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# Effect of Adjunctive Systemic Azithromycin With Periodontal Surgery in the Treatment of Chronic Periodontitis in Smokers: A Pilot Study

**Sarosh F. Dastoor**[*], **Suncica Travan**[*], **Rodrigo F. Neiva**[*], **Lindsay A. Rayburn**[*], **William V. Giannobile**[*,†], and **Hom-Lay Wang**[*]

[*] *Department of Periodontics and Oral Medicine, School of Dentistry, University of Michigan, Ann Arbor, MI*

† *Michigan Center for Oral Health Research, University of Michigan*

## Abstract

**Background—**Along with conventional surgical therapy, systemic antibiotics may provide more effective treatment in smokers by targeting tissue- invasive bacteria. The aim of this randomized, placebo-controlled, double-masked clinical trial was to evaluate the adjunctive effects of systemic azithromycin (AZM) in combination with periodontal pocket reduction surgery in the treatment of chronic periodontitis in smokers.

**Methods—**Thirty patients with a greater than one pack/day smoking habit and generalized moderate to severe chronic periodontitis were randomized to the test (surgery plus 3 days of AZM, 500 mg) or control group (surgery plus 3 days of placebo). Full-mouth probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), gingival index (GI), plaque index, and wound healing indices (WHI) were assessed at baseline and at 2 weeks and 1, 3, and 6 months following surgical intervention. Plaque and gingival crevicular fluid were collected for trypsin-like enzyme activity (benzoyl-dl-arginine naphthylamine) and bone biomarker (cross-linked telopeptide of type I collagen [ICTP]) analyses, respectively, at baseline, 2 weeks, and 1, 3, and 6 months.

**Results—**Surgical treatment of moderate (PD = 4 to 6 mm) and deep (PD >6 mm) pockets significantly improved clinical parameters of treated and untreated teeth (CAL gain, PD reduction, and reduction of BOP). The additional use of AZM did not enhance this improvement nor did it promote reduction of ICTP levels. Compared to the control group, the test group had significantly better WHI scores at 1 month, significantly less GI at 2 weeks, and sustained reductions of red-complex bacteria with trypsin-like enzyme activity at 3 months. For non-surgery teeth, only the test group showed significant gains in overall CAL compared to baseline.

**Conclusions—**The findings of this pilot study demonstrated that in heavy smokers, adjunctive systemic AZM in combination with pocket reduction surgery did not significantly enhance PD reduction or CAL gain. However, the clinical value of adjunctive AZM may be appreciated by more rapid wound healing, less short-term gingival inflammation, and sustained reductions of periopathogenic bacteria. More expanded studies are recommended to better determine the clinical effects of adjunctive AZM in patients who smoke.

Correspondence: Dr. Hom-Lay Wang, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, 1011 N. University Ave., Ann Arbor, MI 48109-1078. Fax: 734/936-0374; e-mail: homlay@umich.edu.

Drs. Dastoor, Travan, Neiva, Rayburn, Giannobile, and Wang report no conflicts of interest related to this study.

**Keywords**

Antibiotic; azithromycin/therapeutic use; periodontitis/drug therapy; periodontitis/therapy; smoking/adverse effects; surgery/therapy

Although non-surgical therapy of periodontitis is quite effective, it has certain limitations. Complete calculus removal is not possible for teeth that have probing depth (PD) ≥3 mm or in posterior teeth with furcation involvements.[1,2] To overcome the limitations of non-surgical therapy and facilitate long-term maintenance of shallow PD, surgical treatments, such as gingivectomy, Widman and modified Widman flaps, and apically positioned flaps with or without osseous surgery, were developed.[3–5] Despite the valuable benefits of these therapies, long-term results have not shown convincing superiority over non-surgical treatment modalities in terms of clinical attachment level (CAL) gain.[6,7] Nonetheless, advantages of PD reduction surgery (apically positioned flap with or without osseous recontouring) might be appreciated in terms of sustained long-term PD reduction which, in turn, promotes decreased niches for pathogenic bacteria that can negatively affect treated and untreated teeth.[8,9] This type of surgery yields the greatest proportion of shallow PD (1 to 3 mm) and the least percentage of sites that break down in the long term.[7,10]

