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Periodontology

Effectiveness of amoxicillin or amoxicillin combined with metronidazole as adjunct to scaling and root planing

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Abstract

Brief Background

Chronic periodontitis is the inflammation of tooth-supporting tissues, caused by microorganisms present in the subgingival biofilm. Anti-infective therapy has been accepted as the cornerstone of periodontal treatment. The aim of the study was to evaluate the efficacy of amoxicillin and amoxicillin in combination with metronidazole as adjunct to scaling and root planing in treatment of chronic periodontitis.

Materials and Methods

A total of 52 participants having moderate to severe chronic periodontitis were included and divided into 2 groups. After thorough scaling and root planing, participants were prescribed Amoxicillin alone (Control group) or Amoxicillin + Metronidazole (Test group), three times a day, for a period of seven days. Plaque Index (PI), Gingival Index (GI), Probing Depth (PD) and Clinical Attachment Level (CAL) were assessed at baseline and 3 months interval.

Results

Significant differences were seen from baseline to 3 months in both test and control groups in terms of reduction in PI, reduction in GI, decrease in PD and gain in CAL ($p<0.001$). Inter-group analysis showed significant differences between the two groups after 3 months, with GI, PD and CAL showing significant differences with p-value <0.001.

Summary and Conclusions

At the end of 3 months, the combination of amoxicillin and metronidazole showed better results after mechanical therapy as compared to amoxicillin alone in the treatment of patients with chronic periodontitis.

Key Words

Chronic periodontitis, amoxicillin, metronidazole, scaling and root planing.

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Introduction

Chronic periodontitis is the inflammation of tooth-supporting tissues, caused by microorganisms present in the subgingival biofilm. This chronic inflammation leads to progressive destruction of periodontal ligament and alveolar bone, resulting in formation of periodontal pocket, gingival recession, or both. Periodontitis has a multi-factorial aetiology, but bacteria are known to be the primary etiologic agents.[1]

From the various bacterial species present in the subgingival biofilm, only a few have been clearly associated with the disease. The ongoing periodontal destruction has been linked to the presence of periodontal pathogens such as Porphyromonas gingivalis, Bacteriodes forsythus and Aggregatibacter actinomycetemcomitans by many authors.[2] If periodontal disease is left untreated, the resulting loss of attachment structures can ultimately lead to tooth loss. Periodontal disease is treated by removal of supragingival and subgingival plaque and calculus which is done by meticulous scaling and root planing in single or multiple stages as well as the institution of proper oral hygiene measures. This is the standard, non-specific treatment for periodontal disease, which helps to reduce the total bacterial load.[3] However, despite this therapy, some of the patients may experience ongoing periodontal attachment loss.

One of the possible reasons for the progression of disease post-treatment is the inability of the therapy to suppress periodontal pathogens to levels that are compatible to periodontal health. Also, not all patients or sites respond uniformly and favourably to conventional mechanical therapy. The reduced effectiveness of the therapy may be explained by a series of patient-related factors (local or generalized), the extent and nature of attachment loss, local anatomic variations, the form of the periodontal disease, and the composition and persistence of periodontal pathogens.[4]

The major goals of periodontal therapy are to suppress bacterial infection, modulate host response, and heal/regenerate periodontal tissues to provide a healthy periodontium favourable for the re-establishment of a long-lasting, host-compatible periodontal microbiota.[5] Periodontal treatment includes surgical and regenerative techniques and mechanical removal of supra- and subgingival microbial plaques, along with locally or systemically administered antimicrobial agents in specific groups of patients. Anti-infective therapy has been accepted as the cornerstone of periodontal treatment.

Studies [6,7] have demonstrated that systemic antimicrobial agents as adjuncts to mechanical therapy may be important in the treatment of chronic as well as aggressive forms of periodontal disease. These antimicrobial agents exert their action at the subgingival areas via gingival crevicular fluid, thus help to reach the areas insufficiently affected by mechanical instrumentation. In addition, antimicrobials reduce the microbial load at extracrevicular sites and at subgingival areas that have been insufficiently treated by mechanical instrumentation.

Various antibiotics have been used for the treatment of chronic periodontitis, such as lincosamides, macrolides, penicillins and tetracyclines. Amoxicillin, a beta lactam antibiotic, exerts its action by interfering with the synthesis of bacterial cell wall. It inhibits cross-linkage between the linear peptidoglycan polymer chains that make up a major component of the cell-wall of Gram-positive and a minor component of Gram-negative bacteria. Amoxicillin has been used alone since a long time for treatment of chronic periodontitis and has shown good results.

