Original Article

pISSN, eISSN 0125-5614
M Dent J 2022; 42 (3) : 199-208

The effect of locally delivered *Andrographis paniculata* gel as an adjunct therapy for periodontitis in well-controlled type 2 diabetes mellitus patients

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Objective: To compare clinical results for the group using a locally delivered *Andrographis paniculata* gel as an adjunct to scaling and root planing (SRP) with those obtained for the group receiving only SRP for periodontal treatment in well-controlled type 2 diabetes mellitus patients.

Materials and Methods: Thirty-two type 2 diabetes patients with periodontitis were included in this split-mouth single-blinded randomized clinical trial. At the start of the study, these patients had a hemoglobin A1c (HbA1c) less than 7%, at least two single-rooted teeth of the same type located on different quadrants of the same dental arch, an initial probing depth (PD) ≥ 5 mm. with bleeding on probing (BOP), radiographic alveolar bone loss, and a periodontal pocket depth that did not differ by > 1 mm. The teeth were randomly assigned to the experimental (SRP and AP gel) and control (SRP only) groups. PD, clinical attachment level (CAL), gingival index (GI), plaque index (PI), and BOP were recorded at the baseline and at the 3-month follow-up.

Results: After treatment, both groups exhibited improved periodontal parameters. In the experimental group, PD, CAL, GI, and BOP significantly improved in comparison with the control group at the 3-month follow-up ($P < 0.05$).

Conclusion: Application of locally delivered AP gel as an adjunct enhanced SRP clinical outcomes for periodontal therapy in well-controlled type 2 diabetes mellitus patients.

Keywords: *Andrographis paniculata*, diabetes mellitus, periodontitis, root planing

How to cite: Sangkum O, Dechosilpa V, Kuphasuk Y. The effect of locally delivered *Andrographis paniculata* gel as an adjunct therapy for periodontitis in well-controlled type 2 diabetes mellitus patients. M Dent J 2022; 42: 199-208.

Introduction

Periodontitis is defined as the inflammation of the periodontium surrounding the teeth. The periodontium comprises the gingiva, cementum, periodontal ligament, and alveolar bone [1]. Although periodontitis is a multifactorial disease, its primary etiology involves the formation of a dental plaque biofilm that stimulates the host immune response, leading to inflammation and periodontal destruction [2]. Clinical signs and symptoms include gingival redness, gingival swelling, gingival bleeding, a periodontal pocket associated with radiographic alveolar bone loss, tooth mobility, and eventual tooth loss.

Diabetes mellitus is a chronic disease that is characterized by continuously elevated blood glucose levels. Type 2 diabetes mellitus is the most common, accounting for ~95% of all diabetes cases, resulting from insulin resistance and insulin production deficiency [3]. Diabetes mellitus and periodontitis exhibit a bidirectional association [4, 5].

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Received: 17 July 2022 **Revised:** 16 October 2022 **Accepted:** 18 October 2022

In other words, diabetes mellitus is a major risk factor for periodontitis prevalence and severity. Meta-analysis revealed that compared to non-diabetic patients, diabetic patients exhibit a 1.24-fold increased incidence risk of periodontitis [4]. Severe periodontitis is significantly associated with poor glycemic control [5], while periodontal therapy reduces blood sugar, as measured by hemoglobin A1c (HbA1c) levels, on average by 0.3–0.5% within 12 months [6]. Treatment of periodontitis in diabetics is essential for good oral health and to support overall health improvement.

Scaling and root planing (SRP) involves the removal of dental plaque and supra- and subgingival calculus to produce a smooth root surface. SRP is considered the gold standard for periodontal treatment and significantly decreases gingival inflammation, decreases the periodontal probing depth (PD), and increases the clinical attachment level (CAL) [7]. However, all teeth do not exhibit the same response to SRP. Several factors affect the treatment outcome, such as deep and tortuous periodontal pockets, root morphology, and intrabony defects, while the invasion ability of bacteria to periodontal tissue limits the accessibility of SRP and reduces treatment response [8, 9].

