Dental Research Journal

Original Article

A multilevel analysis of a randomized clinical trial comparing adjunctive moxifloxacin versus amoxicillin/metronidazole for the treatment of aggressive periodontitis

Carlos-Martín Ardila[1], Jader-Alexander Bedoya-García[1]

[1]Department of Basic Sciences, Faculty of Dentistry, Universidad de Antioquia, Medellín, Colombia

ABSTRACT

Background: It was documented that the clinical outcomes of mechanical periodontal treatment can fluctuate not merely concerning patients but equally among various tooth sites in the subject. This trial evaluates the clinical parameters related with the patient, tooth, and site that generate more changes in clinical attachment level (CAL) gain and probing depth (PD) reduction, using moxifloxacin (MOX) versus amoxicillin plus metronidazole (AMOX + ME) as adjuncts to scaling and root planing (SRP), in comparison to SRP only, post-therapy in generalized aggressive periodontitis (GAgP).

Materials and Methods: The analysis of this clinical trial included 6012 tooth sites at 1002 teeth in 36 patients; they were randomly assigned to three protocols: Systemically intake of MOX or AMOX + ME plus SRP, or SRP + placebo for 7 days. The clinical effect of the patient, tooth, and site characteristics, in terms of CAL gain and PD reduction, was explored using a multilevel linear model. $P < 0.05$ was statistically significant.

Results: Following 6 months of treatment, the differences between the groups were statistically significant, favoring the MOX and AMOX + ME protocols ($P < 0.0001$). Moreover, the multilevel model showed that adjunctive MOX, AMOX + ME, non-molar, and interproximal sites were the features that contribute significantly to CAL improvement, and PD decreases in GAgP ($P \leq 0.001$ for all).

Conclusion: The most relevant characteristics for the changes in CAL increase and PD diminution, after adjunctive antimicrobials, were ascribable to the features related to the tooth. MOX and AMOX + ME, non-multi-radicular-tooth, and interdental sites indicated superior clinical gains at the tooth and site levels in GAgP.

Key Words: Amoxicillin, clinical trial, metronidazole, moxifloxacin, multilevel analysis

Received: 27-Nov-2019
Revised: 30-May-2020
Accepted: 19-Sep-2020
Published: 22-Jun-2021

Address for correspondence:
Prof. Carlos - Martín Ardila, Calle 70 No. 52-21, Medellín, Colombia.
E-mail: martin.ardila@udea.edu.co

INTRODUCTION

Aggressive periodontitis (AgP) presents prompt attachment damage correlated to affected host immune response and significantly pathogenic bacteria. A systematic review proposed that for the management of AgP patients, adjunctive antimicrobials combined with scaling and root planing (SRP) caused a significant supplementary influence in comparison to SRP.[1] A recent consensus also reported that amoxicillin plus metronidazole (AMOX + ME) is the

Access this article online

Website: www.drj.ir
www.drjjournal.net
www.ncbi.nlm.nih.gov/pmc/journals/1480

How to cite this article: Ardila CM, Bedoya-Garcia JA. A multilevel analysis of a randomized clinical trial comparing adjunctive moxifloxacin versus amoxicillin/metronidazole for the treatment of aggressive periodontitis. Dent Res J 2021;18:44.

best successful antibiotic combination.[2] Moreover, a clinical trial documented that moxifloxacin (MOX), in combination with mechanical therapy induces to enhance the advantages in comparison to SRP in generalized aggressive periodontitis.[3] Adjunctive AMOX + ME[4,5] and MOX[3] have revealed higher profits in clinical attachment level (CAL) gain and probing depth (PD) decrease than mechanical treatment in AgP. Although without SRP placebo control group, Guzeldemir-Akcakanat and Gurgan[6] did not find differences between adjunctive AMOX + ME and MOX in PD and CAL after 6 months of AgP treatment.

Nonetheless, it was documented that the clinical outcomes of mechanical periodontal treatment can fluctuate not merely concerning patients but equally among various tooth sites in the subject.[7] Scholars investigated this field in different forms of periodontitis therapies;[8-10] however, most of them have studied chronic periodontitis. Furthermore, a meta-analysis denoted that the improving of AMOX + ME was better in AgP than in patients with chronic periodontitis;[4] similarly, a blinded clinical trial showed superior benefits of MOX in GAgP in comparison to SRP.[3,8] Furthermore, recent meta-analyses showed that the adjunctive advantage observed from antimicrobial management is superior in AgP.[2]

