Adjunctive Systemic Metronidazole to Nonsurgical Therapy of Peri-implantitis with Intrabony Defects: A Retrospective Case Series Study

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Purpose: To show the clinical and radiographic results of intrabony peri-implantitis lesions treated nonsurgically with adjunctive systemic metronidazole with a mean follow-up of 50 months. Materials and Methods: Subjects diagnosed with peri-implantitis (probing depth ≥ 5 mm with concomitant bleeding on probing and/or suppuration) with radiographic evidence of intrabony defects > 2 mm were included in this study. Implants affected received one session of nonsurgical mechanical debridement with ultrasonic and steel curettes. Systemic metronidazole was immediately prescribed for 7 days. Clinical and radiographic variables were registered at baseline and at the end of follow-up. Results: Eighteen patients and 25 implants were included in this investigation. At baseline, the mean radiographic bone level and intrabony component were 4.52 ± 2.14 mm and 3.93 ± 1.51 mm, respectively. After a mean follow-up of 54 (range: 12 to 108) months, the mean radiographic bone level reduction was 2.6 ± 0.21 mm, and the intrabony component reduction was 2.85 ± 0.37 mm (P < .05). A mean probing depth reduction of 4.66 ± 1.33 mm was observed (P < .05). Conclusion: Within the limits of this study, nonsurgical treatment of peri-implantitis with the adjunctive administration of systemic metronidazole has shown potential effectiveness in terms of probing depth and radiographic defect reduction after a mean follow-up of 54 months. Int J Oral Maxillofac Implants 2019;34:1237–1245. doi: 10.11607/jomi.7343

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Peri-implantitis is characterized by soft tissue inflammation accompanied by a rapid loss of hard tissues and pocket formation around dental implants.1 Based on cross-sectional studies, moderate and severe stages of peri-implantitis occur in 15% to 20% of patients with dental implants.2,3 Studies with more than 100 patients and more than 5 years of follow-up (8.6 mean years of follow-up) showed that peri-implantitis (bone loss ≥ 2 mm) occurs in 10% of implants and 21% at the patient level.2–6 Peri-implant and periodontal tissues have common clinical characteristics, but there are also structural differences that may influence host response against infection.7,8 The results obtained from human biopsies have shown that peri-implantitis and periodontitis lesions present a large inflammatory infiltrate of connective tissue (ICT) lateral to a pocket epithelium, but the apical extension of this infiltrate in peri-implantitis is closer to the bone crest than in periodontitis. Another important consideration is the self-limiting process that occurs at teeth but not at implant sites where the ICT extends to the bone crest.9,10 On teeth, the ICT is encapsulated and separated from apical bone for healthy connective tissue attached to the root surface. However, on implants, this ICT reaches the bone, and is more evident on rough implant surfaces.10 Furthermore, peri-implantitis lesions progress in an accelerating pattern. The onset may be initiated within the first 3 years of function.11 It has been shown that microbial colonization of the implant surface is the main causative factor in the pathogenesis of this disease.12 Other factors that have been postulated as potential etiologic factors have been excessive occlusal overload13 and excess of cement as a foreign body reaction.14,15 Moreover, the work by Albrektsson’s group postulates that progressive bone loss is related to a complicating
factor resulting in an immuno-osteolytic reaction accounting for the ongoing bone resorption. This may be caused by numerous factors related to marginal bone level changes such as abutment height, insertion torque, implant position, poor oral hygiene, or absence of maintenance.\textsuperscript{16,17} Moreover, a regularly supportive therapy program seems to be crucial to prevent peri-implantitis. Furthermore, the history of periodontal disease and smoking appear to be factors that increase the appearance of peri-implantitis.\textsuperscript{18-20}

