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BIOCHEMICAL EFFECT OF LOCALLY DELIVERED TEA TREE OIL GEL AS AN ADJUNCT TO NON-SURGICAL PERIODONTAL THERAPY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: This study's main objective was to assess the therapeutic benefits of using Tea Tree Oil (TTO) gel intrapocket as a complement to non-surgical periodontal therapy.

Methods and materials: A three-month, double-blind, randomized, controlled biochemical trial including 22 individuals with Stage III Grade B periodontitis was carried out. Randomly selected patients were allocated to two treatment groups: group I received NSPT plus locally applied TTO gel at the site of the deepest probing pocket depths (PPD); group II received NSPT alone. At 0 and 90 days after treatment, GCF samples were obtained for biochemical analysis for Tumor Necrosis Factor Alpha (TNF -α), as well as Oral Health Impact Profile (OHIP-14) questionnaire.

Results: Outcomes demonstrated that, in comparison to the baseline, both groups' metrics had improved. The test group showed a much greater decrease in TNF-α level. Patients in both groups expressed the same degree of satisfaction.

Conclusion: In combination with non-surgical periodontal therapy, tea tree oil gel may be more successful in lowering periodontal inflammation.

KEYWORDS: Nonsurgical periodontal treatment, Periodontitis, Tea tree oil, Local Drug Delivery

INTRODUCTION

Dysbiotic plaque biofilms are the source of periodontitis, a chronic inflammatory disease that gradually destroys the tissues that support teeth, including the alveolar bone and periodontal ligament. The disease is caused by intricately interacting host immune responses, specific bacterial infections, and environmental factors. Armitage (1999) defined it as either "chronic" or "aggressive". In order to create a single category

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known as "periodontitis," the American Academy of Periodontology and the European Federation of Periodontology combined their staging and grading systems in 2017. The former was determined by the severity of the disease and the complexity involved in managing it, while the latter provided data on the disease's progression, likelihood of recovery, and potential future development [1, 2].

Researchers propose that managing the remaining quantity of periodontal bacteria is a prerequisite for treating periodontal disease [3]. Consequently, it is suggested that non-surgical periodontal therapy (NSPT), which entails mechanical therapy including scaling and root planing as well as oral hygiene practices, be considered the first line of treatment for periodontitis. Chemical therapy, which includes locally or systemically given antimicrobials, could be included to the NSPT [4].

Resistance to microbes and large dosages are the main limitations of systemic antibacterial therapy. For almost thirty years, direct subgingival management has been promoted as a medication that is administered locally[5]. Increasing the concentration of antibiotics at the infection site by Local Drug Delivery (LDD) is a technique that works regardless of patient compliance [6]. It can persist for a few weeks and exceeds the minimum inhibitory concentration (MIC). LDD is available in a number of forms, including systems for nanoparticles, irrigations, fibers, films, injectables, gels, strips, and compacts [7, 8].

Natural goods make up almost half of all pharmaceuticals, and one important source of medications is tea tree oil (TTO). In order to cure periodontal disease, oriental medicines are investigated for their antibacterial, anti-inflammatory, and ability to regenerate periodontal tissue [9].

The well-known essential oil tea tree oil, sometimes referred to as "oil of the Tea tree" or "Melaleuca essential oil," is extracted from the leaves of the Myrtaceae family tree Melaleuca alternifolia. A native of southern Queensland and New South Wales, this plant is referred to as "nature's most versatile healer" by its indigenous populations. It originated in low-lying, marshy, subtropical coastal soils [10].

Numerous antiviral, antifungal, antibacterial, anti-inflammatory, antioxidant, and antiprotozoal qualities are present in tea tree oil (TTO) [10]. TTO exhibits its anti-inflammatory properties by lowering TNF α, IL-1beta, IL-8, IL-10, and PGE2 production. 1,8-cineole and Terpinen-4-ol, two ingredients in TTO, a topical toner, have antibacterial and anti-inflammatory qualities. Despite having distinct mechanisms of action, it has the same antibacterial activity as chlorhexidine (CHX) [11].

Tea tree oil (TTO) has been shown in studies to reduce periodontal infections and inflammatory mediators, which in turn allows periodontal tissue healing by lowering inflammatory cytokines [11]. TTO has demonstrated significant effectiveness as a mouthwash by lowering gingival bleeding in gingivitis and bacterial load, hence validating the anti-inflammatory and antibacterial characteristics[12].

Although tea tree oil offers numerous therapeutic benefits in treating periodontitis, this study aims to evaluate the effects of locally applied TTO gel on TNF-α levels and patient satisfaction as a supplementary treatment for Stage III Grade B periodontitis.