Weiss *et al*.[11] confirmed that MOX impedes the generation of IL-8, TNF-α, and IL-β in lipopolysaccharide-stimulated human peripheral blood monocytes and the THP-1 monocytic cells. Moreover, intensities in saliva and capillary plasma narrowly replicate comparable concentrations in venous plasma;[12] furthermore, although information concerning the level of MOX within gingival crevicular fluid are not existing,[13] comparable levels as measured for ofloxacin (also a fluoroquinolone) could be pretended (eleven percent of ofloxacin presented concentrations of 1700 mg/ml at 3 h after of a controlled-release insertion).[14] MOX is a fourth-generation quinolone that presents good bioavailability, prolonged half-life, and adequate tissue dispersion;[15] and it has recognized tolerability, and there is no report of adverse events in periodontitis clinical trials.[3,16] Besides, MOX features allow a unique posology daily, which decreases prices and augments the patient's fulfillment.[17] Instead, AMOX + ME must be ordered with discretion since were recognized substantial amounts of antimicrobial-resistant periodontopathogens in the different parts of the word.[18-20] Furthermore, various meta-analyses have revealed the adverse events of AMOX + ME: A recent one reported 287 cases of diarrhea, nausea, and vomiting.[21]

Contemplating certain peculiarities of AgP, precisely, age of beginning, rates of progress, configurations of damage, and features of inflammation[22] the repercussion of the intrinsic hierarchical configuration of periodontal features (related to patient, tooth, and site) in the management of AgP should be investigated. It is consistent to consider that taking into account these peculiarities periodontal treatment might differ between persons, tooth and site in AgP.

To our knowledge, no trials have considered the hierarchical structure of periodontal data in deciding the variation of the clinical results following adjunctive MOX and AMOX + ME in comparison to SRP in AgP. Therefore, this clinical trial aimed to study the clinical features related to the patient, tooth, and site that generate more changes in attachment level improvement and pocket diminution, using MOX and AMOX + MET as an adjunct to SRP, in comparison to SRP at 6 months posttreatment in generalized AgP.

MATERIALS AND METHODS

Patients

The participants included in this clinical trial (NCT02839421) presented a minimum of twenty teeth, excepting designated exodontia, and third molars. Each patient signed informed consent. The investigation protocol (IRB 15–60) was accepted by the Ethics Committee of the University Research Center of the University, rendering to the Declaration of Helsinki. All patients were conscious about the purposes, possible threats, and advantages of the therapies. Persons diagnosed with generalized AgP were aspirants for the investigation. This diagnosis was established on standards described at the workshop supported by the American Academy of Periodontology.[22,23]

Patients were ≤30 years old; they had a minimum of six permanent teeth, counting incisors and/or first molars (including at least one site with PD and CAL ≥5 mm), and at least six teeth additional than first molars and incisors (with at least one site each with PD and CAL ≥5 mm). Through the interrogation, patients were requested about

the presence of relatives (manifesting or with a background of periodontitis) to consider the familial aggregation (in negative cases, the patients were excluded). Furthermore, the patients were excluded in cases of diabetes, cardiovascular disorders, immune illnesses, or some other systemic sickness that can modify the progress of periodontitis. Gestating or nursing females, smokers, and hypersensitivity to quinolones, moxifloxacin, amoxicillin, or metronidazole, intake of systemic antibiotics, or anti-inflammatory medicines in the last 6 months, and periodontal treatment in the last semester also were the exclusion reasons.

The trial protocol and therapy

The three treatments included SRP plus oral intake of MOX (400 mg daily for 7 days) or AMOX + ME (500 mg each one tid for 7 days) or SRP + placebo once daily for 7 days. A hygienic phase was done previous to SRP (all patients received instructions in same brushing technique). Subsequently, one-stage full-mouth SRP (using manual curettes and ultrasonic debridement) was finalized in approximately 2 h. The antimicrobials and placebo treatments commenced immediately after the full-mouth session of SRP. MOX, AMOX + ME, and placebo presented equal features concerning the packing and marking.

Randomization was done utilizing computer-generated randomization blocks; numbers were randomly allocated into one of three blocks denoting the three treatment protocols to elude imbalance between them. The therapy protocol distributions were allotted in numbered identical opaque packets, which were then given to a coordinator who did not partake in the experiment. This coordinator unsealed the packets and pointed the participant number on the proper medicine container. An assistant provided the medications to all patients. This information was referred to the director and persisted unidentified to the investigators and the periodontist until statistical analysis was completed.

Compliance

A secretary telephoned all patients the remaining 6 days to emphasize to ingest the resting dosages. This secretary (not intruded in the study methods) verified fulfillment with medications/placebo consumption and the existence of adverse incidents. The patients were solicited to take the containers holding the medications/placebo the week next the first appointment when the prescriptions were totaled to observe some imprecision in pills ingestion. Besides, the patients solved a form concerning self-recognized adverse events of the medications/placebo.

Clinical valuation

Participants were clinically evaluated at baseline and 6 months following therapy. At all patient and examination date, noticeable biofilm (1/0), bleeding on probing (BOP) (1/0), PD, and CAL were established at six sites per tooth in every tooth, disregarding third molars. The clinical distances were recognized to the contiguous millimeter by a regular probe (UNC-15, Hu-Friedy, Chicago, IL, USA).

The same periodontist (blinded, trained, and harmonized) accomplished the assessment at all schedules for designated participants. The periodontist realizing the clinical examinations did not perform the therapy. The intra-examiner accordance was planned previously and through the trial period. The quantitative correspondence data for mean PD and CAL were 0.9 and 0.89, respectively.