As an adjunctive therapy, local drug delivery (LDD) of antimicrobials enhances SRP treatment, which involves the direct delivery of a drug into the periodontal pocket and maintenance of an effective drug concentration for long periods. Compared to systemically administered doses, LDD doses are relatively low, reducing the risks of bacterial resistance and systemic side effects. Tetracycline, doxycycline, and minocycline, etc. are used for LDD [10]. However, these drugs are expensive as they are imported. Recently, herbal medicine has become popular in dentistry, and several herbs for LDD have been developed for periodontal treatment, including green tea, aloe vera, and turmeric. LDD using natural herbs exerts a natural healing effect, and it is safe and affordable [11]. Several studies reported that the use of LDD, either as an antibiotic or in herbal form as an adjunct to SRP, significantly improves the clinical results of periodontal treatment in diabetics [12,13].

Andrographis paniculata (AP) is an herbaceous plant in the family Acanthaceae, which is native to India and Sri Lanka, and it is widely cultivated in Southeast Asia. In 1999, the Thai Ministry of Public Health included *A. paniculata* in the National List of Essential Medicines for treatment benefits [14]. Its active ingredients include andrographolide, dehydrographolide, neoanhydrographolide, and deoxyanhydrographolide that exhibit anti-inflammatory [15] and immunostimulatory properties [16], as well as anti-fungal [17] and antibacterial activities, against *Porphyromonas gingivalis* [18] and *Staphylococcus aureus* [17]. Owing to its extensive range of pharmacological properties, AP has attracted widespread attention, and it is a promising remedy in several fields of dentistry. An aqueous AP extract may be a beneficial adjunct to oral candidiasis and Candida-associated denture stomatitis treatment [19]; it is probably used as an endodontic irrigant to eliminate *Candida albicans* and *S. aureus* similar to sodium hypochlorite [17].

Recently, a group of dentists and pharmacists in Thailand collaborated and developed AP gel in the LDD form for periodontal treatment. Previous studies revealed that the use of the AP gel as an adjunct for periodontal treatment leads to improved clinical outcomes in healthy volunteers with no medical conditions during the initial [20, 21] and supportive periodontal therapy [22]. However, studies have

not examined the impact of AP gel use in other patient groups, especially in patients with type 2 diabetes that exhibit a higher prevalence and severity of the disease than those observed in the general population.

Therefore, in this study, clinical results between the experimental group using AP gel as an adjunct to SRP and the control group treated only by SRP for periodontal treatment are evaluated with well-controlled type 2 diabetes mellitus patients as subjects.

Materials and methods

Study design

This randomized controlled clinical trial was conducted as a split-mouth, single-blinded study. The research assistant was a periodontist who examined and recorded all study data as a single-blinded outcome assessor. The main researcher was a periodontist who treated volunteers until the end of the study. This study was approved by the Bangkok Metropolitan Administration Ethical Committee according to the Declaration of Helsinki, Belmont Report guidelines, CIOMS guidelines, and ICH-GCP guidelines (S017h/63). The study was conducted from April 2021 to March 2022.

Study population

Well-controlled type 2 diabetes volunteers (according to the American Diabetes Association criteria 2017) [23] were recruited from the Diabetes Outpatient Clinic, Taksin Hospital, Bangkok Metropolitan Administration. Inclusion criteria included a HbA1c less than 7%, at least two single-rooted teeth of the same type located on different quadrants of the same dental arch, an initial PD ≥ 5 mm with bleeding on probing (BOP), radiographic alveolar bone loss, and PD that did not differ by >1 mm. Volunteers with history of smoking and herbal medicine allergy, those who received antibiotics or periodontal treatment within the last 6 months, and those who were pregnant or breastfeeding were excluded from this study.

Variable measurements

All clinical parameters including PD, CAL, BOP [24], gingival index (GI) [25], and plaque index (PI) [26] were measured at six sites around each tooth. The only site with the deepest PD and CAL of each tooth was selected, and the periodontal parameters were recorded at the baseline and at the 3-month follow-up. PD and CAL were measured using a standard periodontal probe (UNC 15, Hu-Friedy®, Chicago, IL, USA). Intra-examiner calibration was validated before commencing the study. Interclass correlation coefficients (ICCs) greater than 0.9 were accepted.