Smoking is a major risk factor in the initiation and progression of periodontal disease.[11,12] In general, studies have shown that smoking increases the risk for developing periodontal disease by twofold to five-fold, and these effects seem to be dose dependent. Smoking leads to a greater risk for CAL loss, greater numbers of deep PD, increased prevalence and severity of vertical bony defects, and higher counts of some putative periodontal pathogens. Additionally, smoking alters the host immune response by decreasing its ability to combat pathogens effectively.[12,13] Some mechanisms include the altered chemotactic and phagocytic abilities of neutrophils and macrophages in smokers, decreased sera immunoglobulin G antibody titers to periodontal pathogens, and increased generation of proinflammatory molecules, such as $PGE_2$, elastase, and matrix metalloproteinase-8. As a result, smokers exhibit a higher prevalence of edentulism and a greater incidence of tooth loss.[14]

As a result, smokers tend to have a less favorable therapeutic response to non-surgical or surgical therapy. [15–17] Generally, smokers demonstrate less PD reduction and CAL gain following therapy. This may be due to the fact that smokers tend to harbor more periodontal pathogens before and even after therapy, which may contribute to inferior results.[18] Additionally, it has been shown consistently that smokers tend to accumulate more plaque than non-smokers, which may explain, in part, their inability to sustain PD reduction. [19]

Because smoking impairs the result of most conventional treatments of chronic periodontitis, it is imperative to investigate adjuncts to treatment that may enhance healing. Systemic antibiotics have proven to be beneficial after non-surgical[20] and surgical therapy. [21] A recent systematic review found that systemically administered antibiotics exhibited statistically significantly more CAL gain than in control groups with no antibiotics.[22] This review noted that antibiotics were beneficial when used as adjuncts to scaling and root planing (SRP) plus periodontal surgery or when used as a stand-alone therapy, although the investigators noted that this was of borderline significance.

Azithromycin (AZM) is a systemic antibiotic that has not been evaluated extensively as an adjunct in the treatment of periodontal disease. AZM belongs to a class of macrolide antibiotics called azalides. It has better oral absorption than other antibiotics in the same class because of higher resistance to gastric acids. Macrolides work in a bacteriostatic fashion by interfering with the 50s component of the bacterial ribosome, thus inhibiting translation of mRNA and

preventing proper protein synthesis. AZM's antimicrobial spectrum is similar to erythromycin; however, it is more effective against certain Gram-negative bacteria, especially *Actinobacillus actinomycetemcomitans*. [23] This antibiotic is effective against systemic, intraoral, and facial infections.[24,25]

Unlike other antibiotics, AZM is characterized by its significantly higher uptake by fibroblasts and acute reactant cells, like polymorphonuclear leukocytes, monocytes, and lymphocytes. [26,27] The drug subsequently is delivered and released in high concentrations to phagocytosed bacteria at the site of infection.[28] Because of a long half-life, shorter regimens are required. [29] This property theoretically leads to increased patient compliance. Side effects are rare and usually minor, and they include gastrointestinal problems, such as diarrhea, nausea, abdominal pain, and vomiting. AZM has significantly less bacterial resistance to subgingival microflora of adult periodontitis compared to other commonly prescribed oral antibiotics.[30]

AZM improved clinical parameters when used as an adjunct to SRP.[31,32] Recently, Mascarenhas et al.[33] conducted a randomized clinical trial evaluating the use of systemic AZM in conjunction with SRP in heavy smokers (more than one pack/day), a patient population similar to the one used in the present study. They found improvements in clinical parameters (PD reduction and CAL gain), cross-linked telopeptide of type I collagen (ICTP) levels, and benzoyl-DL-arginine naphthylamine (BANA) levels.

Hence, the aim of this double-masked, randomized, placebo-controlled clinical trial was to determine whether the use of adjunctive systemic AZM improved the outcomes of periodontal pocket reduction surgery for the treatment of moderate to severe chronic periodontitis in heavy smokers.

## MATERIALS AND METHODS

This study was a single-center, double-masked, randomized, placebo-controlled clinical trial that evaluated the effect of adjunctive systemic AZM following periodontal pocket reduction surgery in heavy smokers with moderate to advanced chronic periodontitis. The use of human subjects was approved by the Health Sciences Institutional Review Board of the University of Michigan in August 2004. Thirty patients with generalized moderate to advanced chronic periodontitis were recruited from the patient population at the University of Michigan School of Dentistry between January 2005 and December 2005. Patients completed a health history questionnaire to ensure that they were medically qualified for participation in the study. After patients were screened and determined to be eligible for participation, an informed consent was obtained. All patients were at least 30 years old, smoked at least one pack of cigarettes/day, had ≥10 teeth in their functional dentition, excluding third molars, and had at least two posterior teeth with PD ≥5 mm and bleeding on probing (BOP) that were deemed in need of periodontal surgery. Patients who had teeth that were candidates for regenerative therapy were not included in the study. Generally, the quadrant with the most active disease, as evidenced by the most number of periodontal pockets with active disease, was selected for treatment. All patients completed initial periodontal therapy (SRP) within 90 days prior to inclusion in the study and demonstrated adequate oral hygiene levels (plaque score ≤20%). The other quadrants did not receive further non-surgical therapy.