Result variables

In this multilevel model, a difference in clinical attachment among baseline and 6 months (ΔCAL) was considered as the principal result variable. Subordinate outcome features involved variations for the mean differences of PD. Therefore, a change in probing depth regarding baseline and 6 months (ΔPD) was contemplated as a dependent variable.

The sample calculation to assure adequate power was valued, expecting variations of at least one mm for CAL and a standard deviation of one mm concerning therapies.[24] Thus, it was recognized that at least 12 patients per protocol would be mandatory to source an 80% power an α of 0.05. Therefore, the analysis included 6012 tooth sites at 1002 teeth in 36 patients.

Statistical analysis

Variances in quantitative and qualitative features were studied by independent *t*-test (data were dispersed normally) and Chi-square test, correspondingly. A repeated-measures ANOVA was achieved to identify the changes in clinical parameters (intra-group and between groups). These calculations were applied to operate statistical software (SPSS, Statistical Package for the Social Sciences, version 24, Chicago, IL, USA). $P < 0.05$ was recognized for statistical significance.

Three stages of variability were defined: The patient, the tooth, and the site. Participant features included

age (years), sex, biofilm, BOP, and therapies (Adjunctive MOX and AMOX + ME against SRP + placebo). Tooth features embraced one qualitative characteristic: Molars/non-molars. Site features measured the position (interdental against buccal/lingual).

Variance models (empty models) were generated estimating disparities in CAL (ΔCAL) and PD (ΔPD) considering baseline and 6 months as dependent features without introducing explanatory characteristics. The crude models estimate the whole variability of ΔCAL and ΔPD and to appoint it to the patient, tooth, and site stages. Successions of explicatory variables were explored into the multivariate models to determine the relationship between each explanatory feature and the dependent variable.

Subsequently, multilevel analyses for quantitative variables were run (normality of the residuals were checked). Regression coefficients were computed managing iterative generalized least squares. Nested models were assessed for significant increases in the model fit by equating the reduction in − 2 log likelihood with a Chi-square distribution. All hierarchic models were finalized utilizing a statistical set (MLwin 2.02, London, UK). $P < 0.05$ was standard for statistical significance.

RESULTS

The analysis included 6012 tooth sites at 1002 teeth in 36 patients (12 for each group) that visited the dental clinics of the University (from December 2015 to October 2018).

Fifty-five patients were considered for their acceptability before participating in the research. Then, 19 patients were ineligible because they did not congregate the inclusion features. All 36 patients completed the information for all checking visits, while two patients had one absent call (AMOX + ME and SRP + placebo at 3 months). Intent-to-treat analyses were achieved in the two participants with a nonexistent report, by which the preliminary inspection was moved forward, presenting all patients with complete information that were involved in the analyses. Figure 1 shows the flow chart of the trial.

All participants informed complete adherence to the recommended structure of trial protocols; three patients in the AMOX + ME group informed unfavorable incidents at the beginning of the study (diarrhea, nausea, and vomiting).

The baseline characters of the patients did not show differences between the therapies [Figure 2].

Differences in CAL and PD in the three interventions through the clinical experiment are seen in Figure 3. All protocols caused a significant diminution of PD and CAL contrasted with baseline ($P < 0.0001$), and this variation was conserved at 6 months in all therapies. The variations between treatments were statistically meaningful at 6 months, preferring the antimicrobial groups ($P < 0.0001$).

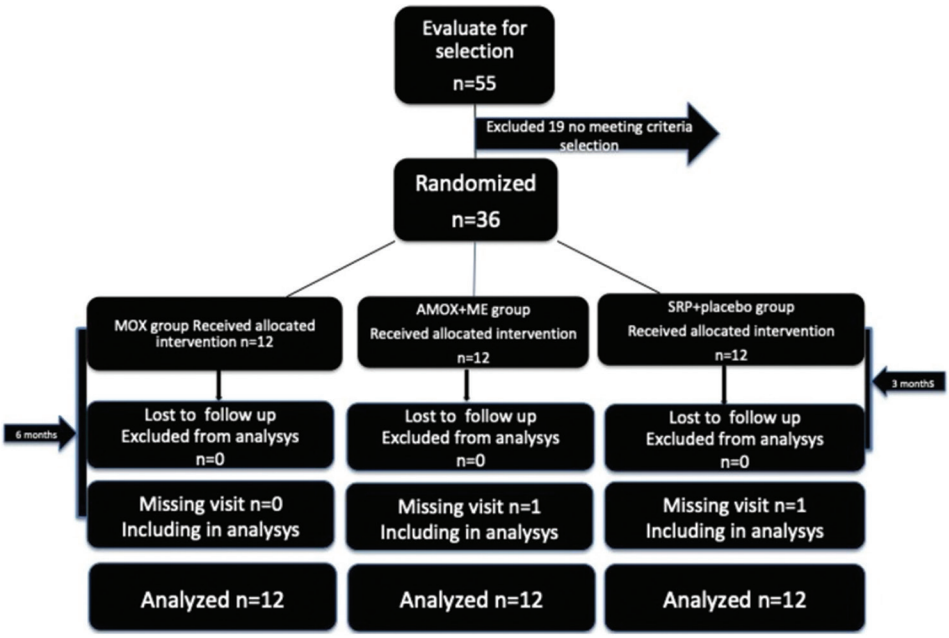

Figure 1: Flow chart of the trial.