Metronidazole is a nitroimidazole, selective toxic to anaerobic microorganisms. After entering the cell, the nitro group is reduced by certain redox proteins in anaerobic microbes to highly reactive nitro radical which exerts cytotoxicity. Azithromycin has a wide antimicrobial spectrum with in-vitro activity against aerobic and anaerobic gram negative microorganisms and a long half-life in human serum and periodontal tissues. Azithromycin is found in high concentrations in fibroblasts and phagocytes and is carried to areas of inflammation as a result of chemotactic effects exerted on the phagocytes.[8]

The combination of amoxicillin and metronidazole was introduced by van Winkelhoff et al in 1989. Combining both the drugs results in a synergistic bactericidal effect that, in turn, reduces the time and dosage level required to obtain optimal effect, and ultimately minimizes the toxicity of both drugs.[9] It has also been suggested that some periodontal pathogens may be inaccessible to mechanical periodontal therapy as they have the ability to invade and hide in the gingiva or dentine of the root. Hence, it is possible that local or systemic administration of antimicrobial agents, effective against such pathogens,

may enhance the outcome of mechanical therapy. Thus the aim of the present study was to to evaluate the efficacy of amoxicillin and amoxicillin in combination with metronidazole as adjunct to scaling and root planing in treatment of chronic periodontitis.

Materials and Methods

This was a comparative clinical study. All the participants signed the informed consent statements after discussing any questions they had with the study investigator(s). Recruitment of the participants and sites were as per the following inclusion and exclusion criteria. Inclusion criteria included systemically healthy participants with untreated moderate to advanced periodontitis, age between 25 and 70 years, presence of >12 scorable teeth (not including third molars and teeth with orthodontic appliances, bridges, crowns, or implants), presence of at least four teeth with a probing depth (PD) >4 mm, clinical attachment loss (CAL) >2 mm, and radiographic evidence of bone loss. Exclusion criteria included systemic illnesses (i.e., diabetes mellitus, cancer, human immunodeficiency syndrome, bone metabolic diseases, or disorders that compromise wound healing, radiation, or immunosuppressive therapy), pregnancy or lactation, systemic antibiotics taken within the previous 2 months , use of non-steroidal anti-inflammatory drugs, confirmed or suspected intolerance to 5-nitroimidazole derivatives or amoxicillin, subgingival scaling and root planing or surgical periodontal therapy in the last year and participants with a history of smoking.

The participants were explained about both the procedures before commencing the treatment After fulfilling the inclusion and exclusion criteria, informed consent of the participants was taken. All the participants were selected according to the defined selection criteria. 52 patients were evaluated clinically at baseline for moderate to severe chronic periodontitis. The participants were then randomly divided into two groups.

After recording of clinical parameters at baseline, all patients received initial periodontal treatment, including scaling and root planing, oral hygiene instructions and plaque control. After thorough scaling and root planing, participants were prescribed either Amoxicillin alone (Control group) or Amoxicillin + Metronidazole (Test group), three times a day, for a period of seven days. Antibiotics were allotted to the patient by co-investigator. Drugs tested were Amoxicillin 500mg and Amoxicillin 500mg + Metronidazole 400mg

All clinical parameters were recorded immediately at baseline before scaling and root planing, and then after 3 months interval. Plaque Index (PI), Gingival Index (GI), Probing Depth (PD) and Clinical Attachment Level (CAL) were assessed at baseline and 3 months interval.

26 chits of Group A (Test group) and 26 chits of Group B (Control group) were made. After Phase I therapy one chit was allotted to each participant after they randomly picked up the chit. All participants in the Group A were given Amoxicillin 500mg + Metronidazole 400mg thrice daily for 7 days and Group B were given Amoxicillin 500mg thrice daily for 7 days, after completion of scaling and root planing. Antibiotics were allotted to the patient by co-investigator and data was collected by primary investigator who was blinded for the allocation. Participants were recalled after an interval period of 3 months after which clinical parameters were recorded again.