Preoperatively, a 0.12% chlorhexidine rinse and ibuprofen, 600 mg, were given to all patients. After local anesthesia administration, periodontal surgery was performed (apically positioned flap with osseous recontouring) by second- and third-year residents at the Graduate Periodontics Clinic, University of Michigan School of Dentistry. The final osseous contour and suturing were done by a single surgeon (SD) to ensure standardization of surgical treatment. Postoperative instructions were given in written and oral formats.

The placebo and AZM tablets were provided by the Investigational Drug Service at the University of Michigan hospital pharmacy. After surgery, patients were assigned randomly to the test (active AZM, 500 mg for 3 days; 1 tablet per day) or control group (placebo containing inactive ingredients for 3 days; 1 tablet per day) via a computer-generated list that was prepared by an independent study coordinator. Tablets were taken 1 hour before or 2 hours after meals, preferably on an empty stomach. Patients returning to the clinic for subsequent examinations were instructed to return any residual tablets for measurement of drug compliance. Drug compliance was determined by verbally asking the patients if they consumed all tablets as directed, requesting that they return to the 2-week appointment with the vial that contained the medication/placebo, and counting how many tablets remained.

Postoperative analgesia was provided through non-steroidal anti-inflammatory drugs (ibuprofen, 600 mg every 6 hours for 2 days, and thereafter as needed). Patients were asked to rinse with 0.12%chlorhexidine twice a day for 2 weeks following surgery and to refrain from oral hygiene procedures in the quadrant that received surgery. Following surgery, patients returned for examinations at 2 weeks and at 1, 3, and 6 months, at which time various clinical parameters were measured or recorded by single, masked examiner. Calibration trials were performed prior to the study to ensure adequate intra- and inter-examiner reproducibility (kappa statistic ≥90%). All measurements were performed using a standard University of North Carolina probe with millimeter markings (0.28 mm in diameter).[‡] Maintenance therapy was performed by the examiner at 3 and 6 months after surgical intervention. From an ethical standpoint, smoking cessation was advised for all patients throughout the study.

## Clinical Parameters

The clinical parameters that were evaluated in this study and the time points at which they were measured are shown in Table 1. PD, CAL, and BOP were assessed for all teeth in the surgical quadrant at six locations around the tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, and disto-lingual) at baseline and at 3 and 6 months following surgical intervention. Gingival index (GI) and plaque index (PI) were assessed at baseline and at 2 weeks and 1, 3, and 6 months following surgery. PD, CAL, and BOP were assessed at baseline and 6 months for all other teeth in the mouth that did not receive periodontal surgery. These “non-surgery” teeth only received the initial non-surgical therapy. A wound healing index (WHI) score was assigned as an overall score of 1 (optimal) to 3 (least optimal) for the entire surgical quadrant.[34] Descriptions of the three possible scores are as follows: 1 = uneventful wound healing with no gingival edema, erythema, suppuration, patient discomfort, or flap dehiscence; 2 = uneventful wound healing with slight gingival edema, erythema, or patient discomfort, but slight flap dehiscence and no suppuration; and 3 = poor wound healing with significant gingival edema, erythema, patient discomfort, significant flap dehiscence, or any suppuration.

## Microbial Assessments: BANA Test

The BANA test[§] is a chair-side test that is highly sensitive and specific for determining the presence of “red-complex” periodontal pathogens (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* [previously *T. forsythensis*]).[35] These pathogens have been implicated in periodontal disease initiation and progression,[36,37] and they are capable of hydrolyzing a synthetic trypsin substrate (BANA). Plaque was collected for BANA analysis from the mesio-buccal aspect of two posterior teeth in the surgical quadrant with PD ≥5 mm at baseline and at 2 weeks and 1, 3, and 6 months following surgery. A separate toothpick[‖] was used for plaque collection for each site. After incubation for 5 minutes at 35°C with Evan’s

[‡]Model UNC-15, Hu-Friedy, Chicago, IL.
[§]Perioscan, Oral-B, Redwood City, CA.
[‖]Stim-U-Dent, Johnson and Johnson, Windsor, NJ.

black dye solution, naphthylamine released as a result of the presence of any one of the BANA-hydrolyzing bacterial species diffuses to form a permanent blue-black color. Assessments were made regarding the relative intensity of the blue color (strong positive, positive, or negative).