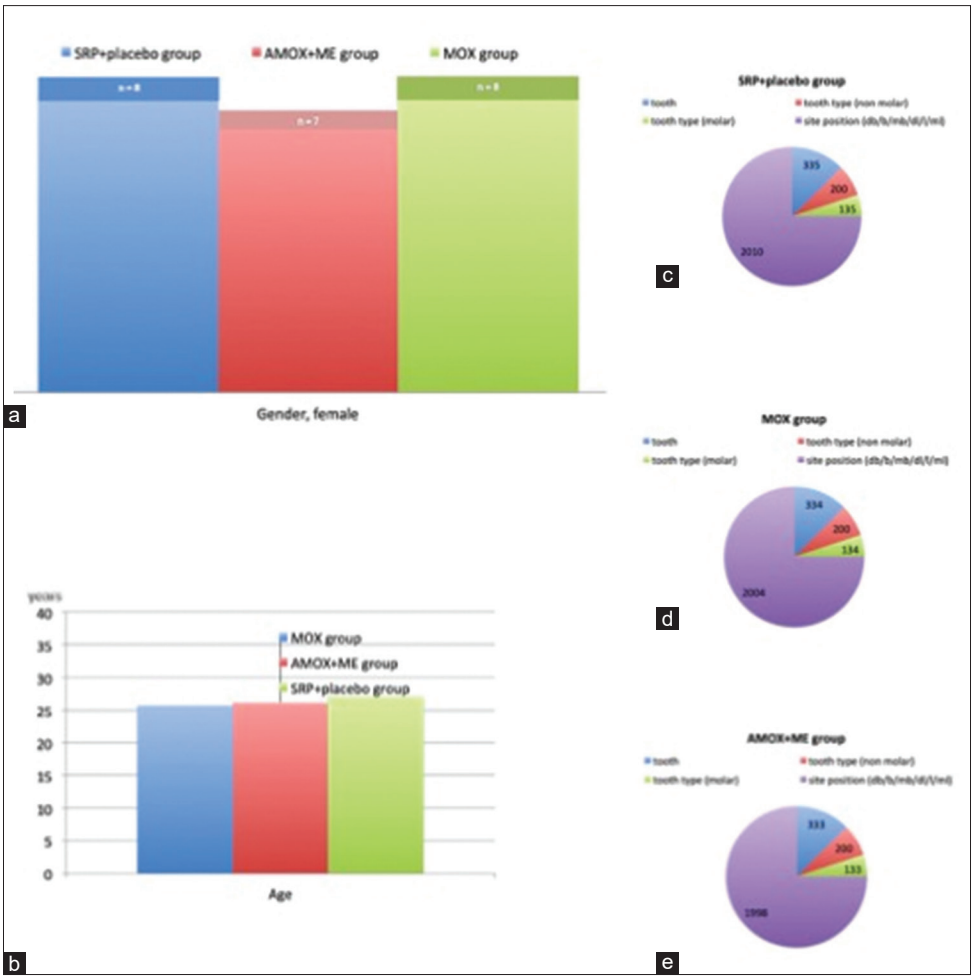

Figure 2: Baseline characteristics. (a) Gender. (b) Age. (c) Tooth, tooth type, and sites in the SRP + placebo group. (d) Tooth, tooth type, and sites in the MOX group. (e) Tooth, tooth type, and sites in the AMOX + ME group.

Contemplating that a multilevel model was used, three units of analysis were considered: The patient, tooth, and site. Thus, all tables depict the results using three levels.

Outcomes from the crude hierarchic prototypes (with ΔCAL and ΔPD as the dependent variables) are depicted in Tables 1 and 2.

The crude analysis for ΔCAL specified an entire inexplicable variability of 1.78; more significant part accredited to the disparity between teeth (56%), succeed by among sites (25%), and between participants (19%). The adding of the explicatory features conducted to a 33% attenuation of the absolute unexplained variance: 24% at the patient stage, 39% at the tooth level, and 26% at the site stage. Substantially superior fitting was obtained, counting the clinical explicatory characteristics at all levels ($P < 0.001$) [Table 1].

The crude multilevel for ΔPD showed a full-unexplained variability of 1.44, the more part assigned to the variability among teeth (59%), followed by among sites (23%), and between participants (18%). The inclusion of the explanatory characteristics conducts to a 25% decrease of the complete unexplained variability: 16% at the subject level, 30% at the tooth stage, and 20% at the site level. Significantly superior fitting was observed incorporating the clinical explicatory features at all levels ($P < 0.001$) [Table 2].