The composition of peri-implantitis microbiota causing inflammation and destruction of hard tissues is similar to periodontitis.\textsuperscript{21} However, there are enough data showing that although periodontal and peri-implant diseases are similar with regard to the bacterial composition, this is not completely similar.\textsuperscript{22} Great counts and proportions of gram-negative anaerobic bacteria and great prevalence of pathogens associated with periodontitis, clinically characterized implants with peri-implantitis.\textsuperscript{23} The microbiologic profile of advanced peri-implantitis lesions is composed mainly by gram-anaerobic bacteria.\textsuperscript{24,25} An important role is played by \textit{Porphyromonas gingivalis}, and also a cluster of \textit{Tannerella forsythia} and \textit{Staphylococcus aureus}.\textsuperscript{26} Moreover, studies have found the presence of \textit{Staphylococcus aureus}, enteric rods, and Candida at peri-implantitis sites due to the attraction of titanium for such bacteria and fungi.\textsuperscript{26}

Thus, the rationale of using a systemic antibiotic such as metronidazole as adjunctive to nonsurgical peri-implantitis therapy may be justified. In fact, it has been shown that there are added benefits to the treatment of refractory periodontitis after nonsurgical periodontal therapy.\textsuperscript{27}

The treatment of peri-implantitis aims to control the infection and reduce bacterial load. The evidence on periodontal treatment is the basis for the treatment of peri-implantitis. Surgical and nonsurgical techniques have been developed in peri-implantitis, but nonsurgical treatment alone has been shown to be ineffective.\textsuperscript{28} However, case series and cohort studies have shown added benefit to nonsurgical therapy when systemic antibiotics were used adjunctively.\textsuperscript{29-32}

Recent publications have shown the potential of nonsurgical periodontal therapy in deep intrabony defects.\textsuperscript{33,34} Moreover, the regression analysis showed a significant radiographic defect fill increase if systemic antibiotics were used as adjunctive to nonsurgical therapy.\textsuperscript{34}

The present case series study shows radiographic and clinical outcomes after nonsurgical peri-implant treatment with adjunctive systemic metronidazole in advanced peri-implantitis lesions.

**MATERIALS AND METHODS**

Files and radiographs of patients with at least one implant diagnosed for peri-implantitis who had received nonsurgical treatment in combination with systemic metronidazole at a Specialist Private Practice in Periodontology (A Coruña, Spain) were analyzed. Patients with periodontitis were treated and included in the maintenance program before.

The diagnosis of peri-implantitis was based on the following parameters:\textsuperscript{35}:

- Probing depth > 5 mm
- Peri-implant sites with bleeding on probing (BOP+) and/or suppuration
- Radiographic evidence of intrabony defect > 2 mm

To be included, patients needed to meet the following criteria:

- Older than 18 years of age
- At least one implant initially diagnosed for peri-implantitis (probing depth > 5 mm with bleeding on probing [BOP+] and/or suppuration and radiographic evidence of intrabony defect > 2 mm)
- Had received nonsurgical treatment in combination with systemic metronidazole
- Full-mouth plaque score < 25%
- Full-mouth bleeding score < 25%
- Cemented or screw-retained single crowns or fixed dental prostheses
- A minimum follow-up of 12 months.

The following exclusion criteria were applied:

- Systemic pathology that contraindicates treatment
- History of taking systemic antibiotics in the last 3 months
- Uncontrolled periodontal disease
- Smoking more than 20 cigarettes per day
- Mobility of the implant

The study was performed in accordance with the principles stated in the Declaration of Helsinki. Oral informed consent for treatment was obtained.

**Nonsurgical Treatment**

After the diagnosis of peri-implantitis, patients were instructed in oral hygiene and motivation was reinforced. After that, one session of nonsurgical treatment consisting of supra- and submucosal mechanical debridement using ultrasound with a metal periodontal tip (EMS, Electro Medical Systems) was performed with no time restriction. Treatment was performed by an experienced periodontist (A.L.). Ultrasonic
debridement was performed with concomitant irrigation of chlorhexidine of 0.12% (Perio Aid, Dentaid). The tip removed granulation tissue and also touched the implant surface. After that, a steel curette Columbia 4R/4L (LM Instruments Oy) was used to remove granulation tissue and minor mucosa curettage. If oral hygiene was not allowed by prosthetic design, a contour correction was made. Immediately after treatment, patients were prescribed to apply a chlorhexidine gel in the area 2 times a day for 2 weeks, and systemic metronidazole 250 mg, 2 tablets every 8 hours for 7 days was also prescribed. The gel was applied by the patient on the peri-implant mucosa after brushing. No microbiologic testing was performed. After a follow-up of 8 to 10 weeks, a clinical re-evaluation was performed, and new periapical radiographs were taken. Long-cone parallel technique was performed for the digital radiographic evaluation.36

After that, the patient entered into a 4- to 6-month recall program, consisting of oral hygiene reinforcement as needed, subgingival instrumentation with low power ultrasonics under anesthesia if required, and annual radiographic control.