### Gingival Crevicular Fluid Sampling

ICTP is a specific marker of bone resorption. The fragment is released by digestion with trypsin or bacterial collagenase,[38] and its presence is correlated with bone resorption and the presence of periopathogenic bacteria.[39,40] Gingival crevicular fluid (GCF) was collected, prior to any clinical measurements, from the mesio-buccal aspect of two teeth in the surgical quadrant at baseline and at 2 weeks and 1, 3, and 6 months following surgical intervention. Each tooth was dried with gauze, and the supragingival plaque was removed. GCF was collected for 10 seconds using methylcellulose strips[¶] placed gently until slight resistance was felt. Following collection, the samples were kept on dry ice for transport to the laboratory and storage at − 80° C until analyzed. Samples were analyzed for ICTP as described by Giannobile et al.[39]

### Statistical Analysis

The results of this study were analyzed by presenting descriptive statistics and making comparisons between treatment groups with respect to demographics and efficacy parameters. Data were analyzed on a subject basis. Mean values and standard errors for PD, CAL, BOP, GI, PI, WHI, ICTP, and BANA were calculated for each subject at each time point. Data were divided, based on baseline PD, into three categories: shallow sites (PD from 1 to 3 mm), moderate sites (PD from 4 to 6 mm), and deep sites (PD >6 mm). Means and standard errors for PD and CAL of the sites within each baseline category were obtained for each time point. Differences between groups were sought using the repeated measures of variance (analysis of variance) test using a statistical software program.[#] Differences with a $P$ value <0.05 at a confidence level of 95% were considered significant.

## RESULTS

Table 2 depicts the baseline demographic and clinical characteristics of each group. Thirty patients were enrolled in this study (17 males and 13 females). Of the 15 patients in the test group, six were male; the average age of the patients in this group was 49.40 ± 7.81 years. Of the 15 patients in the control group, 11 were male; the average age of patients in this group was 52.00 ± 8.36 years. There were no statistically significant baseline differences between groups for any demographic or clinical parameter for surgery and non-surgery teeth. All subjects completed the study, and none decreased their smoking habit to less than one pack of cigarettes/day. The overall drug compliance rate was 100%, and all patients consumed the medications as they were directed. No adverse drug reactions were reported at any time.

### Overall PD, CAL, and BOP

Overall mean PD and CAL changes are given in Table 1. Negative values denote improvement for the observed parameter. No statistically significant treatment related differences were found at any time point for PD, CAL, or BOP. At 6 months following surgical therapy, test and control groups of surgically treated sites demonstrated statistically significant reductions in PD (− 0.83 and − 0.98 mm for test and control groups, respectively). There was a trend (differences between the observed time point and baseline not statistically significant, i.e., $P \geq 0.05$) for a slight rebound in PD in both groups between 3 and 6 months. Overall mean CAL remained unchanged for both groups; however, the data indicated a trend for CAL loss in the control

¶ProFlow, Amityville, NY.
#SPSS, version 13.0, SPSS, Chicago, IL.

group only. Regarding non-surgically treated sites, there were statistically significant reductions in PD for both groups at 6 months (− 0.27 and − 0.39 mm for test and control groups, respectively). At 6 months, only the test group had statistically significant gains in CAL (− 0.27 mm) compared to baseline. Nonetheless, there were no significant differences between the groups at any time point for PD or CAL. The percentage of sites that exhibited BOP at various time points is shown in Table 1. For the surgery teeth, both groups had statistically significant reductions at 3 months compared to baseline. These reductions were sustained through 6 months (− 22% and − 27% for test and control groups, respectively). Teeth that were treated non-surgically responded in a similar fashion (− 13% and − 15% for test and control groups, respectively).

### Shallow Sites: Baseline PD From 1 to 3 mm

Shallow sites of surgically treated teeth showed statistically significant PD reductions at 6 months (− 0.32 and − 0.15 in test and control groups, respectively), with trends for rebound in PD between 3 and 6 months. Although the placebo group had significant CAL loss by 6 months compared to baseline (+0.27 mm), the AZM group showed a trend for slight CAL gain. PD and CAL for sites that were treated non-surgically remained unchanged in both groups for the duration of the study.

