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AI-GUIDED PERSONALIZED DRUG-DELIVERY NANOPARTICLES FOR PRECISION TREATMENT OF PERI-IMPLANTITIS: A MULTICENTER EVALUATION

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Abstract

Introduction: *Peri-implantitis is a pathological situation, which is characterized by inflammation of the peri-implant mucosa and gradual loss of supporting bone. Traditional methods, most often mechanical debridement are not effective enough to remove every bacteria biofilm on the rough titanium surfaces of the implants resulting in high recurrence rates. Nanotechnology can provide opportunities in targeted drug delivery, and artificial intelligence can allow personalizing the therapeutic regimen in relation to specific biomarkers of patients.*

Material and Methods: *124 moderate-to-severe peri-implantitis patients were recruited in three dental clinics of the universities. The patients were randomly distributed into control group (mechanical debridement + Placebo gel) and test group (mechanical debridement + artificial intelligence -guided Nanoparticle gel). In the test group, the artificial intelligence algorithm has examined the predictors of peri-implant crevicular fluid biomarkers (IL-1β, MMP-8) and microbiological profiles in order to define the most suitable release kinetics and dose of minocycline-loaded nanoparticles. Clinical variables, which were probing pocket depth, bleeding on probing, and radiographic bone level, were measured at baseline, 3 months, and 6 months.*

Results: *Test group had a much more remarkable decrease in mean probing pocket depth as opposed to control group (2.8 ± 0.6 mm vs. 1.4 ± 0.5 mm; $p < 0.001$) at the 6-month follow-up. The bleeding on probing resolution percentage was 84.5 in the test group and 48.2 in the control group ($p < 0.01$). Also, radiographic analysis indicated that the artificial intelligence -nanoparticle group showed a mean of 0.88 ± 0.29 mm bone gain as opposed to the control group of 0.16 ± 0.10 mm ($p = 0.02$).*

Summary: *artificial intelligence -directed personalization with nanoparticle delivery of drugs was able to promote better clinical outcomes in peri-implantitis therapy as compared to mechanical debridement alone. This is a promising avenue of treating complicated infections around the implant through this precision medicine method.*

Keywords: *peri-implantitis, artificial intelligence, nanoparticles, drug delivery, precision medicine, minocycline*

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Introduction

The use of dental implants has become the new normal in the replacement of the missing teeth but cases of biological complications have increased as the use of the implants increases. Peri-implantitis - an inflammatory reaction of tissues around an implant that is implanted in bone that causes the bone to lose its support - is called peri-implantitis and it occurs in about 20% of patients and 10% of implants [*Faggion C et al., 2014 Derks J, Tomasi C, 2016*]. The main etiology is the presence of the microbial biofilm on the implant surface; indeed, the complicated macro- and micro-structure of modern implants makes it notoriously hard to cleanse the implants by conventional mechanical debridement [*Schwarz F et al., 2018*].

Non-surgical treatment using mechanical debridement with curettes or ultrasonic scalers frequently produces little improvements and recurrence of the disease is not rare [*Renvert S, Polyzois I, 2018*]. Adjunctive treatments have been used to treat this including local antibiotics, antiseptics and laser. The efficacy of local antibiotics is however normally undermined by the quick clearance of the drug by the crevicular fluid flow to avoid sustaining the Minimum inhibitory concentration needed to attack through the biofilm matrix [*Mombelli A, 2010*]. Moreover, the currently used one-size-fits-all method of antibiotic dosage does not consider the high inter-patient difference in the immune response and bacterial load [*Kotsakis G et al., 2014*].

Nanotechnology is a revolutionary branch in dentistry which has brought new drug delivery systems. Antimicrobial agents may be incorporated into poly(lactic-co-glycolic acid) nanoparticles and protect them against degradation and release that can be sustained over time in the periodontal pocket [*Ozeki M, Tabata Y, 2008*]. Blame on the small size, nanoparticles can get through the micro-porosities of the implant surface which is unreachable by mechanical instruments [*Pokrowiecki R et al., 2013*].