The statistical tests used were Paired T-test to compare baseline data with 3 month data in both test and control groups. Independent T-test was performed to compare clinical parameters between the two groups at baseline and 3 months post-operatively. Differences were considered to be statistically significant at $p<0.05$.

Results

This was a comparative clinical study done to find out the adjunctive clinical effects of the antibiotics, amoxicillin alone, or amoxicillin with metronidazole administered after scaling and root planing three times a day for a period of seven days. The study included 52 patients divided into 2 groups. Both the test and control groups consisted of 26 patients each.

Results were analyzed at baseline and post-treatment after 3 months, within each group and between the two groups with Paired t-test and Independent t-test.

The demographic data is shown in Table 1. The mean age in the test group was 48.5 years and in the control group was 47.65 years. There were 53.8% males and 46.2% females in the test group, and 57.7% males and 42.3% females in the control group. There was no statistical difference between the two groups with respect to age ($p=0.49$). (Table 2)

Table 1: Comparison of males and females among both the groups

			Gender		Total
			Male	Female	
Group	Test	Count	14	12	26
		% within Group	53.8%	46.2%	100.0%
	Control	Count	15	11	26
		% within Group	57.7%	42.3%	100.0%
Total		Count	29	23	52
		% within Group	55.8%	44.2%	100.0%

Table 2: Comparison of age in terms of {Mean (SD)} among both the groups using unpaired t test

Group	N	Mean	Std. Deviation	t value	P value
Test	26	48.50	4.072	0.688	0.495
Control	26	47.65	4.774		

In the test group (SRP + Amoxicillin + Metronidazole), from baseline to 3 months period, statistically significant differences were seen in terms of plaque index from 2.11 ± 0.19 to 0.35 ± 0.14. The gingival index significantly improved from 1.65 ± 0.14 to 0.12 ± 0.05. There was a decrease in probing depth from 5.70 ± 0.21 to 3.78 ± 0.16 and gain in clinical attachment level from 6.43 ± 0.15 to 4.52 ± 0.23 at the end of 3 months which was statistically significant. (Table 3)

In the control group (SRP + Amoxicillin), from baseline to 3 months period, statistically significant differences were seen in terms of plaque index from 2.11 ± 0.20 to 0.34 ± 0.15. The gingival index significantly improved from 1.70 ± 0.13 to 0.35 ± 0.10. There was a decrease in probing depth from 5.66 ± 0.25 to 5.19 ± 0.30 and gain in clinical attachment level from 6.46 ± 0.16 to 5.93 ± 0.15 at the end of 3 months which was statistically significant. (Table 4)

The clinical parameters of the both the test and control group were compared at the end of 3 months. Table 5 shows difference of clinical parameters between test and control group at the end of 3 months period. When the differences between baseline and follow-up in clinical parameters were compared (inter group), gingival index, probing depth and clinical attachment level showed statistically significant differences with p-value <0.001. No significant difference was seen in terms of plaque index (p=0.86).

Discussion

This study evaluated the clinical effects of two antibiotic protocols in subjects with generalized chronic periodontitis. In the test group, after mechanical debridement, combination of amoxicillin and metronidazole was given systemically thrice a day for a period of seven days, whereas in the control group, amoxicillin alone was given after mechanical debridement thrice a day for a period of seven days.

The aim of the study was to evaluate the efficacy of amoxicillin and amoxicillin in combination with metronidazole as adjunct to scaling and root planing in treatment of chronic periodontitis.

Chronic periodontitis can be considered as a complex disease that is mainly caused by intraoral biofilms that harbour periodontal pathogenic microorganisms. One of the major goals of treatment of chronic periodontitis includes reducing the proportion and levels of periodontal pathogens and expanding the quantity of beneficial species. However, non-surgical and surgical mechanical therapies are ineffective at reducing the presence of periodontal pathogenic bacteria in non-dental intraoral habitats.[10] Consequently, recolonization of the subgingival area by pathogens is common after treatment.

Antibiotics are effective means of treating bacterial infections and, therefore, constitute a reasonable consideration in the treatment of periodontal infections.