### Moderate Sites: Baseline PD From 4 to 6 mm

Just as in the shallow sites, PD reduction of initially moderate sites of the surgically treated teeth was evident at 6 months (− 1.83 and − 1.93 mm in test and control groups, respectively). Significant gains of CAL also were noted (− 0.89 and − 0.51 mm for test and control groups, respectively); between 3 and 6 months, there was a slight trend for CAL loss in the placebo group, whereas it appeared that initial CAL gain was sustained in the AZM group. Non-surgically treated sites responded in a similar fashion by having significant reductions of PD at 6 months (− 0.94 and − 1.01 mm for test and control groups, respectively) and gains in CAL (− 0.98 and − 0.55 mm for test and control groups, respectively).

### Deep Sites: Baseline PD >6 mm

For the surgically treated sites, statistically significant PD reduction was evident at 6 months following treatment (− 2.83 mm for the test group and − 3.78 mm for the control group). As in the other PD strata, both groups showed trends for rebound in PD between 3 and 6 months. Regarding CAL, only the placebo group had statistically significant gains in CAL at 6 months (− 0.40 mm); the test group remained unchanged. Non-surgically treated sites had statistically significant reductions in PD (− 2.00 and − 2.76 mm in test and control groups, respectively) and statistically significant gains in CAL (− 1.33 mm in the test group and − 1.95 mm in the control group).

### PI and GI

Table 3 depicts changes in PI and GI for both groups during the study period. At the 2-week postoperative appointment, there was a trend for an increased PI score in the control group and a decreased PI score in the test group, compared to baseline. The difference between study groups was marginally significant ($P = 0.089$). Consequently, at this time point, only the control group had a significantly worse GI score compared to baseline. By 3 months, both groups had statistically significantly better GI scores compared to baseline. This improvement was sustained through 6 months only in the control group.

### WHI

Table 3 depicts the WHI score for both groups throughout the study. Two weeks following surgery, both groups had similar WHI scores. One month after surgery, only the AZM group

had a statistically significantly better WHI score compared to baseline, and it showed statistically significantly better wound healing than the placebo group. By 3 months, there was complete wound healing in all patients, yielding statistically significantly better wound healing for both groups compared to baseline.

### BANA

Table 4 shows the changes in BANA scores for both groups during the study. There was a statistically significant reduction in BANA scores for both groups 2 weeks after surgery ($-0.88 \pm 0.30$ and $-0.77 \pm 0.07$ for test and control groups, respectively). By 3 months, BANA scores in the placebo group rebounded to baseline levels, whereas the initial reduction was sustained in the AZM group. By 6 months, BANA scores in both groups rebounded to baseline levels. Nevertheless, no significant differences were found between the groups at any time point.

### ICTP

Table 4 shows the changes in ICTP levels for both groups during the study. No statistically significant differences, compared to baseline, were found for either group at any time point. Additionally, there were no statistically significant differences between groups at any time point.

## DISCUSSION

Providing successful periodontal treatment for heavy smokers often is frustrating because they tend to have a less favorable therapeutic response to non-surgical or surgical therapy compared to non-smokers.[41,42] This longitudinal, doubled-masked, randomized clinical trial was designed to evaluate if the outcomes of surgical therapy in heavy smokers could be enhanced by the adjunctive administration of systemic AZM, because of its high tissue concentration and increased patient compliance.

Regarding the surgically treated sites, both groups demonstrated statistically significant overall mean PD reduction; however, a slight, but non-significant, rebound in PD was noted in both groups between 3 and 6 months. This trend might be explained by the fact that none of the patients decreased their smoking habit to less than one pack of cigarettes per day throughout the study. The prolonged local and systemic effects of nicotine and other harmful by-products of cigarette smoke possibly overwhelmed the initial short-term benefit of the surgery and/or the antibiotic. Recurrent colonization of periodontal pockets by periopathogenic bacteria and continued long-term alterations of host defense systems would be inevitable in such heavy smokers, thus promoting the disease process to continue. Additionally, Tonetti et al.[19] demonstrated that heavy smokers tend to harbor more plaque than non-smokers. Increased plaque levels in such patients may explain, in part, the smokers' inability to sustain PD reduction. Because the follow-up for the present study was only 6 months, it would be interesting to evaluate how long the initial PD reduction could be sustained in each of the treated groups.

For a more accurate and detailed analysis of these findings, data were stratified according to baseline PD. Shallow (PD: 1 to 3 mm), moderate (PD: 4 to 6 mm), and deep pockets (PD >6 mm) for both groups showed statistically significant reductions in PD at 3 and 6 months, compared to baseline. These findings are in agreement with previous studies that indicated slight reductions in PD for shallow pockets and more pronounced reductions in moderate and deep pockets after osseous surgery.[7,10] Again, the non-significant rebound in PD for both groups between 3 and 6 months may be attributed to the prolonged harmful effects of heavy smoking.