Table 3 shows the multilevel multivariate analyzes revising the explicatory characteristics modeling ΔCAL as the dependent variable. At the patient level, adjunctive antibiotics presented a significantly affirmative reaction in CAL improve ($P = 0.0001$). At the tooth stage, the statistic revealed that non-molars offered the most significant improvements in CAL contrasted to molars ($P < 0.0001$). Finally, at the site stage, interdental sites were the places where CAL increases were higher than at the non-proximal sites ($P = 0.0001$).

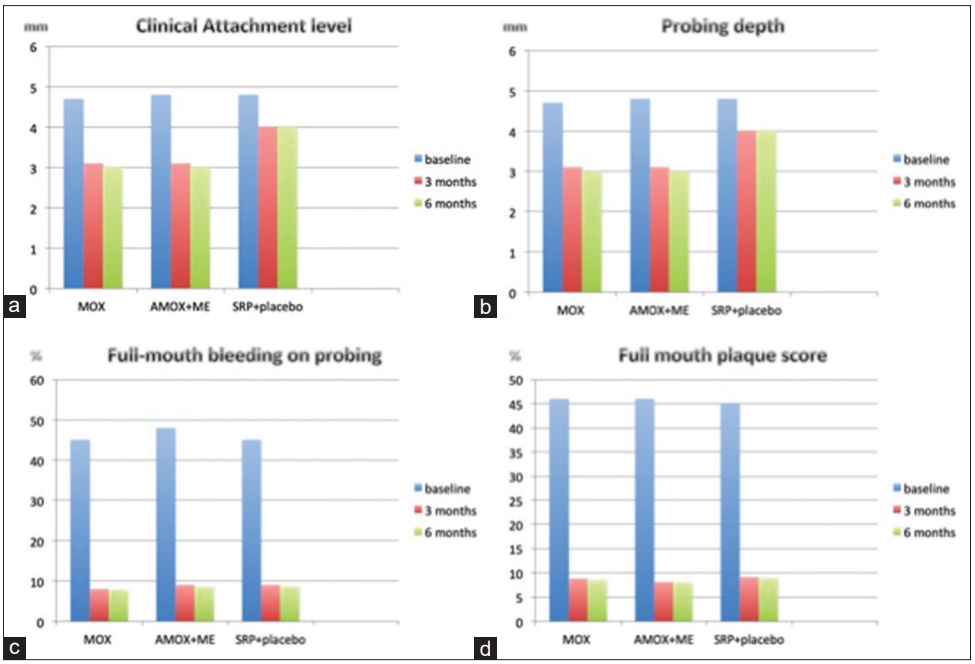

Figure 3: Clinical characteristics through the experiment. Statistically significant differences were observed in clinical attachment level (a) and probing depth (b) at three and six months after treatment, favoring the antimicrobial groups. Even though a significant decrease in bleeding on probing (c) and plaque levels (d) was observed after treatment in all groups, no statistically significant differences were observed in these parameters at three and six months after treatment between the groups

An analogous inclination depicts the multilevel multivariate statistic examining the explanatory features inducing ΔPD as the dependent feature [Table 4]. At the subject stage, adjunctive antimicrobials presented a more priceless reaction in PD diminution ($P = 0.0001$). At the tooth stage, the exploration confirmed that non-molars exposed the most significant diminutions in probing depth compared to molars ($P < 0.0001$). Besides, at the site level, interdental sites were the measures where PD discounts were more significant ($P = 0.001$).

DISCUSSION

The presentation of surrogate factors, including probing depth and clinical attachment level to value the clinical efficacious of some treatments is a common approach.[25] Using a multilevel model, this trial shows variability in CAL and PD between the line of base and 6 months after adjunctive MOX and AMOX + MET in comparison to SRP. Therefore, the principal source of variance in CAL improving and PD decrease after adjunctive antimicrobials was due to the features of the tooth level; succeed by site, and the patient characteristics. Equivalent results were described previously in a multilevel clinical trial contrasting adjunctive MOX and mechanical treatment in aggressive periodontitis.[26] Similarly, features related to the tooth were described (using a multilevel analysis) as significant for the results of adjunctive doxycycline for the re-treatment of chronic periodontitis.[27]

In this trial, the exploration for ΔCAL, incorporating all significant variables, reduced 33% of the complete unexplained variance. Similarly, the analysis for ΔPD decreased 25% of the complete unexplained variance, showing superiority at the tooth level. These

Table 1: Multilevel linear regression model valuing the relative influence of patient, tooth and site factors to variability in clinical attachment level gain

Level	ΔCAL baseline-6-month empty model β±SE	ΔCAL baseline-6-month multivariate model β±SE
Intercept	2.641±0.072	3.298±0.079
Subject (Level 3)	0.340±0.071 (19)‡	0.259±0.017 (−24%)†
Tooth (Level 2)	1.002±0.042 (56)‡	0.608±0.072 (−39%)†
Site (Level 1)	0.447±0.017 (25)‡	0.331±0.011 (−26%)†
Total variance	1.789	1.198
−2 LL	16079.025	11296.019*