Table 3: Comparison of the Plaque index, gingival index, probing depth and clinical attachment level values in terms of {Mean (SD)} pre and post using paired t test (TEST GROUP)

		N	Mean	Std. Deviation	t value	P value
Plaque index	**Pre**	26	2.111	0.192	38.775	<0.001**
	Post	26	0.350	0.147		
Gingival index	**Pre**	26	1.650	0.142	48.881	<0.001**
	Post	26	0.120	0.051		
Probing depth	**Pre**	26	5.703	0.211	36.664	<0.001**
	Post	26	3.782	0.167		
Clinical attachment level	**Pre**	26	6.43	0.159	49.866	<0.001**
	Post	26	4.52	0.238		

(p< 0.05 - Significant*, p < 0.001 - Highly significant**)

Table 4: Comparison of the Plaque index, gingival index, probing depth and clinical attachment level values in terms of {Mean (SD)} pre and post using paired t test (CONTROL GROUP)

		N	Mean	Std. Deviation	t value	P value
Plaque index	**Pre**	26	2.115	0.201	35.180	<0.001**
	Post	26	0.342	0.157		
Gingival index	**Pre**	26	1.703	0.137	40.886	<0.001**
	Post	26	0.357	0.106		
Probing depth	**Pre**	26	5.661	0.254	9.337	<0.001**
	Post	26	5.193	0.309		
Clinical attachment level	**Pre**	26	6.466	0.160	21.945	<0.001**
	Post	26	5.934	0.158		

(p< 0.05 - Significant*, p < 0.001 - Highly significant**)

Table 5: Comparison of the mean difference (pre – post) of Plaque index, gingival index, probing depth and clinical attachment level values in terms of {Mean (SD)} pre and post among test and control group using unpaired t test

Mean Difference	Group	N	Mean	Std. Deviation	t value	P value
Plaque index	**Test**	26	1.761	0.231	0.170	0.866
	Control	26	1.773	0.256		
Gingival index	**Test**	26	1.529	0.159	4.031	<0.001**
	Control	26	1.346	0.167		
Probing depth	**Test**	26	1.921	0.267	20.051	<0.001**
	Control	26	0.467	0.255		
Clinical attachment level	**Test**	26	1.914	0.195	30.462	<0.001**
	Control	26	0.531	0.123		

(p< 0.05 - Significant*, p < 0.001 - Highly significant**)

In the present study, clinical parameters such as plaque index, gingival index, probing depth and clinical attachment level were evaluated at baseline and three months post-treatment.

Although both the groups showed statistically significant improvements from baseline to the end of 3 months, the test group (SRP + Amoxicillin + Metronidazole) showed superior results as compared to the control group (SRP + Amoxicillin) at 3 months interval.

There was statistically significant difference in gingival index, probing depth and clinical attachment level at the end of 3 months ($p<0.001$). The plaque index did not show any statistically significant difference between the two groups at the end of 3 months. ($p=0.86$)

In a similar study done by Silva MP et al[11], the subjects who received metronidazole + amoxicillin exhibited greater mean gain in CAL and PD reduction. SRP+MTZ+AMX was the only treatment which significantly reduced the levels and proportions of all red complex pathogens. In another study by Winkel E.G. et al [12],except for the plaque, there was a significantly larger change in the bleeding, PD and CAL in the test group as compared to the placebo group after therapy.

In a systematic review by Zandbergen D et al [13], SRP+amoxicillin+ metronidazole showed significantly better effects and better PD reduction in periodontal pockets initially measuring > 6mm and gain in CAL. Also, there was significantly greater reduction in full-mouth BoP as compared to SRP alone. Another meta-analysis done by Sgolastra F et al [6] including four randomized trials, significant CAL gain and PD reduction was seen in favour of SRP+AMX/MET.

As the subgingival microbiota in adult periodontitis is constituted of a variety of periodontal pathogens which differ in their anti-microbial susceptibility, several investigators have used a combination of two antibiotics to provide more effective therapy.

Van Winkelhoff [9] in a study stated that when amoxicillin and metronidazole were combined, a synergistic bactericidal effect was observed, and the optimal effect of the drugs was achieved in much less time.

However, there are certain limitations of the study. As dosage is of paramount importance in determining the microbiological and clinical outcomes of adjunctive systemic antimicrobial therapy, future studies are needed to assess the optimal dosage relative to the occurrence of adverse events. Patient adherence to the treatment protocol should also have been considered. Analysis of the effect of adjunctive amoxicillin+metronidazole therapy on the profile of periodontal pathogens that are involved in the pathogenesis of chronic periodontitis, the possibility of acquiring antimicrobial resistance and the influence of smoking on the outcomes should have been assessed. Study could also have included a cost/effectiveness analysis. Future well-designed RCTs with an adequate sample size and longitudinal data are needed to confirm these results.