Clinical Variables
Probing depth was measured to the closest millimeter with a manual PCP15 periodontal probe (Hu-Friedy) at six sites per implant, and the deepest site was recorded.

Demographic data (age, sex, history of periodontitis, smoking) and information related to the implant location, type of implant, implant restoration (cemented or screwed), and type of prosthesis were also recorded. History of periodontitis was determined by assessing the attachment loss using a periodontal probe. Patients with proximal attachment loss of ≥ 3 mm in ≥ 2 nonadjacent teeth were diagnosed with periodontitis.37 Smoking status was classified as: nonsmoker (0 cigarettes/day), light smoker (0 to 10 cigarettes /day), and heavy smoker (> 10 to 20 cigarettes/day).

Radiographic Examination
With the long-cone technique, an intraoral radiograph was obtained at baseline, reevaluation, and at follow-up to evaluate crestal bone level. Those radiographs were imported to digital radiographic examination software (ImageJ 1.47 V Wayne Rasband, National Institutes of Health). All examinations were performed by two independent and calibrated examiners (A.L., A.P.) to the nearest 0.1 mm using ImageJ software, and the mean of the two measurements was calculated. The height of the dental implant was taken as reference for the calibration, which yielded a pixel/mm ratio. The implant shoulder was used as a fixed reference point. All radiographic measurements were made by a trained and calibrated examiner (A.P.).

The following measurements were recorded at the mesial and distal aspects:

- Radiographic bone level: distance between the implant shoulder and the bottom of the defect at bone-level implants. At tissue-level implants, the rough-smooth interface was used as the landmark; thus, the machined collar length was subtracted according to the macro design of the implant.
- Intrabony component: Distance between the bottom of the defect and the line connecting the mesial and distal interproximal bone crest
- Defect resolution: The percentage was calculated as follows:

\[
\frac{\text{Defect resolution} \times 100}{\text{Depth of intrabony (baseline)}} = \% \text{ of defect resolution}
\]

- Intrabony defect angle: Radiographic angle of the defect was measured identifying the most apical extension of the intrabony destruction adjacent to the implant wall and the most coronal position of the alveolar bone crest of the intrabony defect.

As the radiographies were not standardized, the distortion between follow-up and baseline was estimated as it was described in previous investigations.38 In order to calculate this distortion, a fixed distance as the implant length (distance from the implant shoulder to the implant apex [IS-IA]) was measured on the radiographs, and then a correction factor was calculated as follows:

\[
\frac{\text{IS-IA (baseline)}}{\text{IS-IA (follow-up)}} = \text{Correction factor}
\]

When the implant length could not be measured, the implant width was assessed (measured at the implant shoulder). Implant length was obtained from the surgical report at implant placement.

Data Analysis
Clinical (probing pocket depth) and radiographic variables (radiographic bone level, intrabony component, and intrabony defect angle) were measured at baseline and at the last follow-up examination and averaged to represent changes over time; significance of differences between follow-up and diagnosis were compared.

After application of the Shapiro-Wilk test to verify the normality assumptions, parametric paired \( t \) test was applied to analyze probing pocket depth and intrabony defect angle. A nonparametric test (Wilcoxon signed-rank test) was used to analyze differences in radiographic bone level and intrabony component variables. The statistical analysis was performed by an author (A.P.) using SPSS software (Version 20.0 SP5). The level of significance was set at \( P < .05 \). The unit of analysis was patient level.

