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Research Article

The Efficacy of Subgingivally Delivered Andrographis Paniculata Gel to Treat Patients with Periodontitis

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Abstract

This study compared the clinical effects of scaling and root planing (SRP) after the adjunctive subgingival administration of *Andrographis paniculata* (AP) gel or placebo (PB) gel in a 6-month clinical trial for patients with chronic periodontitis. The study was a split-mouth, single-blind, randomized and controlled clinical trial that compared two treatment modalities (SRP+PB and SRP+AP) in single-rooted teeth with a probing depth (PD) of 5 mm or more. The clinical parameters, including PD, clinical attachment level (CAL), plaque index (PI), gingival index (GI), bleeding on probing (BOP), and radiographic examinations were recorded at baseline, 3 months and 6 months. The results showed that both treatment groups significantly improved with regard to clinical parameters ($p<0.05$); however, the between-group

differences were mostly insignificant (p>0.05), although SRP+AP showed a greater PD reduction than SRP+PB (p<0.05) between baseline and 3 months. In conclusion, the adjunctive use of AP gel significantly reduces PD and significantly improves attachment level.

Keywords: Andrographis paniculata gel, chronic periodontitis, non-surgical therapy

Introduction

Chronic periodontitis is an inflammatory disease of the tooth-supporting tissue. The primary etiological agent of this disease is the bacteria in dental plaque. Microorganisms and their products destroy the periodontal tissues (gingiva, cementum, alveolar

bone, and periodontal ligament) resulting in a loss of connective tissue attachment, pocket formation and alveolar bone resorption, the last of which causes tooth mobility and tooth loss. Periodontal therapy seeks to slow or halt disease progression, regenerate the periodontal tissue, and prevent disease recurrence (Haffajee and Socransky, 1994). Thus, preventing and treating chronic periodontitis can decrease tooth loss and promote good overall health.

The goals of an effectively treating chronic periodontitis are to arrest inflammatory processes via the removal of dental plaque, and to establish a local environment and microflora that are compatible with good periodontal health. Clinical outcomes to determine the success of periodontal treatment include reduced probing depth (PD), increased clinical attachment level (CAL),

and reduced bleeding on probing (BOP). This treatment begins with non-surgical therapy, which includes plaque control as well as scaling and root planing (SRP). Surgical therapy may be performed to gain an additional improvement after a successful non-surgical therapy. Considerable evidence supports the plaque control combined with SRP as an essential and effective component of the therapeutic measures for arresting periodontal disease (Badersten et al., 1990; Isidor and Karring, 1986; Pihlstrom et al., 1981; Knowles et al., 1980; Hughes and Caffesse, 1978; Listgarten et al., 1978). Nevertheless, certain factors can limit clinical and microbiological responses; these factors include pocket depth, root morphology, tooth position, and bacterial ability to invade periodontal tissues or dentinal tubules (Knowles et al., 1980; Rabbani et al., 1981; Waerhaug, 1978; Caffesse et al., 1986; Adriaens et al., 1988; Saglie et al., 1982).

The adjunctive use of chemical agents is another part of non-surgical therapy. Controlled-release antibiotic therapy has been introduced as an adjunct to enhance the efficacy of these non-surgical therapies. Many commercially available products exist, such as tetracycline fiber, metronidazole gel (Elyzol®),† chlorhexidine chips (**PerioChip**®),§ and doxycycline polymer (Atridox®).¶ However, these options are expensive because they must be imported from other countries. Thus, controlled-release drug systems using active components from traditional herbs have been developed. One of the most interesting plants is *Andrographis paniculata* Nees (AP), a medicinal herb that is widely found and cultivated in tropical and subtropical areas of Asia, including Thailand. AP contains a large quantity of bitters, which are primarily diterpenoid lactone compounds (Jewvachdamrongkul et al., 1987). The interesting

pharmacological activities of AP for periodontal therapy are its antibacterial activity against *Porphyromonas gingivalis* and its anti-inflammatory and immunostimulatory activities (Amornchat et al., 1991; Anju et al., 1993; Meenatchisundaram et al., 2009). Several studies have shown that AP gel can be used effectively as an adjunct to SRP to treat periodontitis (Rassameemasmaung et al., 1998; Atsawasuwan et al., 1998; Boonchaipanichwatana, 2001; Sirirat and Rojanapanthu, 2003; Thawornrungroj et al., 2011).