Conclusion

The present study evaluated the effectiveness of amoxicillin alone or amoxicillin in combination with metronidazole after full mouth scaling and root planing in patients with chronic periodontitis. The results of the study permitted the following conclusions to be drawn. In both the test and control groups, significant results were obtained in terms of PI, GI, PD and CAL.

When inter-group difference was compared, SRP+amoxicillin+metronidazole group showed to have significant result as compared to SRP+amoxicillin with respect to GI, PD and CAL. PI did not show significant difference between the groups. The results indicate that at the end of 3 months, the combination of amoxicillin and metronidazole showed better results after mechanical therapy as compared to amoxicillin alone in the treatment of patients with chronic periodontitis.

Key Messages

The combination of amoxicillin and metronidazole has shown to have a synergistic effect in the treatment of chronic periodontitis, thereby reducing the need for surgical therapy.

Conflict of Interest: None

Source of Support: Nil

References

1. Oteo A, Herrera D, Figuero E, O'Connor A, Gonza´lez I, Sanz M. Azithromycin as an adjunct to scaling and root planing in the treatment of Porphyromonasgingivalis associated periodontitis: a pilot study. J ClinPeridontol 2010;37(11):1005–1015
2. Bragd L, Dahle´n G, Wikström, M, Slots, J. The capability of Actinobacillusactinomycetemcomitans, Bacteroidesgingivalisand Bacteroides intermedius to indicate progressive periodontitis; a retrospective study. J ClinPeriodontol 1987;14(2):95-99
3. Hung HC, Douglass CW. Meta-analysis of the effect of scaling and root planing, surgical treatment and antibiotic therapies on periodontal probing depth and attachment loss. J ClinPeriodontol. 2002;29(11):975-986
4. A. P. V. Colombo, S. K. Boches, S. L. Cotton et al. Comparisons of subgingival microbial profiles of refractory periodontitis, severe periodontitis, and periodontal health using the human oral microbe identification microarray. J Periodontol 2009; 80(9):1421–1432
5. Haffajee AD, Teles RP, Socransky SS. The effect of periodontal therapy on the composition of the subgingival microbiota. Periodontol 2000 2006;42:219- 258
6. Sgolastra F, Gatto R, Petrucci A, Monaco A. Effectiveness of systemic amoxicillin/metronidazole as adjunctive therapy to scaling and root planning in the treatment of chronic periodontitis: a systematic review and meta-analysis. J Periodontol 2012;83(10):1257-1269
7. Yek EC, Citan S, Topcuoglu N, Kulekci G, Issever H, Kantarci A. Efficacy of amoxicillin and metronidazole combination for the management of generalized aggressive periodontitis. J Periodontol 2010;81(7):964-974
8. McDonald PJ, Pruul H. Phagocyte uptake and transport of azithromycin. Eur J ClinMicrobiol Infect Dis 1991;10(10):828–833
9. Van Winkelhoff AJ, Rodenburg JP, Goené RJ, Abbas F, Winkel EG, de Graaff J. Metronidazole plus amoxycillin in the treatment of Actinobacillusactinomycetemcomitans associated periodontitis. J ClinPeriodontol 1989;16(2):128-131
10. Danser MM, Timmerman MF, van Winkelhoff AJ, van der Velden U. The effect of periodontal treatment on periodontal bacteria on the oral mucous membranes. J Periodontol 1996;67(5):478-485
11. Silva MP, Feres M, Sirotto TAO, Soares GMS, Mendes JAV, Faveri M et al. Clinical and microbiological benefits of metronidazole alone or with amoxicillin as adjuncts in the treatment of chronic periodontitis: a randomized placebo-controlled clinical trial. J ClinPeriodontol 2011;38(9):828–837
12. Winkel EG, Van Winkelhoff AJ, Timmerman MF, Van der Velden U, Van der Weijden GA: Amoxicillin plus metronidazole in the treatment of adult periodontitis patients. A double-blind placebo-controlled study. J ClinPeriodontol 2001;28(4): 296–305
13. Zandbergen D, Slot DE, Niederman R, Fridus A, Weijden V. The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planning alone in treating periodontitis: a systematic review. BMC Oral Health 2016; 1-11