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(Randomized Controlled Clinical Study)

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Title page

Clinical efficacy of flurbiprofen 2.5% in comparison to 98% Aloe Vera gel as adjunctive therapy in the initial treatment of stage III chronic periodontitis in smoking patients (Randomized Controlled Clinical Study)

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Author's contribution:

A.I. [1], N.A. [2] and H.Z. [3] formulated the study design and drafted the protocol. M.S. [5] formulated the drugs A.I. [1] and N.A. [2] H.Z [3] performed the experiments. A.I. [1], N.A. [2] and H.Z. [3] collected the data. N.A. [4] analyzed and interpreted the results then revised the entire manuscript. All authors read and approved the final manuscript.

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Clinical efficacy of flurbiprofen 2.5% in comparison to 98% Aloe Vera gel as adjunctive therapy in the initial treatment of stage III chronic periodontitis in smoking patients.

Background: In recent years, various methodologies have been introduced to enhance the outcomes of scaling and root planing (SRP), with the intent of potentially eliminating the necessity for periodontal surgical interventions under specific circumstances. Noteworthy among these novel approaches are the utilization of non-steroidal anti-inflammatory drugs (NSAIDs) and herbal remedies like Aloe Vera. This present study endeavors to clinically assess the impact of flurbiprofen gel in contrast to Aloe Vera gel, as supplementary agents to SRP, in the elimination of periodontal pocket depths among individuals afflicted by stage III chronic periodontitis, particularly focusing on the subset of smoking patients. **Materials and Methods:** In this study, 60 patients with stage III/grade C periodontitis were enrolled. They were divided into three groups using the split mouth method: Group one (G1), which received Flurbiprofen and placebo, Group two (G2), which received Aloe Vera and placebo, and Group three (G3), which received Flurbiprofen and Aloe Vera. At the baseline, the fourth, eighth-, twelfth weeks and six months following treatment, the plaque index (PI), gingival index (GI), bleeding on probing (BOP), clinical attachment level (CAL), and probing depth (PD) were all measured. **Statistical Analysis**: Statistical analysis was done using SAS 9.4 Software (SAS Institute Inc., Cary, NC, USA). Means and standard deviations (SD) were calculated for all continuous variables (periodontal parameters: CAL, PD, BOP, GI, PI) at the baseline, fourth week, eighth week, and twelfth week and 6 months.

Keywords: periodontitis, flurbiprofen, aloe vera, root planing.

Introduction:

Inflammation and periodontal tissue destruction is a consequence of periodontal pockets originating from chronic periodontitis. [1] The latter is an infectious disease resulting from the interaction between the invasion of biofilm microorganisms and periodontal immune response in a vulnerable host. [2]

During periodontal attachment loss, PGE2 production levels primarily by macrophages and fibroblasts are increased in the tissues and gingival crevicular fluid (GCF). [3,4] PGE2 promotes the release of MMPs, in addition to osteoclastic bone resorption, and it play a significant role in the alveolar bone loss observed in periodontitis. [5]

Smoking has been identified as a major risk factor in the development and progression of periodontal disease. Epidemiological studies have presented a significantly higher risk for periodontal disease in smokers compared to non-smokers, and the increased risk is proportional to the duration and rate of smoking (Eke et al., 2016).[6]

The first main goal during the treatment of periodontal disease is eliminating microbial source and causative factors, thus preventing further progression of the disease and maintaining periodontal tissue health. [7] Surgical and non-surgical modalities are available for the treatment of periodontal diseases. [7] The non-surgical option consisting of mechanical debridement of the tooth surface with scaling and root planning (SRP), [8] improves pocket depth (PD) and increases clinical attachment level (CAL) to some extent, [9]

However, mechanical debridement alone may not be enough in patients with deep periodontal PD or having areas of furcation involvements. [10] Some pathogens like Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella Intermedia, Bacteroides forsytus, peptostreptococci micros may not be eliminated as a result of the limited access in deep subgingival areas, thus increasing the risk of treatment failure. [10]

Research have shown the significance of PGE2 in the development of periodontal diseases, [11]and since prostaglandins are inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs), [12] researchers have explored the possible use of NSAIDs as possible host–response modulators in the treatment of periodontal disease.[13] However, achieving noticeable periodontal improvements requires daily administration of NSAIDs for extended periods which may lead to undesirable side effects gastrointestinal (GI), renal, cardiovascular (CV), cerebrovascular, and central nervous system (CNS) adverse effects [14]