This study compared the clinical effects of SRP with the adjunctive subgingival administration of AP or PB gels to treat patients with chronic periodontitis in a 6-month clinical trial.

Materials and Methods

The Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand approved the study protocol (No. 61/2009). All patients were provided with both verbal and written information regarding the study and included in the trial only after providing informed consent.

Patient Selection

A total of 35 patients diagnosed with chronic periodontitis (aged 35 years or older) were recruited from the Section of Periodontics, Department of Oral Medicine and Periodontology, Faculty of Dentistry, Mahidol University. The inclusion criteria were: 1) the presence of at least two single-rooted teeth in each

quadrant with a PD of at least 5 mm and BOP; 2) radiographic evidence of alveolar bone loss; and 3) no periodontal treatments for at least 6 months prior to the study. Patients were excluded from participation if they 1) had diabetes; 2) had a systemic disease requiring daily medication; 3) had a history of antibiotic use over the previous 6 months; or 4) were pregnant or lactating.

Gel Preparations

The Faculty of Pharmacy, Mahidol University, Bangkok, Thailand created the preparations of AP and PB gel bases. The AP and PB gels were stored at 4°C throughout the study.

Please see Figure 1 in the PDF version

Clinical Procedures

This study used a split-mouth, single-blind controlled clinical trial to compare two treatment modalities: SRP+PB and SRP+AP. Each modality was applied to the teeth in each quadrant based on a randomized list using a computer-generated table. The two remaining quadrants were using SRP alone.

An intra-examiner calibration was performed prior to the study, achieving intraclass correlation coefficients (ICCs) of ≥0.9. All clinical parameters were measured at 6 sites around each tooth; however, only the two sites with the deepest PDs, CALs, or both (from different teeth within the same quadrant) were selected for the study. The clinical parameters included PD, CAL, the plaque index (PI; Silness & Löe, 1964), the gingival index (GI; Löe &

Silness, 1963), BOP (Ainamo & Bay, 1975), and tooth mobility (Miller, 1943).

One trained examiner recorded all clinical parameters and administered all radiographic examinations (using the parallel technique) at baseline, 3 months and 6 months. After the baseline examination, oral hygiene instructions were provided to the patients to perform self-plaque control using the Modified Bass method for brushing with either dental flossing or an interdental brush for interdental cleansing. The participants were asked to abstain from using antibacterial mouthwash for the entire study. Every tooth was mechanically debrided with an ultrasonic scaler (MiniPiezon, EMS®, Ivoclar Vivadent, Schaan, Principality of Liechtenstein) and hand instruments (Gracey curettes, Hu-Friedy®, Chicago, IL, USA) until the subgingival root surface was

hard and smooth. Local anesthesia was used as necessary for patient comfort. In the SRP+PB and SRP+AP groups, the periodontal pockets were gently irrigated with 2 ml of 0.9% sterile saline in a syringe fitted with a 21-gauge blunted needle after SRP. Then, the PB or AP gels were gently applied subgingivally into the periodontal pockets around the selected teeth (Figure 2). A sufficient amount of gel was administered to fill each periodontal pocket to the gingival margin. The excess was removed using sterile cotton pellets. Strict guidance was provided to the patients not to rinse, drink, or eat for 1 hour after the gel was applied. This gel application was repeated 1, 2, and 3 weeks following the baseline. All clinical parameters and radiographic examinations were re-examined at 3 and 6 months after 1 week of gel administration. The AP or PB gels were also re-administered at the 3-month re-examination. An examiner

(CS) who was masked to the type of treatment received recorded all clinical parameters and performed SRP, whereas other operators (MS & JK) administered the AP and PB gels. The patients were motivated to use an oral hygiene regimen for plaque control throughout the study.