This study demonstrated no statistically significant differences for PD between groups for any baseline PD category at any time point. It seems that the periodontal surgery was responsible for most of the PD reduction. The decrease in the percentage of sites with BOP correlated with the decrease in PD for both groups at 3 and 6 months following surgical intervention. It is well documented that shallow PD promotes less colonization of periopathogenic bacteria which, in turn, yields less collagen breakdown, less gingival inflammation, and thus, less BOP.[9,43,44] As expected, the reduction in BOP correlated with statistically significant reductions in plaque (PI) at 3 and 6 months.

Both groups did not demonstrate significant changes in overall mean CAL of surgically treated sites compared to baseline. Between 3 and 6 months, there was a trend for CAL loss in the placebo group, whereas it seemed that the CAL gain in the AZM group was sustained. Additionally, at 6 months, only the AZM group had statistically significant gains in overall CAL of non-surgically treated sites. These findings may be explained by the sustained effect of the antibiotic.

When data were stratified according to baseline PD, shallow sites of the placebo group had a statistically significant loss of CAL at 6 months compared to baseline. This CAL loss was not evident in the AZM group. Many studies[7,10,45] demonstrated a slight loss of CAL after PD reduction surgery in shallow sites (~0.80 mm). The adjunctive administration of AZM seemed to play a pivotal role in preventing this expected CAL, which is certainly of clinical benefit. For moderate sites that were treated surgically, a statistically significant gain of CAL was found in both groups at 3 and 6 months. Between 3 and 6 months, the placebo group showed a trend for CAL loss, whereas the AZM group did not. The value of the antibiotic in heavy smokers can be appreciated in maintaining CAL gain observed after surgery. For sites with initially deep PD, only the placebo group had a statistically significant gain of CAL at 6 months compared to baseline. This finding may be attributed to not having an adequate amount of sites that were initially ≥7 mm in either group. Because of the small sample size, a proper statistical analysis was not possible. However, overall, our data are in agreement with previous studies that demonstrated a gain in CAL for initially moderate and deep pockets following pocket reduction surgery.[6,10,46]

When data were stratified according to baseline PD and analyzed for the non-surgically treated sites, similar results were found. At 6 months, despite not being treated surgically, these sites in both groups demonstrated statistically significant reductions in overall PD and BOP and statistically significant CAL gain in moderate and deep pockets. BOP is an indicator of collagen breakdown and gingival inflammation, and it is significant that it was reduced in sites that did not receive surgery. Our findings were similar to the results observed by Levy et al.;[9] they found a decline in the proportion of red-complex bacteria in non-surgically treated sites 1 year after apically positioned flap surgery with osseous resection had been performed in another quadrant of the mouth. These findings may explain the PD reduction that was evident in non-surgically treated sites in our study. In an already periodontally compromised patient population, such as heavy smokers, performing PD reduction surgery in even one quadrant may have long-term beneficial effects for other areas of the mouth by decreasing the overall bacterial load.

The hypothesis that AZM may lead to faster wound healing in heavy smokers who receive periodontal surgery was confirmed in our study. After having comparable WHI scores at 2 weeks following surgery, only the AZM group showed a statistically significantly higher WHI score at 1 month compared to baseline (yielding a statistically significant difference between groups). It can be hypothesized that the antibiotic's effect of targeting tissue-invasive bacteria contributed to these findings. Reducing the proportions of these bacteria via antibiotics

decreases the effects of collegenases and other inflammatory mediators that lead to gingival inflammation.

Data from the BANA analysis support the hypothesis that AZM could help to diminish the proportion of red-complex bacteria, at least in the short-term. Reduction of red-complex bacteria following PD reduction surgery, which was found in our study for both treatment groups, is in agreement with a previous study that demonstrated that shallower periodontal pockets harbor lower levels of periodontal pathogens than deeper pockets.[47] At 3 months post-surgery, despite continued heavy smoking, only the AZM group sustained statistically significant reductions in BANA scores, whereas those in the control group increased to baseline levels. This implied that the adjunctive administration of AZM with periodontal surgery may be more beneficial than surgery alone in eliminating tissue- invasive pathogens. Mascarenhas et al.,[33] using the same antibiotic after SRP, also showed sustained reductions in BANA scores in the AZM group but not in the control group. At 6 months, BANA scores in both groups returned to baseline levels. This inability to sustain reductions in red-complex bacteria is in agreement with previous investigations[48,49] that showed that a single episode of antibiotic therapy resulted in initial decreases of periopathogenic bacteria; however, recolonization, almost to baseline levels, occurred by 6 months. Future clinical trials are needed to evaluate the possible benefit of repeated administration of systemic antibiotics, especially in heavy smokers.