MATERIALS AND METHODS

Clinical trial design & sample size calculation

This study was a randomized, controlled, parallel-design clinical trial with two arms, conducted over three months. It involved two study groups, and the participants were selected from the outpatient clinic of the Department of Oral Medicine, Periodontology, and Oral Diagnosis at the Faculty of Dentistry, Ain Shams University. The study adhered to the research guidelines of Ain Shams University and received approval from the

Research Ethics Committee (ID: FDASU-Rec IM 1045). The procedure was thoroughly explained to the participants, and informed consent was obtained from each patient before beginning treatment.

A power analysis was completed with sufficient power to conduct a two-sided statistical test of the null hypothesis, assuming no difference between the tested groups. Based on past study results [11], the required sample size (n) was calculated to be 22 instances (11 per group), with an alpha level of 0.05, a beta of 0.2 (corresponding to 80% power), and an effect size (d) of 1.32. The sample size was calculated using G*Power 3.1.9.7.

Subject selection

This study involved 22 systemically healthy patients with Stage III, Grade B periodontitis. The inclusion criteria included: age between 25 and 50 years, pocket depth of ≥ 6 mm, bleeding on probing (BOP), and radiographic bone loss extending to the middle and apical thirds of the root [13]. The patients must be able to follow and maintain oral hygiene instructions (OHI). Exclusion criteria include pregnant or breastfeeding women, smokers, individuals with a history of tea tree oil allergy, asthmatic patients [14], and those who received periodontal treatment in the last 6 months. [15].

Tea tree oil gel

A 5% tea tree oil gel (Sigma Aldrich® Steinheim, Germany) was formulated for subgingival local application was prepared by NAWAH (NAWAH Scientific, Research institute, Egypt).

Method: For two hours, the gelling agent Carbopol 940 was steeped in distilled water before mixing with TTO in propylene glycol. 0.2% w/v of methyl paraben was utilized as a preservative. After 30 minutes of magnetic stirring the gel, 1 N NaOH was added to change the pH. The gel was autoclaved for 20 minutes at 110°C. The gel was then placed in syringes, each containing 3 ml, for easy administration to periodontal pockets [11].

Primary outcome measures

Clinical Parameters including: Patient satisfaction using Oral Health Impact Profile (OHIP-14) questionnaire [16–19].

Secondary outcome measures

To measure the amount of Tumor Necrosis Factor-Alpha (TNF-α) in GCF samples, an Enzyme-Linked Immunosorbent Assay (ELISA) was used, which is a readily available commercial method, following the guidelines provided by the manufacturer [20].

Treatment Protocol:

Clinical Parameters and Procedures

Using sealed envelopes, twenty-two participants were randomized to either the test or control group. At the screening visit preoperative periapical radiographs were conducted using a standard technique and a digital sensor, using a Woodpecker i-scan digital intraoral radiographic sensor (Guilin Woodpecker Medical Instrument Co. Ltd, China) utilizing an image plate with photostimulable phosphor size 2 (26 x 36mm) as the image receptor [21]. Full mouth one stage debridement was done to the patients using ultrasonic scalers, manual scalers and curettes. *Melaleuca Alternifolia* Gel was carefully applied to the deepest pocket using a syringe with a blunt tip. The syringe was then slowly withdrawn to prevent tissue damage for patients in group I (n = 11) two weeks after phase I therapy[22]. Regular check-ups were done to ensure proper oral hygiene and plaque removal and patients were advised to brush and floss daily, avoid hard or sticky foods or brush close to treated area.

The 14-item Oral Health Impact Profile (OHIP-14) survey used to assess the degree to which oral problems are self-reportedly responsible for functional limitation, discomfort, and disability. It is derived from a 49-item, original extended

version that is modified for oral health established on a theoretical framework developed by the World Health Organization (WHO) and translated from their primarily published and used English version, to Arabic, and completed by the patients three months after treatment [18].

GCF samples were collected at baseline 48 hours after finishing phase I therapy and recollected again 3 months after therapy [22]. Cotton rolls were used to isolate the sample area in order to prevent saliva contamination, and sterile perio-paper strips (Oraflow Inc., Plainview, NY, USA) were used to collect GCF. As directed, the perio-paper was carefully placed into the gingival crevice until a small amount of resistance was felt, and then it was left there for 30 seconds. Strips with evident blood or debris contamination was eliminated [23] For later analysis, the samples were promptly stored at -20°C in sterile, labeled Eppendorf containers [20, 24].

