when comparing the treatment groups. When testing the role of the employed surgical approach (involving or not regenerative procedures) as possible effect modifier, there was no interaction observed.

Table 2. Clinical and radiographic outcomes of the included implants.

	Overall (N=53)	**Control group (NS+S)** (N=29)	**Test group (S)** (N=24)
PPD (deepest) changes (mm), mean (±SD)			
Baseline - Surgery	-0.19 (±1.60)	0.19 (±1.93)	-0.27 (±1.07)
Baseline – 6m	-3.13 (±1.75)	-2.98 (±1.77)	-3.30 (±1.74)
Baseline – 1y	-3.03 (±1.96)	-2.96 (±1.85)	-3.11 (±2.12)
Soft-tissue dehiscence (highest increase) (mm), mean (±SD)			
Baseline - Surgery	0.68 (±1.06)	0.91 (±1.21)	0.40 (±0.77)
Baseline – 6m	1.84 (±1.48)	2.02 (±1.60)	1.63 (±1.33)
Baseline – 1y	1.92 (±1.72)	2.30 (±1.94)	1.48 (±1.31)
Soft-tissue dehiscence>1 mm (highest increase), N (%)			

Baseline - Surgery	10 (18.87)	8 (27.59)	2 (8.33)
Baseline – 6m	29 (56.86)	16 (57.14)	13 (56.52)
Baseline – 1y	29 (58.00)	16 (59.26)	13 (56.52)
KMH* (lowest) changes (mm), mean (±SD)			
Baseline - Surgery	0.06 (±0.86)	0.05 (±0.97)	0.06 (±0.73)
Baseline – 6m	-0.37 (±1.49)	-0.32 (±1.49)	-0.43 (±1.53)
Baseline – 1y	-0.33 (±1.44)	-0.33 (±1.43)	-0.33 (±1.49)
BoP+, N (%)			
Surgery	50 (94.34)	27 (93.10)	23 (95.83)
6 m	44 (86.27)	24 (85.71)	20 (86.96)
1 y	33 (66.00)	20 (74.07)	13 (56.52)
SoP+, N (%)			
Surgery	16 (30.19)	5 (17.24)	11 (45.83)
6 m	1 (1.96)	0 (0.00)	1 (4.35)
1 y	5 (10.00)	3 (11.11)	2 (8.70)
Peri-implant mucosa inflammation (BoP+ or SoP+), N (%)			
Surgery	51 (96.23)	27 (93.10)	24 (100.0)
6 m	44 (86.27)	24 (85.71)	20 (86.96)
1 y	33 (66.00)	20 (74.07)	13 (56.52)
Profuse bleeding, N (%)			
1 y	10 (20.00)	6 (22.22)	4 (17.39)
Bone level changes (deepest) (mm), mean (±SD)			
Baseline** – 6m	-1.78 (±2.01)	-1.77 (±2.12)	-1.79 (±1.92)
Baseline** – 1y	-1.60 (±1.96)	-1.54 (±1.89)	-1.67 (±2.08)
Bone loss >0.5 mm (deepest), N (%)			
6 m	3 (6.00)	1 (3.57)	2 (9.09)
1 y	6 (12.00)	3 (11.11)	3 (13.04)
Bone gain >0.5 mm (deepest), N (%)			
6 m	31 (62.00)	15 (53.57)	16 (72.73)
1 y	30 (60.00)	16 (59.26)	14 (60.87)
Implant loss, N (%)			
6 m	1 (1.92)	0 (0.00)	1 (4.17)
1 y	2 (3.85)	1 (3.57)	1 (4.17)

Footnote:
NS, non-surgical; S, surgical; N, number; SD, standard deviation; VAS, visual analogue scale.
* P<0.05

Only minor changes in the deepest PPD were observed between baseline and surgery with both interventions. At the 12-months examination, a mean reduction of 3.03 (±1.96) mm in the deepest

PPD was observed, but no statistically significant differences were found between groups. No covariates showed a significant confounding effect on the lack of effect of treatment group allocation on PPD reduction at the 12-months examination.
Peri-implant mucosa inflammation at surgery was observed in 100.0% of the cases in the test group and in 93.1% of the control group. Indeed, two adjacent implants of the control group, from the same patient, showed no signs of BoP/SoP at surgery (implant n.1 with a PPD=7 mm; implant n.2 with a PPD=5 mm), but both underwent surgery. At the 12-months examination there was however a non-statistically significant higher mucosal inflammation in the control group than in the test group (74.1% vs. 56.5%). Profuse bleeding at the 12-months examination was present in 22.2% and 17.4% of the implants of the control and the test group, respectively.
A mean bone gain of 1.60 (±1.96) mm was observed between baseline and the 12-months examination, without statistically significant differences between groups. At this examination, 12.0% of the implants presented a bone loss >0.5 with respect to the baseline radiograph, while 60.0% of the implants presented a bone gain >0.5 mm.
Two implants (3.9%), one for each group, were lost in total during the entire 12-months observation period.