It is advised to consider using local drug delivery (LDD) as an adjunct to conventional periodontal therapy to reach the best clinical outcomes. LDD is an effective method of delivering drugs. Higher drug concentrations at the targeted area can be reached using LDD with a lower drug dose than the usual systemic delivery and thus fewer side effects. [15]

A topic that seems of particular interest is the development local NSAID formulations (e.g., gels, toothpaste, and rinses) with daily usage. These products may lead to an improvement in the reduction of detrimental systemic effects of non-selective NSAIDS in the long-term host modulation of periodontitis-susceptible patients. [16] Moreover, studies demonstrated that prostaglandin production inhibitors, like NSAIDs, can affect bone loss in periodontal disease. [17]

The available data suggests that when flurbiprofen, an NSAID, is delivered locally through gel media during SRP, it enhances the benefits of the latter treatment and expedites the resolution of inflammation [18].

Numerous adjunctive therapies to SRP have been explored in the field of periodontics. Among these, laser treatment [19], topical and systemic antibiotics like azithromycin [20] and clarithromycin [21], as well as chemicals such as hyaluronic acid [22] and various antiseptic and anti-inflammatory agents with immunomodulatory properties [19,23], have been documented to offer potential advantages.[24]

Herbal products have gained preference over conventional drugs due to their considerable natural efficacy, enhanced safety profile, and cost-effectiveness. Conversely, modern pharmaceuticals are associated with various adverse effects. Prolonged use of these drugs has, at times, led to antibiotic resistance, prompting a gradual integration of herbal medicines as dietary supplements to address prevalent human health and oral issues.[25]

Numerous natural/herbal medications, including green tea and salvadora persica, have been the subject of investigation as potential adjuncts to SRP for the management of periodontal diseases, offering the advantage of reduced side effects [26,27].

Among these herbal options, Aloe Vera, a cactus-like plant belonging to the Liliaceae family, stands out with its rich composition of approximately 360 species, containing 75 active ingredients such as vitamins, enzymes, minerals, lignins, sugars, saponins, amino acids, and salicylic acids [28]. In vitro and animal model studies have demonstrated medicinal effects of Aloe Vera, encompassing anti-inflammatory, anti-arthritic, and anti-bacterial properties [28-29]. Moreover, the treatment effects of Aloe Vera on systemic disease such as cancers, regulation of blood glucose levels, wound and infection healing have been investigated in some studies. [28-

30] Aloe Vera also inhibits the cyclooxygenase pathway, dropping the production of prostaglandins, thus decreasing the inflammation. [31]

Some studies stated the use of aloe Vera in dentistry in numerous areas like disinfecting dental unit water network, [32] gutta-percha sterilization, [33] antiseptic effect on candida albicans, [34] Aphthous stomatitis management, [35] as an ingredient in toothpastes [36-37] and mouthwashes.[28] Up to date, limited studies have been reported in relation to the effect of topical application of aloe Vera in the periodontal pocket for periodontal disease management. [38]

The null hypothesis is that flurbiprofen has no statistically significant effect in comparison to Aloe Vera gel as an adjunctive to SRP in the reduction of periodontal pockets in smoking patients with chronic periodontitis stage III.

Aim of this study:

This study aims to evaluate clinically the effect of flurbiprofen gel in comparison to Aloe Vera gel as adjunctive to SRP in the reduction of periodontal pockets in patients with chronic periodontitis stage III in smoking patients.

Materials and methods:

Participants:

This study was conducted at the Department of Oral Surgical Sciences, Division of Periodontology, Faculty of dentistry, Beirut Arab University (BAU)-Lebanon after approval of Institutional Review Board (IRB) with trial NO 2022-H-0100-D-R-0487.Patients were first briefed about the study and written consent was obtained. The study was performed in compliance with the principles of the Declaration of Helsinki.

The estimated sample size will be calculated according to http://epitools.ausvet.com.au/, by taking the means of clinical attachment level at 3 months in both groups from a previous similar study conducted by (39) where mean for test site = 5.75±0.35 and mean for control site is = 6.4±0.3, where the variance will be calculated to be 0.35 , assuming a confidence level of 95% and a study power of 80%. The calculated sample size will be 14 patients per group (28 operating sites). However, as some dropouts may be expected, a minimum of 20 patients per group were recruited

Inclusion criteria: 60 patients were selected who had clinical periodontal loss and radiographic bone loss of stage III/grade C with no history of systemic disease. They had at least 2 periodontal sites with a pocket depth of six mm or greater, radiographic evidence of bone loss extending to the middle third of the root, and clinical attachment loss of five mm or more. Eligible subjects were categorized as current smokers if they consistently smoked more than 10 cigarettes per day for a minimum of 5 years. Additionally, individuals with no record of undergoing any periodontal treatment within the six months preceding the study were considered for inclusion. These stringent criteria aimed to ensure a relevant and homogeneous patient cohort for the research investigation.