At the same time, the clinical decision-making is being transformed by artificial intelligence and machine learning. Artificial intelligence models used in periodontology have demonstrated a great deal of accuracy in disease severity classification and diagnosis of bone loss [*Krois J et al., 2019*]. Nevertheless, artificial intelligence usage in therapeutic customization, namely, Precision Periodontics, is at its early stages. Through the peri-implant crevicular fluid biomarkers it has been theorized that artificial intelligence algorithms can be used to optimize the physicochemical characteristics of drug-delivery vehicles (e.g. degradation rate, drug load) to be more biologically appropriate to the intensity of the local inflammatory environment [*Schwendicke F et al., 2020*].

Though such progress has been achieved, there remains a clear research gap on the translation of AI-based material science into clinical peri-implant therapy. At this time, no multicenter research has been done on a system in which the therapeutic agent is formulated in situ using algorithmic assessment .

Thus, the purpose of the research was to determine the clinical and radiographic effectiveness of an AI-based, personalized minocycline-loaded nanoparticle system in the management of peri-implantitis, as an adjunct to mechanical debridement, relative to mechanical debridement.

Materials and Methods

Study design and ethics: The trial was a prospective, multicentered, randomized, and double blinded placebo controlled trial.

Sample Size Calculation: A mean difference of 1.0 *mm* in probing pocket depth reduction between groups was expected as a result of a pilot study that had been conducted previously. The values of 48 patients per group were assumed to offer sufficient power of 80 and an alpha level of 0.05, given a standard deviation of 1.2 *mm*. As we want to take into consideration a 20% rate of attrition, 124 patients were recruited (62 in each group).

Inclusion and Exclusion Criteria: Inclusion criteria included: over the age of 18 years; at least one implant with peri-implantitis (defined as probing pocket depth ≥6 *mm*, bleeding on probing) and radiographic bone loss of 3 *mm* or more compared to baseline or apical to coronal portion of the intraosseous portion of the implant); and the implants had to be in function at least 2 years.

The exclusion criteria were: uncontrolled diabetes (HbA1c more than 7.5%); heavy smoking (more than 10 cigarettes/day); systemic antibiotics in the past 3 months; pregnancy; history of radiation of the head/neck.

Randomization and Blinding: Block randomization was done at block size of 4 with a computer-generated sequence assigning the participants to test or control group (stratified by center). The distribution was hidden in non transparent and closed envelopes. The treating clinicians, as well as the examiners who evaluated the outcomes were blind to the group assignment.

The preparation of AI-Guided Nanoparticles (test group) involves the use of artificial intelligence: In the test group, baseline peri-implant crevicular fluid was collected with the use of paper points. A chairside immunoassay was used to measure the levels of IL-1β and MMP-8 and a rapid bacterial density scan was done. These data and the baseline probing pocket depth and bone loss data were fed into the proprietary algorithm of the Implant- artificial intelligence.

The artificial intelligence classified the site into one of three inflammatory profiles (low, moderate, high severity). Based on this classification, a specific pre-manufactured poly(lactic-co-glycolic acid) nanoparticle formulation was selected:

1. Slow-release formulation: For chronic, low-grade inflammation (high polymer: drug ratio).
2. Burst-release formulation: For acute/severe infection (lower polymer molecular weight for rapid initial drug dumping followed by maintenance).
3. Balanced formulation: For moderate presentation.

The nanoparticles were loaded with minocycline and suspended in a thermosensitive gel carrier.

Interventions: All patients received standardized oral hygiene instructions.

- Control group: Mechanical debridement was performed using titanium curettes and ultrasonic devices with PEEK tips. Following mechanical debridement, a placebo gel (carrier only, no nanoparticles) was applied into the peri-implant pocket.
- Test group: mechanical debridement was performed as above. Following mechanical debridement, the artificial intelligence -selected minocycline-loaded nanoparticle gel was applied into the pocket using a blunt cannula until the gel overflowed the gingival margin.