Treatment success
Table 3 reports the evaluation of treatment success according to the different combinations of variables. Depending on the used criteria, treatment success at the 12-months examination was observed between 26.9% and 59.6% of the cases, and differences between groups were not statistically significant. No interaction was observed when testing whether the used surgical approach could be an effect modifier.

Table 3. Treatment success in the included implants.

	Overall (N=53)	**Control group (NS+S)** (N=29)	**Test group (S)** (N=24)
Criteria n.1: **No implant loss, no bone loss >0.5 mm, BoP/SoP-, PPD≤5 mm**, N (%)			
6 m	6 (11.76)	4 (14.29)	2 (8.70)
1 y	14 (26.92)	6 (21.43)	8 (33.33)
Criteria n.2: **No implant loss, no bone loss >0.5 mm, BoP/SoP-**, N (%)			
6 m	6 (11.76)	4 (14.29)	2 (8.70)
1 y	14 (26.92)	6 (21.43)	8 (33.33)
Criteria n.3: **No implant loss, no bone loss >0.5 mm, no PPD≥5 with concomitant BoP/SoP+**, N (%)			
6 m	33 (64.71)	20 (71.43)	13 (56.52)
1 y	27 (51.92)	17 (60.71)	10 (41.67)
Criteria n.4: **No implant loss, no bone loss >0.5 mm, no profuse bleeding, no SoP**, N (%)			
1 y	31 (59.62)	15 (53.57)	16 (66.67)
Criteria n.5: **No implant loss, no bone loss >0.5 mm, no profuse bleeding, no SoP, PPD≤5 mm**, N (%)			
1 y	24 (46.15)	13 (46.43)	11 (45.83)

Footnote:
NS, non-surgical; S, surgical; N, number; SD, standard deviation; VAS, visual analogue scale.
* P<0.05

The treatment success criteria n.1 (no implant loss, no bone loss >0.5 mm, BoP/SoP- and PPD≤5 mm) was present at the 12-months examination in 26.9% of the implants, but differences between groups were not statistically significant (21.4% in the control and 33.3% in the test group). No tested covariates confounded the effect of treatment group allocation on this outcome.

Exploratory outcomes
Table 4 reports the results of the exploratory outcomes.

Table 4. Exploratory outcomes (patient-level).

	Overall (N=42)	**Control group (NS+S)** (N=21)	**Test group (S)** (N=21)
Early Wound Healing - VAS (mm), mean (±SD)			
2w	59.02 (±27.38)	56.52 (±27.57)	61.52 (±27.64)
Self-reported smile esthetics – VAS changes (mm), mean (±SD)			
Baseline - Surgery	3.61 (±19.78)	1.29 (±21.78)	5.95 (±17.77)
Baseline – 6m	-13.61 (±23.99)	-17.9 (±26.28)	-9.52 (±21.42)
Baseline – 1y	-19.05 (±29.28)	-23.35 (±29.43)	-14.95 (±29.24)
Treatment time (minutes), mean (±SD)			
Non-surgical appointment	17.33 (±11.79)	24.48 (±11.68) *	10.19 (±6.42) *
Surgery	84.55 (±30.92)	84.00 (±31.25)	85.10 (±31.35)
Total active treatment time	101.88 (±35.37)	108.48 (±34.38)	95.29 (±35.94)
Surgeon VAS (mm), mean (±SD)			
Surgery difficulty	52.36 (±29.50)	54.85 (±30.65)	49.86 (±28.85)
Intra-operative bleeding	51.74 (±30.90)	52.38 (±28.94)	51.10 (±33.44)
Adverse events – probably/possibly related with treatment allocation (other than implant loss), N (%)			
1y	9 (21.43)	5 (23.81)	4 (19.05)

Footnote:
NS, non-surgical; S, surgical; N, number; SD, standard deviation; VAS, visual analogue scale.
* p<0.001

There were no differences between groups in early wound healing at 2-weeks, in self-reported smile esthetics, surgery difficulty, intra-operative bleeding and adverse events. Among the adverse events, two implants in two patients, both in the test group and belonging to the same center, experienced acute re-infection during follow-up, making necessary a re-intervention (supra-gingival polishing in one patient, and surgical re-intervention in the second one). However, the rate of adverse events did not differ between groups (23.8% in the control group and 19.1% in the test group).

While the surgical and total active treatment times did not show statistically significant differences between groups, the net duration of the non-surgical appointment was higher in the control group than in the test group (24.48 ± 11.68 min – vs. 10.19 ± 6.42 min; p<0.001).