Gel preparation

The AP gel was manufactured by Bangkok Lab & Cosmetic Co., Ltd. (Ratchaburi, Thailand) according to good manufacturing practice (GMP) standards following the original formula reported in a previous study [27]. The AP gel was packaged in a plastic tube and stored in a pharmaceutical refrigerator to retain drug stability throughout the study period. The drug was stored in an air-conditioned room for 1 hour and transferred to a syringe with a needle when required.

Study methodology

At the beginning of the study, volunteers were subjected to periodontal examination and intraoral periapical radiography, and their blood tests were conducted for HbA1c level measurement in the hospital laboratory. The main researcher conducted full-mouth SRP treatment using

a piezoelectric dental scaler (Acteon Newtron® P5 XS, France) and hand instruments (Gracey Curettes, Hu-Friedy®, Chicago, IL, USA) and instructed patients about oral hygiene. The single-rooted teeth located on different quadrants of the same dental arch were randomized equally into two groups by drawing lots. The experimental group received AP gel as an adjunct to SRP (n = 57), while the control group received only SRP (n = 57). After SRP treatment and irrigation with a syringe of saline, AP gel was subgingivally delivered into the experimental group pockets until the gel overflowed from the pockets. The excess gel was wiped off using cotton pellets. Patients were instructed not to rinse their mouths, drink water, or eat for 1 hour after gel application and not to use mouthwash or take oral *A. paniculata* medicine. In the experimental group, AP gel was re-applied thrice at weekly intervals. Periodontal parameters were re-examined at a 3-month follow-up from the last gel application visit, and supportive periodontal therapy was performed on all volunteers.

Data analysis

Data were analyzed using SPSS for Windows Release 26.0 computer software. Mean PD and CAL values were analyzed at the baseline and at the 3-month follow-up using the Mann–Whitney U test to determine differences between the experimental and control groups. The Wilcoxon signed-rank test was applied to examine intra-group differences. BOP, GI, and PI were analyzed at the 3-month follow-up using the Chi-square test to determine the association with the different treatment groups. A *P*-value of < 0.05 was considered statistically significant.

Results

The study included 32 volunteers, comprising 27 females and 5 males. The mean age was 54.59 ± 8.53 years (age range 30–68 years), and the mean initial HbA1c was 6.23 ± 0.42% (HbA1c range 5.1–6.9%). All volunteers were treated for diabetes mellitus with oral medication and diet control. The total number of teeth in this study was 114 (114 sites). None of the volunteers displayed allergic reactions or side effects, while one volunteer complained of a bitter taste in the mouth after gel application. No statistically significant differences in the periodontal parameters were observed between the experimental and control groups at the baseline. After treatment, all periodontal parameters in both groups improved when compared to the baseline data.

PD and CAL

Comparisons within the experimental and control groups revealed that PD and CAL exhibit a statistically significant decrease at the 3-month follow-up in comparison to the baseline. The comparison of both groups at the 3-month follow-up revealed that the statistically significant decrease of PD and CAL in the experimental group is greater than that in the control group (Table 1).

BOP and GI

The comparison of the groups at the 3-month follow-up revealed a significant relationship between the different treatment groups and BOP and degree of GI. The experimental group exhibited BOP at 28.07%, while the control group exhibited BOP at 56.14%. Approximately one-third of the sites (31.58%) in the experimental group exhibited GI = 0, while the control group exhibits only 14.04% (Table 2).

Table 1 Mean (SD) and Median (IQR) values of PD and CAL for both groups at the baseline and at the 3-month follow-up.