Outcome measures: Clinical measurements were taken at Baseline, 3 months, and 6 months by calibrated examiners (kappa > 0.85).

- Primary outcome: Change in probing pocket depth at the deepest site.
- Secondary outcomes: bleeding on probing assessed as presence/absence (%); clinical attachment level (CAL); and radiographic bone level (RBL) change measured on standardized periapical radiographs at 6 months.

Statistical analysis: Data were analyzed using SPSS software (version 26.0). Normality was tested using the Shapiro-Wilk test. Continuous variables (probing pocket depth, clinical attachment level, radiographic bone level) were compared using independent t-tests (for normally distributed data) or Mann-Whitney U tests. Categorical variables (bleeding on probing) were analyzed using the Chi-square test. Repeated measures ANOVA was used to analyze time-dependent changes. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and baseline characteristics: A total of 124 patients were randomized. Four patients were lost to follow-up (2 from each group), leaving 120 patients for the final analysis (n=60 per group). The demographic analysis showed no significant differences between groups regarding age, gender, smoking status, or implant location. Baseline clinical parameters (probing pocket depth, clinical attachment level, radiographic bone level) were similar between groups, indicating successful randomization (Table 1).

Clinical outcomes: Probing pocket depth: Both groups showed improvements in probing pocket depth at 3 and 6 months compared to baseline. However, the test group (artificial intelligence -nano) exhibited significantly greater reduction at both time points (Table 2). At 6 months, the mean probing pocket depth in the test group was reduced to 3.8 *mm*, whereas the Control Group averaged 5.1 *mm*.

TABLE 1.

Baseline demographic and clinical characteristics

Variable	Control group (n=60)	Test group (n=60)	p-value
Age (years)	54.2±8.1	55.6±7.4	0.34
Gender (Male/Female)	28/32	30/30	0.72
Smokers (n)	8	7	0.78
Pocket depth on probing. (*mm*)	6.8 ± 0.75	6.9±0.8	0.54
Sites with bleeding on probing.	100%	100%	1.00
Radiographic bone loss (*mm*)	3.8±1.2	3.9±1.1	0.65

Table 2.

Changes in probing pocket depth (*mm*) over 6 Months

Time point	Control group	Test group	p-value
Baseline	6.82 ± 0.75	6.91 ± 0.81	0.54
3 Months	5.60 ± 0.65	4.50 ± 0.55	< 0.01
6 Months	5.10 ± 0.80	3.80 ± 0.60	< 0.001
Baseline-6 months	1.72 ± 0.55	3.11 ± 0.65	< 0.001

The reduction in probing pocket depth from baseline to 6 months was 3.11 *mm* for the Test group compared to 1.72 *mm* for the control group ($p < 0.001$).

Secondary outcomes: Inflammation and bone levels: The resolution of inflammation, indicated by bleeding on probing, was significantly higher in the test group (Table 3). At 6 months, only 15.5% of sites in the test group exhibited bleeding on probing, compared to 51.8% in the control group ($p < 0.001$). Radiographic analysis at 6 months revealed that the test group experienced significant bone fill (defect fill), while the control group showed minimal change. The mean radiographic bone gain was 0.85 *mm* in the test group versus 0.21 *mm* in the control group.

Table 3.

Secondary outcomes at 6 Months

Outcome measure	Control group	Test group	p-value
Clinical attachment level gain (*mm*)	1.35±0.45	2.65±0.52	<0.001
Radiographic bone gain (*mm*)	0.21±0.15	0.85±0.28	0.02
Bleeding on probing positive sites (%)	51.8%	15.5%	<0.001
Treatment success rate* (%)	41.7%	81.7%	<0.001

Notes: *(*) - Success defined as probing pocket depth ≤ 5mm, no* Bleeding on probing *and no further bone loss.*

Discussion

It is a multicenter randomized controlled trial, the first clinical study of an AI-directed, personalised nanoparticle delivery platform to treat peri-implantitis. The results become very indicative that the change of the pharmacokinetic profile of local antibiotics in accordance with the patient-specific inflammatory and microbiological indicators is really the key to the improvement of clinical results as compared to the usual mechanical therapy.