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Study Sample
Eighteen patients and 25 implants were included in this study (Table 1). The mean age was 60 (range: 32 to 79) years. Two patients were smokers. Sixteen patients were systemically healthy. Two patients were diabetics. Eight patients were diagnosed with chronic periodontitis and treated before implant placement. At the diagnosis of peri-implantitis, four patients also needed to be treated for periodontitis.

Fourteen tissue-level and 11 bone-level implants, all with rough surface, were diagnosed and treated. The tissue-level implants had a 1.8-mm smooth collar length. Eleven patients had one implant with peri-implantitis, and seven patients had two implants affected. The majority (16 implants) were placed in the mandible. Twenty were screw-retained restorations, while only five were cemented. All implants were placed in pristine bone since no guided bone regeneration technique was performed previously. A total of 13 implants were included in fixed partial restorations, seven in single crowns, and five in full-arch prostheses. The mean period of implant function at baseline was 79 (range: 4 to 276) months with a mean follow-up of 54 (range: 12 to 108) months after therapy. In 21 implants, peri-implantitis was diagnosed at least 1 year after implant placement, while in four implants, the diagnosis was made before.

Clinical Data
At the end of follow-up, a mean probing depth reduction of 4.66 ± 1.33 mm was observed (P < .05). After treatment, mean probing depth changed from 8.72 ± 2.13 mm at baseline to 4.06 ± 0.8 mm (Table 2).

Radiographic Data
At diagnosis, the mean radiographic bone level was 4.52 ± 2.14 mm and the intrabony component (IC) was 3.93 ± 1.51 mm. After a mean follow-up of 54 (range: 12 to 108) months, the mean radiographic bone level was 1.92 ± 1.93 mm, and the intrabony component was 1.08 ± 1.14 mm (P < .05). The mean radiographic bone level improved 2.6 ± 0.21 mm (P < .05). The mean intrabony component was reduced 2.85 ± 0.37 mm (P < .05), from 3.93 ± 1.51 mm at the diagnosis to 1.08 ± 1.4 mm at the end of follow-up. This means a 62.63% radiographic defect resolution. The mean angle of the intrabony defects was augmented after treatment. A statistically significant difference was observed (34.3 ± 9.45 degrees; P < .05) between the two time points (Table 2). No differences were observed between mesial and distal locations for any of the parameters analyzed. Examples of radiographic outcomes are displayed in Fig 1. Clinical and radiographic outcomes are also shown in Figs 2 and 3.

DISCUSSION
The present cases series study shows the potential successful clinical and radiographic outcomes following nonsurgical peri-implant treatment with adjunctive systemic metronidazole. The adjunctive use of systemic antibiotics could be justified based on the rapid progression of peri-implantitis and the differences between advanced peri-implantitis lesions and periodontitis lesions against the recognized putative pathogens.9–11 The capacity of certain bacteria to invade soft tissues in periodontal lesions has been shown in classic studies.39,40 No studies have addressed the potential of bacterial invasion in peri-implant lesions. However, studies have shown that peri-implantitis lesions presented pocket epithelium ulceration with potential invasion of the subepithelial connective tissue.41–43 This may be a reason why conventional nonsurgical therapy has no improvements in treating
peri-implantitis, since infection may be present not only within the pocket but also within the connective tissue. This feature of bacteria invasion may be more severe on implants with rough surfaces since the inflammatory infiltrate is larger when compared with the lesions in the periodontium and reaches the bone.10

In the consensus report from the Sixth European Workshop on Periodontology, it was concluded that surgical therapy is usually required due to the incapacity of nonsurgical treatment to resolve the majority of peri-implantitis lesions.44 The review provided by Renvert and coworkers identified just one randomized controlled clinical trial on nonsurgical mechanical debridement of peri-implantitis with no clinical changes after 6 months of treatment.28,45 Thus, it seems that conventional nonsurgical peri-implant therapy alone