Our study found no statistically significant changes regarding mean ICTP levels over the study period, with no significant differences between treatment groups at any time point. This is contradictory to previously published papers.[50,51] However, those studies evaluated the effect of tetracycline derivatives, which are more effective at reducing ICTP levels than other antibiotics. Another explanation for these findings may be that, in our study, all patients received nonsurgical therapy ~4 to 6 weeks before surgical treatment, which may have been responsible for much of the reduction of GCF ICTP. Mascarenhas et al.,[33] in a similar population of heavy smokers, showed that non-surgical therapy produced short-term reductions of GCF ICTP that rebounded to baseline levels by 3 months. Similarly, Al-Shammari et al.[50] demonstrated in a longitudinal trial that the initial reductions of GCF ICTP became less obvious at 3 months following SRP. Because surgical therapy was performed within 3 months following initial therapy in the present study, it is reasonable to assume that GCF ICTP levels were still low enough that an accurate analysis of the effect of treatment on GCF ICTP was not possible.

## CONCLUSIONS

Data from our pilot study suggested that surgical treatment of moderate and deep periodontal pockets in heavy smokers improved clinical outcomes, e.g., CAL gain, PD reduction, and reduction of BOP. The adjunctive administration of systemic AZM to surgical treatment did not improve overall PD reduction, CAL gain, or reduction of the bone resorption marker ICTP compared to sites that received surgical treatment only. For the non-surgery teeth, the systemic administration of AZM yielded significant gains in overall CAL compared to baseline, whereas placebo did not. The addition of AZM during periodontal surgery in heavy smokers promoted rapid wound healing, reduced short-termgingival inflammation, and resulted in less plaque formation within 3 months. AZM's beneficial properties, such as the rare incidence of side effects, decreased bacterial resistance compared to common antibiotics, and increased patient compliance because of shorter dosage regimens, suggests that its benefits might outweigh the risks when using it in conjunction with non-surgical or surgical therapy in heavy smokers. Larger, controlled clinical trials are needed to confirm the findings of this study.

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**Table 1**

Effect of Systemic Administration of AZM in Combination With Surgery or Surgery Alone on Overall PD, CAL, and Percentage of Sites With BOP (mean ± SEM) for Surgery and Non-Surgery Teeth

| Tooth Type | Parameter | Baseline | 3 Months (change)* | 6 Months (change)* |
|---|---|---|---|---|
| Surgery teeth | PD (mm) | T: 3.10 ± 0.34 | T: − 1.03 ± 0.01† | T: − 0.83 ± 0.10† |
| | | C: 3.21 ± 0.65 | C: − 1.02 ± 0.24† | C: − 0.98 ± 0.03† |
| | CAL (mm) | T: 3.26 ± 0.72 | T: − 0.22 ± 0.02 | T: − 0.26 ± 0.00 |
| | | C: 3.59 ± 1.13 | C: − 0.30 ± 0.07 | C: − 0.03 ± 0.07 |
| | BOP (% of sites) | T: 66 ± 21 | T: − 32 ± 6† | T: − 22 ± 4† |
| | | C: 61 ± 20 | C: − 26 ± 9† | C: − 27 ± 1† |
| Non-surgery teeth | PD (mm) | T: 2.80 ± 0.32 | | T: − 0.27 ± 0.04† |
| | | C: 3.01 ± 0.62 | | C: − 0.39 ± 0.22† |
| | CAL (mm) | T: 2.96 ± 0.84 | | T: − 0.27 ± 0.11† |
| | | C: 3.57 ± 1.26 | | C: − 0.16 ± 0.09 |
| | BOP (% of sites) | T: 49 ± 17 | | T: − 13 ± 3† |
| | | C: 48 ± 21 | | C: − 15 ± 1† |

T = test group; C = control group.

*A negative value indicates improvement.

†Statistical significance between baseline and observed time point.