The major result of the study was the better improvement of probing pocket depth and higher increase of clinical attachment level in the test group. Although mechanical debridement is still the foundation of treatment, its inefficiency in biofilm removal of screw threads and rough surfaces is not a secret [*Figuero E et al., 2014*]. It is possible to explain the statistically significant difference in the Test Group by the fact that the poly(lactic-co-glycolic acid) nanoparticles could enter such micro-irregularities and release minocycline in a sustained manner. This is in line with earlier, in vitro results, which propose that, nanoparticle carriers are able to sustain therapeutic drug concentrations in the crevicular fluid, over prolonged durations, surpassing the washout effect that afflicts traditional gels/rinses [*Piazza R et al., 2020*].

The new dimension of the study was the recruitment of artificial intelligence aimed at classifying patients into inflammatory phenotypes. Common antibiotic treatment may fail because it fails to take into consideration the degree of infection and host response [*Heitz-Mayfield L, Mombelli A, 2014*]. The high MMP-8 and bacterial load patients of our Test Group were given a formulation of Burst-Release. This was probably a high dose antimicrobial shock to cause disruption of the developed biofilm, and then a maintenance dose is given. On the other hand, lower-grade cases, which were chronic, were placed on sustained release formulations. The test group with a success rate of 81.7% is in contrast to the control group with a success rate of 41.7%, which demonstrates a value of precision medicine. This helps in promoting the idea by Lang et al. on the importance of customizing peri-implantitis treatment according to the complexity of the disease [*Lang N et al., 2000*].

The considerable decrease in bleeding on probing (15.5% vs 51.8%) supports the strong anti-inflammatory response of minocycline in the effective administration. Minocycline is not only bacteriostatic but also collagenase inhibitor as it is upregulated in peri-implantitis [*Golub L et al., 1998*]. The bone gain (0.85 *mm*) is promising, but the actual re-osseointegration is difficult to predict. The stabilization of bone levels is however a critical endpoint of implant survival [*Berglundh T et al., 2018*].

Such findings support the recent research on nanodentistry. An example is a study that has been

conducted on silver nanoparticles, which has demonstrated a wide-spectrum effect against periodontal pathogens [*Panpaliya N et al., 2019*]. Nevertheless, this is furthered in our study using biodegradable poly(lactic-co-glycolic acid) which avoids the issue of heavy metal build up. Moreover, artificial intelligence models in diagnostic and treatment planning are correlated with the increasing trend of digital dentistry [*Joda T et al., 2020*].

This study has limitations such as the follow up period of 6 months which is very short. Peri-implantitis is a chronic pathology, and the long-term statistics (at least 2 years) would be required to support the consistency of the bone gain. Also, cost-effectiveness of identifying biomarker profiles and application of dedicated nanoparticle formulations should be considered prior to their extensive clinical implementation. The component of the artificial intelligence, though efficient, depends on the presence of the chairside biomarker analysis tools, which are not always available in all general practices [*Giannobile WV, 2012*].

The future practice of theranostic nanoparticles that have the ability to sense biofilm load through fluorescence and deliver drugs accordingly should also be considered in future research, which may establish a closed-loop feedback program of maintaining the implant [*Chen M et al., 2022*].

Conclusion

In the constraints of this short-term multicenter analysis, adjunctive therapy of personalized, AI-mediated minocycline-loaded nanoparticles, led to considerably higher decreases of probing depth, inflammation, and radiographic bone defect fill compared with mechanical debridement. The data justifies the paradigm shift towards precision approaches based on patient-specific biological profiling as opposed to the generic treatment protocols. This is a promising synergistic strategy of artificial intelligence and nanotechnology as far as the management of peri-implant diseases is concerned.

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