Fig 1 Radiographic outcome cases included in the study. (a) Baseline radiograph in a male nonsmoker 69 years of age. (b) 9-year follow-up radiograph. Note radiographic bone fill on distal implants. (c) Baseline radiograph of a female nonsmoker 72 years of age. (d) 6-year follow-up radiograph. (e) Baseline radiograph of a male nonsmoker 75 years of age. (f) 5-year follow-up. (g) Baseline radiograph of a male diabetic nonsmoker 60 years of age. (h) 9 years after therapy. (i) Baseline radiograph of a peri-implantitis lesion in a male nonsmoker 40 years of age. (j) Follow-up radiograph taken 5 years after therapy. (k) Baseline radiograph of a male light smoker 68 years of age. (l) 2-year follow-up radiograph.
is unable to reduce peri-implantitis lesions. Adjunctive therapy to nonsurgical mechanical debridement has been studied, such as laser, local, and systemic antibiotics (for review, see Renvert et al [2008]). Some minor improvements have been observed when local antibiotics were applied adjunctively. The use of lasers showed almost null improvements. A recent randomized controlled trial studied the adjunctive use of light-activated disinfection (LAD) therapy with mechanical cleaning of implants affected by peri-implantitis. After a year of follow-up, the results showed that there was not any improvement in clinical outcomes compared with mechanical cleaning alone. After 2-year follow-up, a significant reduction in probing pocket depth and in the percent of implants with ≥ 1 site with bleeding on probing was observed, showing the need for randomized clinical trials to obtain more evidence on this topic.

On the other hand, promising results were observed in case series studies when systemic antibiotics were used in combination with nonsurgical mechanical debridement. Mombelli and Lang observed a significant reduction of probing depths and microbial parameters after nonsurgical treatment and systemic antimicrobial therapy (1,000 mg ornidazole for 10 consecutive days) of implants affected by a marked bone loss. After 12 months of treatment, probing pocket depth was reduced from 5.9 to 3.4 mm. Gram-anaerobic rods were also reduced from 40% to 16%. Moreover, in some cases, a radiographic bone gain was observed. Other case series showed probing depth reduction of 2.5 mm and radiographic bone fill of 1.6 mm after nonsurgical treatment of peri-implantitis with different systemic antibiotics according to a susceptibility test. A recent study analyzed the clinical outcomes of nonsurgical treatment with adjuvant povidone-iodine application and an adjuvant administration of systemic antibiotics. The nonsurgical therapy consisted of the use of ultrasonic devices with metal tips, the use of curettes to remove the mucosal tissues facing implant surfaces, and glycine powder air polishing accompanied by repeated submucosal application of povidone-iodine. In such patients diagnosed with severe periodontitis, amoxicillin and metronidazole were prescribed for 7 days. After 12 months of follow-up, implants treated without antibiotics showed significant reductions of mean pocket depth (1.4 ± 0.7 mm), clinical attachment level (1.3 ± 0.8 mm), and bleeding on probing. In the deepest pocket, the analysis revealed more pronounced changes in comparison with shallow pockets. There were no significant changes in clinical outcomes in the group of antibiotics. However, the presence of implants with deep pockets and bleeding on probing after therapy was lower in patients taking systemic antibiotics than in those without (31.8% ± 12.6% vs 20.8% ± 14.7%). It is important to mention that in that study the mean probing depth at baseline was 4.8 ± 0.9 mm. This is substantially smaller than the baseline mean probing depth presented in the present investigation (8.72 ± 2.13 mm). Thus, the potential added benefit of systemic antibiotics may be related to disease severity as also occurs in periodontitis. In the present study, it was shown that metronidazole as adjunctive to nonsurgical therapy of peri-implantitis has the potential to improve clinical/radiographic outcomes.
Some improvements have been shown when nonsurgical therapy was combined with local antibiotics (for review, see Renvert et al [2008]). No controlled clinical trials have tested the potential adjunctive benefits of systemic antibiotics in the nonsurgical therapy of peri-implantitis. However, three case-series studies have shown a clear improvement in terms of clinical and radiographic outcomes. The rationale behind why clinical and radiographic improvements were achieved in those studies remains unclear. It is important to point out that peri-implantitis lesions (particularly rough surfaces) reach the bone and are much more aggressive than periodontitis. Moreover, the histology of peri-implantitis lesions has shown clear signs of epithelium ulceration. It can be hypothesized that bacterial invasion of subepithelial connective tissue may be present in peri-implantitis lesions. This concept of bacterial invasion was first described by Listgarten (1965) with human biopsies of acute necrotizing periodontitis lesions. Later on, bacterial invasion in localized aggressive and advanced chronic periodontitis lesions was shown. Thus, mechanical debridement alone may leave an important colony of bacteria within the connective tissue. In fact, studies performed in localized aggressive periodontitis lesions and advanced chronic periodontitis showed that scaling alone could not reduce the number of Aggregatibacter actinomycetemcomitans; however, with gingival curettage or flap surgery, Aggregatibacter actinomycetemcomitans numbers could be decreased. This is also the rationale of performing minor peri-implant mucosa curettage. Moreover, systemic antibiotics have been shown to improve clinical outcomes in aggressive forms of periodontitis. Diffusion of antibiotics within the subepithelial connective tissue may be achieved after systemic administration. The rationale of using metronidazole as adjunctive to nonsurgical therapy comes from the microflora of peri-implantitis lesions, where gram-anaerobic bacteria are predominant. Thus, it is the hypothesis that metronidazole could be the antibiotic of choice in treating advanced peri-implantitis lesions. Not only is there a lack of controlled clinical trials with systemic antibiotics, but also of those comparing different antibiotics and/or regimens. Thus, the potential benefit of other forms of systemic antibiotics cannot be discarded. Care should be taken with metronidazole in avoiding alcohol intake during treatment, and patients under anticoagulant therapy drugs, since metronidazole may increase the international normalized ratio (INR) of those patients. Another advantage of metronidazole is low resistance profile. A big concern is occurring nowadays with the increase of bacteria resistance to some systemic antibiotics. Moreover, some clinical data of using systemic antibiotics after surgical therapy have shown no added benefits in treating peri-implantitis lesions on implants with a smooth surface. However, that study showed a clear benefit in treating rough surfaces surgically with adjunctive systemic antibiotics. Successful outcomes at 1 year were almost double in the group treated surgically plus systemic antibiotics compared with those of the no antibiotic group. This may be explained due to a less aggressive form of lesion in smooth surfaces, and it may be hypothesized that bacteria invasion in those peri-implantitis lesions of smooth surfaces may not be present. This is a reason for a classification proposal of peri-implantitis lesions into aggressive forms (mainly in rough surfaces and rapid progression), and chronic peri-implantitis lesions (smooth surfaces and slow progression).