‡Percentage of variance in the dependent variable ΔCAL attributed by the multilevel model at the patient, tooth, and site level, †Difference in the percentage of variance in the dependent variable ΔCAL at the patient, tooth, and site level when explanatory variables were included in the model, *−2 LL change significant ($P<0.001$) tested by Chi-square. β±SE: Mean β±standard error; CAL: Clinical attachment level

Table 2: Multilevel linear model calculating the relative impact of patient, tooth and site factors to variability in probing depth diminution

Level	ΔPD baseline-6 months empty model β±SE	ΔP baseline-6 months multivariate model β±SE
Intercept	2.619±0.079	3.428±0.044
Patient (Level 3)	0.261±0.033 (18)‡	0.219±0.042 (−16%)†
Tooth (Level 2)	0.849±0.013 (59)‡	0.597±0.079 (−30%)†
Site (Level 1)	0.339±0.019 (23)‡	0.271±0.078 (−20%)†
Total variance	1.449	1.087
−2 LL	13670.139	10131.327*

‡Percentage of variance in the dependent variable ΔPD attributed by the multilevel model at the patient, tooth, and site level, †Difference in the percentage of variance in the dependent variable ΔPD at the patient, tooth, and site level when explanatory variables were included in the model, *−2 LL change significant (*P*<0.001) tested by Chi-square. β±SE: Mean β±standard error; PD: Probing depth

Table 3: Multilevel linear regression model measuring the significance of patient, tooth and site issues in describing the variability in clinical attachment level gain

Level and parameters	ΔCAL baseline-6 months (β±SE)	*P*
Subject level		
Adjunctive MOX/SRP+placebo	0.609±0.291	0.001
Adjunctive AMOX+ME/SRP+placebo	0.599±0.272	0.001
Tooth level		
Tooth position (nonmolar/molar)	0.7436±0.012	<0.0001
Site level		
(db-mb-dl-ml/b-l)	0.041±0.019	0.001

β±SE: Mean β±Standard error; db: Distobuccal; b: Buccal; mb: Mesiobuccal; dl: Distolingual; l: Lingual; ml: Mesiolingual; MOX: Moxifloxacin; SRP: Scaling and root planning; AMOX+ME: Amoxicillin plus metronidazole; CAL: Clinical attachment level

Table 4: Multilevel linear regression model assessing the significance of patient, tooth and site parameters in explaining the variability in probing depth reduction

Parameters	ΔPD baseline-6 months (β±SE)	*P*
Subject level		
Adjunctive MOX/SRP+placebo	0.697±0.037	0.0001
Adjunctive AMOX+ME/SRP+placebo	0.669±0.041	0.0001
Tooth level		
Tooth position (nonmolar/molar)	0.701±0.049	<0.0001
Site level		
(db-mb-dl-ml/b-l)	0.039±0.015	0.001

β±SE: Mean β±Standard error; db: Distobuccal; b: Buccal; mb: Mesiobuccal; dl: Distolingual; l: Lingual; ml: Mesiolingual

results emphasized the implication of contemplating features correlated with the tooth to select periodontal treatment correctly. A comparable advice can operate in aggressive periodontitis.[27]

This multilevel model related attachment gain and probing diminution with adjunctive MOX and AMOX + ME (at the patient level); non-molar (at the tooth level); and interproximal sites (at the site level). Similar results were described previously in a multilevel model comparing adjunctive MOX and SRP + placebo in treating generalized AgP.[26]

This experimental research valued the influence of distinct features at the patient, tooth, and site levels using adjunctive MOX and AMOX + ME in generalized AgP. The effectiveness of adjunctive MOX in AgP using a multilevel model was assessed before but without compares it with AMOX + MET;[26] nevertheless, the effectiveness of adjunctive MOX in terms of probing reduction and attachment gain was corroborated. Similarly, implementing a multilevel analysis, it was presented that adjunctive amoxicillin plus metronidazole lead to more clinical profits than any other therapy.[9] Therefore, the outcomes of the present trial validate the published data documented previously, presenting that therapy outcomes in different sites and teeth in the same subject are not independent.[9,27]

In this trial, lower outcomes were noticed in molars, corroborating the findings of others publications that also studied multilevel models in the valuation of the therapies results;[9,24,26] this statement can be interrelated to problematic approachability for mechanical treatment in molars.[27] Complementing this information, two multilevel researchers described more marked probing reduction and attachment improving in the uniradicular teeth.[26-29]

This multilevel trial founded that at the site stage, additional reductions in probing depth were identified for interproximal sites in comparison to buccal/lingual areas, confirming anterior data and consistent with the predominance of more profound sites in the interproximal spaces.[28]

A review presented that systemic antimicrobials offered a supplementary probing depth decrease and clinical attachment increase for moderate and profound pockets.[4] Similarly, in this trial, adjunctive MOX and AMOX + ME occasioned CAL improving and PD diminution with information equivalent to preceding researches that administrated MOX or AMOX + ME in generalized AgP.[3,5,6,30,31]