Please see Figure 2 in the PDF version

Data Analyses

Data analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA). The significance threshold was α=0.05 for all tests. The intra-examiner reliability was calculated using ICCs. Between-treatment group comparisons of PD, CAL; the PI and the GI were analyzed using the Mann-Whitney U test.

Within-treatment group comparisons and the differences between each time interval were analyzed using Friedman's test and **Wilcoxon's signed-rank test.** In addition, between-treatment group comparisons of BOP were assessed using the Chi-square test. Cochran's Q test was used to analyze within-treatment group comparisons of BOP, followed by pairwise comparisons using McNemar's test.

Results

A total of 35 participants with chronic periodontitis (13 men and 22 women, aged 35 to 73 years; mean age 45.31±9.16 years) were enrolled in the study. A total of 526 sites were collected from 235 teeth. The study group consisted of four former smokers and five current smokers**.** No participants were

excluded during the study. No side effects were noted in any of the participants, although some patients complained of a bitter taste after the AP gel application.

No significant differences were found between the groups with regard to any of the baseline clinical parameters except for the PI (Table 1&2).

Please see Table 1 in the PDF version

Please see Table 2 in the PDF version

Within-Group Analysis

The data obtained at the 3-month and 6-month examinations are presented in Table 1. The within-group analyses revealed that both treatment modalities resulted in significant differences from baseline with regard to PD reduction, CAL gain, PI reduction, GI reduction, and BOP reduction at 3 and 6 months. However, no changes were observed with regard to tooth mobility. Nevertheless, mobility decreased (SRP+PB=10.34%, SRP+AP=14.29%), whereas mobility increased (SRP+PB=6.89%, SRP+AP=15.97%; data not shown).

Between-Group Analysis

PD Reduction

Significant between-group differences were found in PD reduction from baseline to 3 months in the SRP+AP group; however, no significant differences were found from baseline to 6 months within either group (Table 3).

Please see Table 3 in the PDF version

When baseline PD was used to divide each treatment group into 5- to 6-mm and 7- to 12-mm subgroups, no significant between-group differences were found at any observed time (Table 4). The

percentage of resolved sites (i.e., PD reduction ≥2 mm) in SRP+AP (76.43%) and in SRP+PB (68.06%) was no significant differences (Table 5)

Please see Table 4 in the PDF version

Please see Table 5 in the PDF version

CAL gain

No significant differences were found between the two groups at either 3 months or 6 months (Table 2). When the baseline PD was used to divide each treatment group into 5- to 6-mm and 7- to 12-mm subgroups, no significant differences were found between the two treatment groups at any time (Table 3). At 6

months, 51.33% of the sites in the SRP+AP group demonstrated an attachment increases of ≥2 mm compared with 46.77% of those in the SRP+PB group; however, there were no significant differences between SRP+AP and SRP+PB (Table 6).

Please see Table 6 in the PDF version

Please see Figure 3 in the PDF version

Discussion

This study evaluated the effectiveness of subgingivally delivered AP gel as an adjunct to treat patients with chronic periodontitis. This study used a split-mouth, single-blind, randomized

controlled design to compare results between SRP+PB and SRP+AP groups. The one operator collected data and the others who were blind to gel type administered PB or AP gels. Thus, examination bias did not occur. However, a double-blind design was not realistic for this study due to limitations regarding the color and bitter taste of the AP gel.

The split-mouth design allowed carryover effects to influence the treatment comparisons. The results of previous pharmacokinetic studies (Kuphasuk et al., 2004a, 2004b, 2008) suggest that these effects would not occur in the current study because andrographolide concentrations can be found in gingival crevicular fluid up to 24 hours after administration, and in saliva up to ½ hour after administration; furthermore, the maximum concentration of andrographolide was less than the MIC (537.70

μg/ml). Examiner calibration was performed prior to the study, thereby resulting in strong reliability.