Parameters	Timeline	SRP+AP gel†		SRP†		*P*-value
		Mean (SD)‡	Median (IQR)‡	Mean (SD)‡	Median (IQR)‡	
PD‡	Baseline	6.35 (1.13)	6.00 (1.00)	6.21 (1.10)	6.00 (2.00)	0.491
	3-month follow-up	3.33 (0.74)	3.00 (1.00)	4.09 (0.91)	4.00 (2.00)	<0.001*
		<0.001**		<0.001**		
CAL‡	Baseline	6.79 (1.77)	7.00 (2.50)	6.77 (1.67)	7.00 (3.00)	0.977
	3-month follow-up	4.21 (1.25)	4.00 (2.00)	5.12 (1.50)	5.00 (2.00)	0.003*
		<0.001**		<0.001**		

*Statistically significant difference between the experimental and control groups (Mann-Whitney U test)

**Statistically significant difference between the baseline and 3-month follow-up (Wilcoxon signed-ranks test)

†SRP = Scaling and root planing, AP gel = *Andrographis paniculata* gel

‡PD = Probing depth, CAL = Clinical attachment level, SD = Standard deviation, IQR = Interquartile range

Table 2 BOP, GI and PI values for both groups at the baseline and at the 3-month follow-up.

Parameters	Timeline	SRP+AP gel†	SRP†	*P*-value
		n (%)	n (%)	
BOP‡	Baseline	57 (100%)	57 (100%)	
	3-month follow-up	16 (28.07%)	32 (56.14%)	0.002*
GI	Baseline	2 = 53 (92.98%)	2 = 55 (96.49%)	
		3 = 4 (7.02%)	3 = 2 (3.51%)	0.402
	3-month follow-up	0 = 18 (31.58%)	0 = 8 (14.04%)	
		1 = 23 (40.35%)	1 = 17 (29.82%)	
		2 = 16 (28.07%)	2 =32 (56.14%)	0.006*
PI	Baseline	1 = 16 (28.07%)	1 = 22 (38.60%)	
		2 = 36 (63.16%)	2 = 30 (52.63%)	
		3 = 5 (8.77%)	3 = 5 (8.77%)	0.414
	3-month follow-up	0 = 3 (5.26%)	0 = 2 (3.51%)	
		1 = 45 (78.95%)	1 = 44 (77.19%)	
		2 = 9 (15.79%)	2 =11 (19.30%)	0.874

*Statistically significant association between the different treatment groups and the degree of the periodontal parameters (Chi-square test)

† SRP = Scaling and root planing, AP gel = *Andrographis paniculata* gel

‡ BOP = Bleeding on probing, GI = Gingival index, PI = Plaque index

PI

No significant association was observed between the groups at the 3-month follow-up (Table 2).

Discussion

This split-mouth randomized controlled trial aimed at evaluating the effectiveness of using locally delivered *A. paniculata* gel as an adjunct to SRP compared to the use of only SRP in well-controlled type 2 diabetes mellitus patients. The comparison between the two treatment groups was not ideal. A gel-based vehicle was not used as a placebo in the control arm. However, according to a previous study, no difference in the clinical outcome was observed between the SRP only group and gel-based treatment as an adjunct to the SRP group; hence, gel-based vehicles do not promote the healing of the periodontium [20].

In this study, 32 volunteers were included: 27 females and 5 males; in Thailand, the prevalence of diabetes in females is greater than that in males [28]. A study on gender differences in general health habits revealed that women tend to have better oral health behavior, with greater cooperation in receiving dental treatment than men [29]. However, gender did not affect the outcome of periodontal treatment [30].

Periodontitis is a major oral complication of diabetes mellitus [31]. Several mechanisms are involved in the relationship between diabetes and periodontitis, including white blood cell function abnormalities [32], reduction of collagen synthesis, elevation of enzymes that break down collagen [33], increase rate of advanced glycation end products (AGEs) binding to the receptor for AGEs in the periodontal tissue, and stimulation of the release of the inflammatory mediator from white blood cells [34]. Previous studies reported changes in periodontal disease pathogens in diabetic patients. Colonization levels of *P. gingivalis* in diabetic patients are greater than those in patients without diabetes, but other periodontal disease pathogens such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia,* and *Fusobacterium* did not exhibit any difference [35]. The results are in agreement with those reported previously: In Thailand, regardless of glycemic control, the colonization of *P. gingivalis* in diabetic patients is greater than that in non-diabetic patients [36]. *P. gingivalis* is a non-motile Gram-negative anaerobe that is considered as the main etiological pathogen of periodontitis, producing virulence factors that induce inflammation and cause tissue destruction directly and indirectly. In addition, *P. gingivalis* can locally invade the periodontal tissue [37], and it is difficult to eradicate. All these mechanisms induce severe inflammation and destruction of the periodontium in diabetic patients.