This research no founded an effect of factors as age, sex, biofilm, and bleeding at the subject level on the clinical gain and probing decrease. Analogous conclusions were knowledgeable in multilevel reports.[26-28] As

was observed in this trial, an uncertain impact of subject-factors in the multilevel model has been commonly recognized.[28] In consonance with precedent multilevel trials, more factors are linked to tooth level than patient factors in the therapy outcomes.[26,29]

Participants of the MOX protocol did not manifest adversative incidents through this research, confirming the findings of diverse publications regarding aggressive periodontitis.[3,6] Instead, three patients from the AMOX + ME protocol informed mild adverse events validating the results of other trials.[6,30,32]

In this clinical trial, the recommended regimen of AMOX + ME (500 mg tid each one for 7 days) was used, based on the attitudes of responsible antimicrobials consumption.[32]

One limitation of this multilevel trial is the observation period. Longitudinal studies will be required to conclude if these adjunctive protocols would establish satisfactory variations in the clinical features over time. On the other hand, it is relevant to clarify that in this trial the periodontal diagnosis[22,23] was based on the parameters established previously to the current classification;[33] this trial protocol was registered in 2015 and the enrolling of the patients commenced on December 2015. However, a very recent study that pointed to evaluate in what way the 2018 and 1999 categorizations of periodontitis replicate subjects' features, "disease severity/extent/progression, and tooth loss", concluded that considering the 2018 classification, and by CAL as principal measure, patients formerly established as AgP, were all reclassified as "Grade C most with Stage III."[34]

CONCLUSION

Adjunctive MOX and AMOX + ME, non-molar, and interdental areas were the features in defining clinical attachment gain and probing depth reduction in AgP. The leading source of variance in clinical attachment improving and probing diminution, after adjunctive MOX or AMOX + ME was derivable to the tooth characteristics. Besides, patients better tolerate MOX protocol; therefore, it could become an alternative when intolerance or hypersensitivity to AMOX + ME is reported.

Acknowledgments

The authors would like to thank to the School of Dentistry of the University of Antioquia.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

REFERENCES

1. Teughels W, Dhondt R, Dekeyser C, Quirynen M. Treatment of aggressive periodontitis. Periodontol 2000 2014;65:107-33.
2. Pretzl B, Sälzer S, Ehmke B, Schlagenhauf U, Dannewitz B, Dommisch H, *et al*. Administration of systemic antibiotics during non-surgical periodontal therapy-a consensus report. Clin Oral Investig 2019;23:3073-85.
3. Ardila CM, Martelo-Cadavid JF, Boderth-Acosta G, Ariza-Garcés AA, Guzmán IC. Adjunctive moxifloxacin in the treatment of generalized aggressive periodontitis patients: Clinical and microbiological results of a randomized, triple-blind and placebo-controlled clinical trial. J Clin Periodontol 2015;42:160-8.
4. Keestra JA, Grosjean I, Coucke W, Quirynen M, Teughels W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated aggressive periodontitis: A systematic review and meta-analysis. J Periodontal Res 2015;50:689-706.
5. Guerrero A, Griffiths GS, Nibali L, Suvan J, Moles DR, Laurell L, *et al*. Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: A randomized placebo-controlled clinical trial. J Clin Periodontol 2005;32:1096-107.
6. Guzeldemir-Akcakanat E, Gurgan CA. Systemic moxifloxacin vs. amoxicillin/metronidazole adjunct to non-surgical treatment in generalized aggressive periodontitis. Med Oral Patol Oral Cir Bucal 2015;20:e441-9.
7. Van der Weijden GA, Timmerman MF. A systematic review on the clinical efficacy of subgingival debridement in the treatment of chronic periodontitis. J Clin Periodontol 2002;29 Suppl 3:55-71.
8. Ardila CM, Guzmán IC. Benefits of adjunctive moxifloxacin in generalized aggressive periodontitis: A subgroup analyses in *Aggregatibacter actinomycetemcomitans*-positive/negative patients from a clinical trial. J Investig Clin Dent 2017;8:10.1111/jicd.12197.
9. Mdala I, Haffajee AD, Socransky SS, de Blasio BF, Thoresen M, Olsen I, *et al*. Multilevel analysis of clinical parameters in chronic periodontitis after root planing/scaling, surgery, and systemic and local antibiotics: 2-year results. J Oral Microbiol 2012;4:10.3402/jom.v4i0.17535.
10. Mombelli A, Cionca N, Almaghlouth A, Décaillet F, Courvoisier DS, Giannopoulou C. Are there specific benefits of amoxicillin plus metronidazole in *Aggregatibacter actinomycetemcomitans*-associated periodontitis? Double-masked, randomized clinical trial of efficacy and safety. J Periodontol 2013;84:715-24.
11. Weiss T, Shalit I, Blau H, Werber S, Halperin D, Levitov A, *et al*. Anti-inflammatory effects of moxifloxacin on activated human monocytic cells: Inhibition of NF-kappaB and mitogen-activated