The biochemical parameters were measured twice, once at baseline and again three months later. Mean values were calculated per patient and group.

Statistical Analysis

Frequency and percentage numbers were used to depict both ordinal and categorical data. Fisher's exact test was utilized to assess the categorical data. Numerical information was presented using the mean and standard deviation figures. They were tested for normality using the Shapiro-Wilk method. Paired and independent t-tests were used to analyze the parametric data for intragroup and intergroup comparisons, respectively. When examining non-parametric numerical and ordinal data, intragroup comparisons were conducted using the signed rank test, whereas intergroup comparisons were conducted using the Mann-Whitney U test. A significance threshold of $p \leq 0.05$ was used for each test. The statistical analysis was carried out using R statistical program, version 4.3.0 for Windows [25].

RESULTS

Twenty-two out of twenty-two subjects completed the study. There were no dropout, major adverse effects nor complications reported throughout the study period. Group I (test group) n=11, Group II (control group) n=11. All patients committed to treatment protocol and to the follow up visits. (Table 1)

TABLE (1) Intergroup comparisons and summary statistics for demographic data

Parameter	Value		Test	Control	p-value
Gender	**Male**	**n**	6	5	**1ns**
		%	54.5%	45.5%	
	Female	**n**	5	6	
		%	45.5%	54.5%	
Age	**(Mean±SD) years**		34.69±3.12	35.17±5.23	**0.806ns**

; significant (p ≤ 0.05) ns; non-significant (p>0.05)

Patient satisfaction:

Table 3 shows the contrast of the test and control groups' responses to the OHIP-14 items. None of the OHIP-14 items showed significant divergence in statistics between the groups ($p > 0.05$). This implies that functional limits, psychological and physical pain, interpersonal conduct, psychological and social disabilities, handicap, and total impact on oral health did not significantly differ across the groups.

Biochemical assessment of TNF-α:

As compared to baseline, both groups had a significant decrease in TNF-α levels after three months. Additionally, there was a statistically significant difference between both test group (126.96±24.32) and control group (214.58±48.77). (Table 2)

TABLE (2) Clinical and biochemical assessment at baseline and 3 months and statistical difference between these parameters

	Test group			Control group			P- value
(Mean±SD)	Baseline	3months	P-value	Baseline	3months	P-value	
TNF-α (ng/dl)	290.99±43.88	126.96±24.32	<0.001*	309.45±11.73	214.58±48.77	<0.001*	<0.001*
TNF-α (ng/dl) difference		164.03±33.76			94.87±40.73		

; significant (p ≤ 0.05) ns; non-significant (p>0.05)

TABLE (3) Comparison between test group and control group according to OHIP

OHIP-14 item	Total (n=22)	Test group (n=11)	Control Group (n=11)	t-test	p-value
Functional limitation	**0.73±0.37**	**0.68±0.40**	**0.77±0.34**	**0.568**	**0.576**
1. Had trouble pronouncing any words.	0.77±0.43	0.73±0.47	0.82±0.41	0.488	0.631
2. Felt sense of taste has worsened.	0.68±0.48	0.64±0.51	0.73±0.41	0.439	0.666
Physical Pain	**0.45±0.43**	**0.36±0.39**	**0.55±0.47**	**0.982**	**0.338**
3. Had painful aching.	0.41±0.50	0.27±0.47	0.55±0.52	1.291	0.211
4. Found it uncomfortable to eat any food.	0.5±0.51	0.45±0.52	0.55±0.52	0.408	0.687
Psychological Pain	**0.25±0.40**	**0.14±0.32**	**0.36±0.45**	**1.356**	**0.190**
5. Been self-conscious.	0.27±0.46	0.09±0.30	0.45±0.52	2.00	0.59
6. Felt tense.	0.23±0.43	0.18±0.41	0.27±0.47	0.488	0.631
Interpersonal manner	**0.25±0.34**	**0.14±0.23**	**0.36±0.39**	**1.648**	**0.115**
7. Felt diet has been unsatisfactory.	0.27±0.45	0.18±0.40	0.36±0.51	0.933	0.362
8. Had to interrupt meals.	0.23±0.42	0.09±0.30	0.36±0.50	1.539	0.139
Psychological Disability	**0.16±0.32**	**0.09±0.30**	**0.23±0.34**	0.989	0.334
9. Found it difficult to relax.	0.18±0.39	0.09±0.31	0.27±0.47	1.085	0.291
10. Been a bit embarrassed.	0.14±0.35	0.10±0.29	0.18±0.40	0.598	0.557
Social Disability	**0.15±0.36**	**0.09±0.31**	**0.22±0.41**	**0.889**	**0.385**
11. Been a bit irritable.	0.18±0.39	0.08±0.30	0.27±0.47	1.080	0.291
12. Had difficulty doing usual jobs.	0.14±0.35	0.10±0.29	0.18±0.41	0.598	0.557
Handicap	**0.23±0.40**	**0.36±0.45**	**0.09±0.30**	**1.664**	**0.112**
13. Felt life less satisfying.	0.18±0.39	0.27±0.47	0.09±0.30	1.090	0.291
14. Been totally unable to function.	0.27±0.45	0.45±0.52	010±0.31	2	0.059
Overall	**0.25±0.40**	**0.18 ±0.39**	**0.36 ±0.41**	**1.080**	**0.338**