Predictors of PPD reduction

Table 5 reports the final multilevel multivariate linear regression model on the predictors of PPD reduction (deepest site) at the 12-months examination.

Table 5. Predictors of PPD changes: multilevel multivariate linear regression analysis.

	Final Model		
Variable	**MD**	**95% CI**	***p-value***
Smoking Status			
Non-Smoker	*Ref*	*Ref*	*Ref*
Former Smoker	0.28	-0.42 – 0.98	0.431
Current Smoker	-1.08	-1.86 – 0.30	0.007
Vitamin D intake			
No	*Ref*	*Ref*	*Ref*
Yes	-1.26	-2.20 – -0.33	0.008
SoP (baseline)			
No	*Ref*	*Ref*	*Ref*
Yes	-0.79	-1.39 – -0.18	0.010
KMH (baseline)			
<2 mm	*Ref*	*Ref*	*Ref*
≥2 mm	1.17	0.54 – 1.81	<0.001
Deepest PPD (baseline)	0.91	0.75 – 1.06	<0.001
Bone level (baseline)			
≤8 mm	*Ref*	*Ref*	*Ref*
>8 mm	-4.41	-6.52 – -2.30	<0.001
Phenotype (lingual, baseline)			
Thin	*Ref*	*Ref*	*Ref*
Thick	-2.47	-3.31 – -1.62	<0.001
Reason of Tooth Loss			
Caries	1.99	1.15 – 2.83	<0.001
Periodontitis	1.55	0.70 – 2.40	<0.001
Other reason	*Ref*	*Ref*	*Ref*
Unknown	0.91	-1.09 – 2.91	0.372
Implant Brand			
N	0.92	0.06 – 1.79	0.035
S	0.29	-0.62 – 1.19	0.536
Other	1.64	0.60 – 2.68	0.002
Unknown	*Ref*	*Ref*	*Ref*
Surgical Approach			
Resective	0.76	0.01 – 1.50	0.046
Combined (resective+regenerative)	0.98	0.33 – 1.63	0.003
Regenerative	*Ref*	*Ref*	*Ref*
Open flap debridement	1.20	-0.24 – 2.63	0.101
Plaque (1y)			
0 sites/implant	*Ref*	*Ref*	*Ref*

1-5 sites/implant	-0.38	-0.97 – 0.20	0.198
6 sites/implant	-1.55	-2.67 – -0.42	0.007

Footnote:
MD, mean difference; CI, confidence interval; Ref, reference category.
Implant brands: S, Straumann; N, Nobel Biocare; Other included the following brands: Euroteknica, Sweden & Martina, Astra, Biomet 3i and Prodent.

Smoking status (current smokers: mean difference - MD= -1.08 mm), Vitamin D intake (MD= -1.26 mm), presence of SoP at baseline (MD= -0.79 mm), bone levels at baseline (>8 mm: MD= -4.41 mm), lingual phenotype (thick: MD= -2.47 mm) and presence of plaque at 12-months examination (6/sites implant: MD= -1.55 mm) were associated with an inferior PPD reduction. On the contrary, KMH ≥2 mm at baseline (MD=1.17 mm), deepest PPD at baseline (for each mm increase: MD=0.91 mm), reason of tooth loss (caries: MD=1.99 mm; periodontitis: MD=1.55 mm), implant brand (Nobel Biocare: MD=0.92 mm; other: MD=1.64 mm) and surgical approach (resective: MD=0.76 mm; combined: MD=0.98 mm) were associated with a higher PPD reduction at the 12-months examination.

Predictors of treatment success criteria n.1

Table 6 reports the final multilevel multivariate logistic regression model on the predictors of treatment success criteria n. 1 (no implant loss, no bone loss >0.5 mm, BoP/SoP- and PPD≤5 mm) at the 12-months examination.

Table 6. Predictors of treatment success criteria n.1 (No implant loss, no bone loss >0.5 mm, BoP/SoP-, PPD≤5 mm): multilevel multivariate logistic regression analysis.

	Final Model		
Variable	**OR**	**95% CI**	***p-value***
SoP (baseline)			
No	*Ref*	*Ref*	*Ref*
Yes	0.05	0.00 – 0.56	0.016
KMH (1y)			
<2 mm	*Ref*	*Ref*	*Ref*
≥2 mm	15.47	1.84 – 130.13	0.012
Periodontal status (AAP, baseline)			
No/Mild/Moderate Periodontitis	*Ref*	*Ref*	*Ref*
Severe Periodontitis	60.38	1.99 – 1829.67	0.018
Edentulous	12.59	0.45 – 351.57	0.136
Number of PPD≥6 mm (baseline, other than study implant)			
≤3	*Ref*	*Ref*	*Ref*
>3	0.11	0.13 – 0.84	0.034

Footnote:
OR, odds ratio; CI, confidence interval; Ref, reference category.