This is the first study to report the use of AP gel in diabetic patients with periodontitis. The use of the AP gel as an adjunct to SRP in type 2 well-controlled diabetics led to reduced GI, enhanced PD reduction, and CAL gain better than those in the SRP group alone. The pharmacological properties of AP gel including anti-inflammatory [15], immunostimulatory [16], and antibacterial effects on *P. gingivalis* [18], and also enhance wound healing by the increase in collagen synthesis [38], are speculated to be accountable for the significant improvements in clinical parameters in this study.

After treatment, PD and CAL in both groups significantly improved in comparison with the

baseline data. In the initial moderately deep pocket, the SRP + AP gel group also exhibited better PD reduction (0.90 mm) and CAL gain (0.93 mm) compared with those in the SRP only group at 3-months-follow-up. Compared to previous studies on healthy patients with periodontitis, the results of PD reduction and CAL gain are quite similar. In those studies, the AP gel group exhibited improvement in PD reduction (0.81 mm) [20] and CAL gain (0.78–0.96 mm) [20, 21] in comparison with those of the SRP only group. This result suggested that the use of AP gel in diabetic patients with good glycemic control renders good outcomes that are similar to healthy volunteers [20, 21] and supports evidence that short-term non-surgical treatment responses exhibit effects similar to those of non-diabetic patients [39].

The use of AP gel as an adjunct to SRP was demonstrated to be a beneficial alternative treatment for well-controlled diabetic patients. The application of AP gel reduced the need for periodontal surgery and the incidence of site breakdown during supportive treatment [40]. This is one of the considerable methods for sites where periodontal surgery is contraindicated.

This result should be interpreted with caution. First, this study was conducted with well-controlled type 2 diabetic patients, so the results may not be generalizable to all diabetic patients, especially those with poor glycemic control. Although evidence shows that poor metabolic control results in a worse response to periodontal treatment [41] and the clinical results of using LDD of antimicrobials in poorly controlled patients remain limited and controversial [12], one previous study found a significant improvement in PD and CAL when antimicrobial LDD was used as an adjunct to SRP [42]. Due to the broad properties of AP gel as mentioned above, the use of AP gel may have some benefits for poorly controlled diabetic patients. However, further research should be conducted to confirm our assumption and to determine whether poor glycemic control affects the effectiveness of AP gel. Second, the diversity of research methodologies used previously on the use of LDD in diabetic patients precludes the direct comparison of the AP gel effect [12]. Therefore, AP gel was as effective as or superior to other drugs, cannot be concluded. Comparative research with other LDD of antimicrobials is intriguing for the benefit of diabetic treatment. Finally, there was a short follow-up period in this study. Long-term treatment outcomes depend on an appropriate recall frequency, personal oral hygiene, and glycemic control. Additional research includes at least 6–12 months of long-term follow-up should be required in this study group.

Conclusion

Well-controlled type 2 diabetic patients exhibited good responses to periodontal treatment. Using AP gel as an adjunct therapy to SRP had a significant improvement in periodontal parameters compared to SRP treatment alone at the 3-month follow-up.

Acknowledgments

This project was supported by grants from Taksin Hospital, Bangkok Metropolitan Administration. We would like to thank Bangkok Lab & Cosmetic Co., Ltd. (Ratchaburi, Thailand) for providing the AP gel. Associate Professor Dr. Pleumchitt Rojanapanthu offered excellent advice during this research study, Dr. Jintanan

Jungsiripornpakorn provided diabetes mellitus information, and Dr. Ruangyod Juwarahawong conducted the periodontal examinations. We would also like to thank all staff members at the Dental Department and Diabetic Clinic in Taksin Hospital for their assistance throughout the study.

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