Scores range from 0 (Never indicator most satisfied) to 4 (Very often indicator least satisfied).
Using: t-Independent Sample t-test for Mean ± SD
p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.001 is highly significant

DISCUSSION

In the field of periodontal treatment, locally delivered antimicrobial drugs are becoming more and more popular because to the developing issues around the use of systemic antibiotics. This investigation's goal was to assess the effectiveness of nonsurgical periodontal therapy against adjunctive TTO gel. To the best of the author's knowledge, the evaluation included clinical assessment, patient satisfaction, and biochemical examination of the amount of TNF-α in the GCF.

Locally administered antimicrobial drugs have garnered significant motivation in the field of periodontal treatment due to the mounting issues pertaining to systemic antibiotic usage. The goal of the current study was to evaluate the impact of adjunctive TTO gel to nonsurgical periodontal therapy. Patient satisfaction and biochemical assessment of the level of TNF-α in the GCF where evaluated which to the author's knowledge have not been published before.

Variable forms and concentrations of TTO were used for the treatment of gingivitis and periodontitis that includes toothpaste (0.5%), gels (2.5%, 5%), and solutions (0.2%, 1.5%) [24]. A systematic review conducted by Casarin et al.,2017 found that 5% TTO gel significantly reduced probing depth (PD) and clinical attachment loss (CAL) [26]. Therefore, similar to Elgendy et al., 2013 and Taalab et al.,2021 this study used 5% TTO gel [9, 11].

The consequences and management of periodontal disease on patients' well- being has attracted more attention, that is why short-form OHIP-14 was used in this study [27]. The results regarding the OHIP14 showed that there is no statistically significant variation found between the two groups. Our results follow that of Liss et al.,2021 which concluded that both patient satisfaction and adherence to self-performed periodontal infection control seem to be highly influenced by the patient's experiences participating in therapeutic decisions, irrespective of the treatment approach [28].

Also, the results of OHIP14 were in accordance with Shah & Kumar, 2001 who reported that a positive quantitative clinical response to non-surgical periodontal therapy is well established. As a result of the condition's successful treatment, these results demonstrate that there are also subjective advantages for the patients and offer more proof that periodontal disease adversely impacts oral health quality of life [18].

Over the past few years, clinical studies have been conducted and revealed that the level of TNF-α can be detected in human GCF, and showed an increased level in cases of periodontitis [29, 30].

This study focused on TNF-α, the primary endogenous generated proinflammatory agent in the periodontal environment. Besides, it affects bone remodeling homeostasis, alters bone metabolism, and promotes bone tissue loss in the inflammatory microenvironment. In fact, Ren & Li, 2022 stated that after periodontal therapy the levels of TNF-α in GCF and serum were considerably lowered [29].

Regarding TNF- α levels, both groups showed that there was significant reduction in TNF- α levels after 3 months when compared to baseline, as well as a difference that is statistically significant in comparison to each other were test group (126.96±24.32) showed lower level than control group (214.58±48.77). The results of this study were in agreement with Taalab et al.,2021 who proved the efficacy of tea tree oil to suppress the production of TNF- α, IL-10, IL-1beta, IL-8, and PGE2 [11].

Moreover, a systematic review completed by Casarin et al., 2017 showed that M. alternifolia played a crucial role in management of inflammatory response and important immunomodulatory events by suppressing interleukin-6 (IL-6), interleukin 1-beta (IL-1β), Prostaglandin E2, tumor necrosis factor (TNF-α), and interleukin-10 (IL-10) [26].

CONCLUSION

The findings of this study suggest that combining TTO with NSPT provides greater therapeutic advantages than using NSPT on its own. Additionally, it emphasizes the anti-inflammatory properties of TTO help to repair periodontal tissues by lowering pro-inflammatory processes.

Role of the funding source

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Conflict of Interest

The authors affirm that they have no conflicting interests with regard to this research.

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