The presence of SoP at baseline (OR=0.05) and the presence of more than 3 sites with a PPD≥6 mm in the mouth other than study implants (OR=0.11) resulted associated with lower rates of treatment

success, while the presence of severe periodontitis (OR=60.38) and the presence of KMH ≥2 mm at the 12-months examination (OR=15.47) were associated with higher rates.

Discussion

The findings of this multi-center randomized clinical trial have clearly shown that the sub-mucosal instrumentation did not provide any added benefit on the outcomes of surgical treatment of moderate/severe peri-implantitis. Thus, the null hypothesis of this study could not be rejected.

A similar magnitude of PPD reduction (≅3 mm) at the 6- and 12-months examinations to the one found in the present study was also observed in several other randomized clinical trials on the surgical treatment of moderate/severe peri-implantitis, regardless of the application of sub-mucosal instrumentation before surgery or the employed surgical approach [14,15,18-20]. However, when applying similar criteria, the treatment success rates reported in the present clinical trial (26.9%), although similar to other reports[18] , are inferior to other studies which achieved values close to 50% [14]. This may be explained, similarly to de Tapia et al. (2019) [18] but contrarily to Carcuac et al. (2016) [14], by the inclusion in the present trial of regenerative surgeries. Indeed, the predictor models revealed how regenerative approaches resulted associated with a lower PPD reduction, which is one of the parameters considered to define treatment success.

Despite patients of the test group experienced a shorter non-surgical treatment time than the ones of the control group, readers may argue that this difference was of only ≅15 minutes. However, it should be considered that it was measured as a net treatment time, thus in real-life clinical settings this difference may be higher (especially in case of multiple-affected implants). Moreover, sub-mucosal instrumentation requires local anesthesia with the related patient discomfort, and a longer waiting time before surgery to allow proper tissue healing. These disadvantages may be clinically less relevant in cases of patients requiring in the same mouth-zone a sub-gingival instrumentation as part of Step 2 of periodontitis treatment, but still they are – at least in the remaining cases - not balanced by any added value of this therapeutic phase in the affected implants.

The present study managed to identify several factors able to predict PPD changes and treatment success 12-months after surgical treatment of peri-implantitis. Presence of SoP at baseline was associated with both lower PPD reduction and treatment success rates, while the presence of KMH ≥ 2 mm had a positive impact on both outcomes. As previously reported, peri-implantitis severity at diagnosis (expressed in terms of baseline bone level) and implant brand influence the outcome of peri-implantitis treatment [14,21,22]. Similarly to periodontitis treatment, current smoking [23] and lack of plaque control during follow-up [24] demonstrated a negative impact on PPD reduction. Moreover, as also reported for periodontitis affected teeth, the deeper the baseline PPD the higher its reduction [25]. Other identified predictors for PPD reduction were vitamin D intake, thick phenotype, reason of tooth loss and surgical approach, while the presence of severe periodontitis and its control (presence of more than three PPD≥6 mm other than in study implants) influenced treatment success.

The results of this trial answer to a clinically-relevant question, and they are supported by a solid study design (e.g., randomization procedures, blinding, allocation concealment, sample size). Their generalizability is favored by the multi-center setting. A limitation worth mentioning is represented by the need to standardize the sub-mucosal instrumentation protocol in the control group, which was required in order to preserve the internal validity of the study. Potentially, different results may be observed employing different protocols of sub-mucosal instrumentation.

In conclusion, the findings from the present multi-center randomized clinical trial question the value of non-surgical sub-mucosal instrumentation before surgical treatment of moderate/severe peri-implantitis. Depending on the case characteristics (e.g. need for sub-gingival instrumentation to treat

periodontitis), clinicians may individualize the decision to perform or not this preparatory step before surgery. Several predictors of the results of surgical treatment of peri-implantitis were also identified. Their presence may guide clinicians in the decision to treat or to remove the affected implants, as well as in the personalization of the frequency and type of secondary prevention measures (i.e. SPIC recalls) in case treatment is provided.

Acknowledgments
The authors declare no conflicts of interest related to this study. This study was funded by a Young Research Grant from the Osteology Foundation to Dr Mario Romandini (YRG-15-251) and by the Proclinic Scholarship 2018 to Dr Mario Romandini. Moreover, part of the biomaterials used in this study and normally used in the surgical regenerative treatment of peri-implantitis were donated by Geistlich AG (Wolhusen, Switzerland), titanium curettes and surgical kits were donated by Hu-Friedy (Chicago, USA), and antiseptic mouthwashes/gels were donated by Dentaid (Barcelona, Spain).
The authors are extremely grateful to Mariano del Canto (Madrid), Liliam León (Madrid), Isabel Moraza (Rome), Pierluigi Romandini (Rome), and Erminia Squillace (Turin) for their kind support during part of the data collection process.

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