Although there was significant improvement in clinical and radiologic parameters obtained in this study, differences in length of follow-up, radiographic standardization, and the absence of a control group without systemic antibiotics need to be taken into account. However, data from clinical trials of nonsurgical therapy without antibiotics have shown no improvements. The radiographic improvement of the present cases series may be related to four important points: (1) improvement in oral hygiene; (2) debridement and curettage of the defect; (3) elimination of pathogenic bacteria with antibiotics; and (4) the stability of clot formation after debridement may lead to improvement of radiographic bone fill. In fact, clot stability may be a key point in periodontal regeneration. This feature may be related to defect morphology. In periodontal studies, surgical and nonsurgical treatments of intrabony defects have shown that the narrower the defect angle, the higher the chance to obtain more defect resolution. Moreover, it was shown that defect configuration on surgical treatment of peri-implantitis plays an important role in clinical and radiographic outcomes. Self-contained crater defects showed a higher chance of resolution than defects that present some missing bony wall. Case-series studies are important to create new research hypotheses. Thus, randomized controlled clinical trials are needed to test the null hypothesis that nonsurgical treatment of peri-implantitis with or without systemic antibiotics shows no difference.

**CONCLUSIONS**

Within the limits of this study, nonsurgical treatment of peri-implantitis with adjunctive administration of systemic metronidazole has shown favorable probing depth reduction and radiographic defect reduction in patients with good oral hygiene and maintenance. Controlled studies are needed to test this proof of principle treatment protocol.
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REFERENCES