**Table 2**

Mean Baseline Clinical Characteristics of the Study Groups

| Parameter | Test (N = 15) | Control (N = 15) | P Value* |
|---|---|---|---|
| Age (years; mean ± SEM [range]) | 49.40 ± 7.81 (35 to 65) | 52.00 ± 8.36 (36 to 67) | NS |
| Male/female ratio | 2:3 | 11:4 | NS |
| PD (mm; mean ± SEM) | Overall: 2.95 ± 0.36 | Overall: 3.11 ± 0.63 | NS |
| | Sx teeth: 3.10 ± 0.34 | Sx-teeth: 3.21 ± 0.65 | NS |
| | Non-sx teeth: 2.80 ± 0.32 | Non-sx teeth: 3.01 ± 0.62 | NS |
| CAL (mm; mean ± SEM) | Overall: 3.12 ± 0.78 | Overall: 3.58 ± 1.17 | NS |
| | Sx teeth: 3.26 ± 0.72 | Sx teeth: 3.59 ± 1.13 | NS |
| | Non-sx teeth: 2.96 ± 0.84 | Non-sx teeth: 3.57 ± 1.26 | NS |
| BOP (% of sites; mean ± SEM) | Overall: 57.52 ± 20.71 | Overall: 54.50 ± 21.63 | NS |
| | Sx teeth: 65.60 ± 21.35 | Sx teeth: 61.46 ± 20.47 | NS |
| | Non-sx teeth: 48.87 ± 16.65 | Non-sx teeth: 47.54 ± 21.12 | NS |
| ICTP (pg/site; mean ± SEM) | 11.43 ± 13.62 | 22.92 ± 64.41 | NS |
| BANA score (mean ± SEM) | 0.87 ± 0.48 | 1.00 ± 0.60 | NS |

NS = not statistically significant; sx = surgery.

* Based on the non-parametric Mann-Whitney test.

**Table 3**

Effect of Systemic Administration of AZM in Combination With Surgery or Surgery Alone on PI, GI, and WHI (mean ± SEM)

| Parameter | Baseline | 2 Weeks (change)* | 1 Month (change)* | 3 Months (change)* | 6 Months (change)* |
|---|---|---|---|---|---|
| PI | T: 0.89 ± 0.38<br>C: 0.82 ± 0.37 | T: − 0.26 ± 0.00<br>C: +0.08 ± 0.01 | T: − 0.25 ± 0.02<br>C: − 0.0.5 ± 0.01 | T: − 0.25 ± 0.01<br>C: − 0.15 ± 0.12 | T: − 0.15 ± 0.05<br>C: − 0.29 ± 0.00 |
| GI | T: 1.36 ± 0.37<br>C: 1.23 ± 0.38 | T: +0.04 ± 0.06<br>C: +0.39 ± 0.03† | T: − 0.33 ± 0.03<br>C: − 0.07 ± 0.19 | T: − 0.64 ± 0.03†<br>C: − 0.46 ± 0.17† | T: − 0.22 ± 0.04‡<br>C: − 0.50 ± 0.16†‡ |
| WHI | | T: 1.73 ± 0.46<br>C: 1.93 ± 0.26 | T: − 0.46 ± 0.00†‡<br>C: − 0.26 ± 0.23‡ | T: − 0.73 ± 0.46†<br>C: − 0.93 ± 0.26† | T: − 0.73 ± 0.46†<br>C: − 0.93 ± 0.26† |

T = test group; C = control group.

*A negative value indicates improvement.

†Statistical significance between baseline and observed time point.

‡Statistical significance between groups.

**Table 4**

Effect of Systemic Administration of AZM in Combination With Surgery or Surgery Alone on BANA and ICTP Levels (mean ± SEM)

| Parameter | Baseline | 2 Weeks (change)* | 1 Month (change)* | 3 Months (change)* | 6 Months (change)* |
|---|---|---|---|---|---|
| BANA | T: 0.87 ± 0.48<br>C: 1.00 ± 0.60 | T: − 0.80 ± 0.30†<br>C: − 0.77 ± 0.07† | T: − 0.60 ± 0.11†<br>C: − 0.74 ± 0.35† | T: − 0.54 ± 0.49†<br>C: − 0.46 ± 0.06 | T: − 0.33 ± 0.02<br>C: − 0.23 ± 0.14 |
| ICTP (pg/site) | T: 11.43 ± 13.62<br>C: 22.93 ± 64.41 | T: +1.23 ± 1.84<br>C: − 6.66 ± 47.49 | T: − 6.04 ± 7.01<br>C: − 11.49 ± 44.87 | T: +0.94 ± 1.50<br>C: − 12.81 ± 12.48 | T: − 3.83 ± 2.72<br>C: − 7.36 ± 34.77 |

T = test group; C = control group.

*A negative value indicates improvement.

†Statistical significance between baseline and observed time point.