A within-group analysis revealed that both treatment modalities improved clinical conditions with regard to PD reduction, CAL gain, PI reduction, GI reduction, and BOP reduction at 3 months and 6 months after baseline. This study resulted in PD reductions in the SRP+AP group that were slightly less than those observed in a previous study (2.22 mm vs. 2.29 mm; Boonchaipanichwatana, 2001), because PD reductions are greater for deeper PDs without surgery. Therefore, subgroups were created based on baseline PD by dividing each treatment group into 5- to 6-mm and 7- to 12-mm categories. Nevertheless, significant differences were not found between these subgroups at any observed time. This outcome might be because fewer sites

existed within the 7- to 12-mm subgroup than in the 5- 6-mm subgroup with regard to baseline PD (55 vs. 208 in SRP+PB; 65 vs. 198 in SRP+AP).

The expected PD reductions and CAL gains after performing SRP in deep pockets were 2.16 mm and 1.19 mm, respectively (Cobb, 1996). Between-group analyses did not demonstrate significant differences in PD reduction or CAL gain. At 6 months, 76.43% of the SRP+AP group demonstrated PD reduction ≥2 mm compared with 68.06% of those in the SRP+PB. In addition, 51.33% of the sites in the SRP+AP group demonstrated CAL gain of ≥2 mm compared with 46.77% of sites in the SRP+PB group. However, the percentage of resolved sites (i.e. PD reduction ≥2 mm, and attachment gain ≥2 mm) in the SRP+AP and in SRP+PB was no significant differences. Non-surgical treatments using AP gel as

an adjunctive therapy tended to improve clinical reductions in PD and increases in CAL.

Both treatment groups showed improvements from baseline with regard to the PI, the GI, and BOP, and significant between-group differences were not observed. The GI lowered by one scoring level (i.e., the baseline score of 2.01 decreased to 1.03), which matches the results reported in an earlier study (Cobb, 2002). All three of these indices decreased after treatment in both groups; however, these differences were not significant. This finding might be due to the effectiveness of the regular oral hygiene that patients practiced to control supragingival plaque, which might also have resolved gingival inflammation and BOP. AP gel might not affect the PI, the GI, or BOP. These findings match those

reported in previous studies (Axelsson & Lindhe, 1978, Helldén et al., 1979).

Previous studies showed that AP gel is a useful adjunctive treatment in periodontal therapy (Rassameemasmaung et al., 1998, Atsawasuwan et al., 1998, Boonchaipanichwatana, 2001, Sirirat & Rojanapanthu, 2003, Thawornrungroj, 2011). The effects of AP gel are due to its antibacterial activity (Amornchat et al., 1991), its anti-inflammatory action (Farnworth & Bunyaprephatsara, 1992), and its biocompatibility with dentin surfaces, which enhances fibroblast attachment and migration (Hamasakwattanakul, 2004). The present study demonstrated that SRP+AP enhances PD reduction and increases CAL, but these differences were not significant compared with the SRP+PB group. This result might be because SRP alone improves clinical

parameters, and most of the selected sites were horizontal defects. Apart from this efficacy, importantly, the same local drug-delivery system might not work equally well in all sites or all patients due to significant variability (Kornman, 1993) in the composition of microorganisms, the effectiveness of AP gel against *P. gingivalis* and individual host response.

Decreased mobility is a desirable outcome after non-surgical periodontal therapy (Kerry et al., 1982). However, 27 of 235 teeth (11.49%) showed deteriorated mobility. This outcome might be due to traumatic occlusion. Furthermore, heavy calculus deposits that splinted the teeth at baseline might have led to tooth mobility underestimation.

The results of the present single-center study, which represent a portion of a multicenter study, must be interpreted in the context of the limitations of the small number of selected sites with initial PDs of ≥7 mm or vertical defects. The improvements in PD and CAL might have been minimally influenced by the adjunctive use of AP gel due to improvements in the oral hygiene. Therefore, additional studies are needed with deep initial PDs and vertical defects according to radiographs.

Conclusions

The adjunctive use of *AP* gel significantly reduced PD and significantly improved attachment level from baseline. Additional studies are needed to assess this gel's performance in deep initial PDs with vertical defects according to radiographs.

Acknowledgments

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