protein kinase activation and of synthesis of proinflammatory cytokines. Antimicrob Agents Chemother 2004;48:1974-82.
12. Conway TB, Beck FM, Walters JD. Gingival fluid ciprofloxacin levels at healthy and inflamed human periodontal sites. J Periodontol 2000;71:1448-52.
13. Tsaousoglou P, Nietzsche S, Cachovan G, Sculean A, Eick S. Antibacterial activity of moxifloxacin on bacteria associated with periodontitis within a biofilm. J Med Microbiol 2014;63:284-92.
14. Higashi K, Seike M, Mitani Y, Morisaki K, Hayashi S, Kitamura M, *et al*. Concentration of ofloxacin in human gingival crevicular fluid after oral administration of Tarivid. J Periodontal Res 1989;24:409-11.
15. Cachovan G, Nergiz I, Thuss U, Siefert HM, Sobottka I, Oral O, *et al*. Penetration of moxifloxacin into rat mandibular bone and soft tissue. Acta Odontol Scand 2009;67:182-6.
16. Guentsch A, Jentsch H, Pfister W, Hoffmann T, Eick S. Moxifloxacin as an adjunctive antibiotic in the treatment of severe chronic periodontitis. J Periodontol 2008;79:1894-903.
17. Krasemann C, Meyer J, Tillotson G. Evaluation of the clinical microbiology profile of moxifloxacin. Clin Infect Dis 2001;32 Suppl 1:S51-63.
18. Ardila CM, Granada MI, Guzmán IC. Antibiotic resistance of subgingival species in chronic periodontitis patients. J Periodontal Res 2010;45:557-63.
19. Rams TE, Degener JE, van Winkelhoff AJ. Prevalence of β-lactamase-producing bacteria in human periodontitis. J Periodontal Res 2013;48:493-9.
20. van Winkelhoff AJ, Herrera D, Oteo A, Sanz M. Antimicrobial profiles of periodontal pathogens isolated from periodontitis patients in The Netherlands and Spain. J Clin Periodontol 2005;32:893-8.
21. Doña I, Barrionuevo E, Blanca-Lopez N, Torres MJ, Fernandez TD, Mayorga C, *et al*. Trends in hypersensitivity drug reactions: More drugs, more response patterns, more heterogeneity. J Investig Allergol Clin Immunol 2014;24:143-53.
22. Armitage GC, Cullinan MP. Comparison of the clinical features of chronic and aggressive periodontitis. Periodontol 2000 2010;53:12-27.
23. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.
24. Varela VM, Heller D, Silva-Senem MX, Torres MC, Colombo AP, Feres-Filho EJ. Systemic antimicrobials adjunctive to a repeated mechanical and antiseptic therapy for aggressive periodontitis: A 6-month randomized controlled trial. J Periodontol 2011;82:1121-30.
25. Greenstein G. The use of surrogate variables to reflect long-term tooth survivability. J Periodontol 2005;76:1398-402.
26. Ardila CM, Guzmán IC. Clinical factors influencing the efficacy of systemic moxifloxacin in the therapy of patients with generalized aggressive periodontitis: A multilevel analysis from a clinical trial. Glob J Health Sci 2015;8:80-8.
27. Tomasi C, Leyland AH, Wennström JL. Factors influencing the outcome of non-surgical periodontal treatment: A multilevel approach. J Clin Periodontol 2007;34:682-90.
28. D'Aiuto F, Ready D, Parkar M, Tonetti MS. Relative contribution of patient-, tooth-, and site-associated variability on the clinical outcomes of subgingival debridement. I. Probing depths. J Periodontol 2005;76:398-405.
29. Kim TS, Schenk A, Lungeanu D, Reitmeir P, Eickholz P. Nonsurgical and surgical periodontal therapy in single-rooted teeth. Clin Oral Investig 2007;11:391-9.
30. Aimetti M, Romano F, Guzzi N, Carnevale G. Full-mouth disinfection and systemic antimicrobial therapy in generalized aggressive periodontitis: A randomized, placebo-controlled trial. J Clin Periodontol 2012;39:284-94.
31. Mestnik MJ, Feres M, Figueiredo LC, Soares G, Teles RP, Fermiano D, *et al*. The effects of adjunctive metronidazole plus amoxicillin in the treatment of generalized aggressive periodontitis: A 1-year double-blinded, placebo-controlled, randomized clinical trial. J Clin Periodontol 2012;39:955-61.
32. McGowan K, McGowan T, Ivanovski S. Optimal dose and duration of amoxicillin-plus-metronidazole as an adjunct to non-surgical periodontal therapy: A systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Periodontol 2018;45:56-67.
33. Caton GJ, Armitage G, Berglundh T, Chapple IL, Jepsen S, Kornman SK, *et al*. A new classification scheme for periodontal and peri-implant diseases and conditions Introduction and key changes from the 1999 classification. J Clin Periodontol 2018;45 Suppl 20:S1-8.
34. Graetz C, Mann L, Krois J, Sälzer S, Kahl M, Springer C, *et al*. Comparison of periodontitis patients' classification in the 2018 versus 1999 classification. J Clin Periodontol 2019;46:908-17.