Exclusion criteria: Patients with systemic illnesses such as diabetes mellitus or conditions that could potentially impair wound healing were excluded from participation. Additionally, individuals who were pregnant or lactating were not considered for inclusion in the study. Subjects who had been prescribed systemic antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs) within the three months preceding the study were also excluded. Furthermore, individuals with confirmed or suspected hypersensitivity to Flurbiprofen or aloe Vera, the focus of the investigation, were not included in the study population. These stringent exclusion criteria aimed to control for potential confounding factors and establish a well-defined and relevant patient group for the research analysis.

Clinical protocol

Initial therapy was performed on all patients and consisted of full mouth scaling and root planing on 2-4 sessions, by hand and ultrasonic instrumentation, with oral hygiene instructions reinforcement and proper brushing technique (modified Bass technique) instructions. Note that patients received the same toothbrushes, toothpaste, and interdental brushes. Oral hygiene was reinforced at every visit.

The selected patients were allocated into three groups (each containing 20) with the help of a computerized randomizer (Randomizer.org), and using a split mouth design, sites were randomly allocated for each patient into either test or control group using a coin flip method:

- Group one (G1): comprised of 20 patients who received treatment involving the application of flurbiprofen gel as an adjunct to scaling and root planing. Specifically, on the test site of each patient, one milliliter of 2.5% flurbiprofen gel was applied, while on the contralateral side, scaling and root planing were performed as the control intervention.
- Group two (G2): comprised of 20 patients who received treatment involving the application of aloe Vera gel as an adjunct to scaling and root planing. Specifically, on the

test site of each patient, one milliliter of 98% aloe Vera was applied, while on the contralateral side, scaling and root planing were performed as the control intervention.

- Group three (G3): The intervention involved applying flurbiprofen gel on one site, while the contralateral side received an application of 98% aloe vera.

Clinical measurements:

The clinical periodontal parameters were recorded by one blinded examiner from the mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual, and mesio-lingual surfaces of each tooth using a colour coded periodontal probe (PQWBR - Hu Friedy Mfg. Inc. Chicago, IL, USA): and checked by another blinded examiner. Examiners were calibrated to ensure intra-examiner as well as inter-examiner agreement when measuring PD and CAL values. Fifteen patients were examined twice before the trial, 24 hours apart. Calibration was considered accepted if both measurements at the baseline and after 24 hours were similar to one mm at the 90% level.

In this clinical study, various clinical measurements were undertaken to assess the oral health status of the participants. These measurements included the clinical attachment level (CAL), probing depth (PD), plaque index (PI), gingival index (GI), and bleeding on probing (BOP).

Initially, the PI and GI were measured at four sites per tooth, with gingival bleeding being recorded within 15 seconds. To prevent misinterpretation of gingival bleeding as BOP, patients were asked to rinse with water after this assessment. Subsequently, all teeth were probed at six different locations per tooth. CAL was determined as the distance from the cemento-enamel junction (CEJ) to the pocket depth, while the PD was measured as the distance from the gingival margin to the base of the pocket. BOP was recorded 15 seconds after probing. It is important to note that these clinical parameters were recorded at the baseline (1st visit) before the treatment and were repeated at the fourth week (2nd visit), eighth week (3rd visit), twelfth week (fourth visit), and at 6 months (5th visit). During this observation period, participants received reinforcement of plaque control and additional instructions to maintain optimal oral hygiene

Preparation of gels:

Aloe Vera:

Aloe vera gel used in this study was %98 aloe vera® gel concentration (Avivir; Denmark) and 2% normal saline. Commercial preparation method of %98 concentration of aloe vera gel was washing the ripe aloe Vera leaves thoroughly under water and cutting off their skin. Each leaf was cut into several pieces and seeping gel from the pieces were collected in a sterile container and stored at 4°C until the time of application. [38]

Flurbiprofen:

Gel was made of 20% poloxamer and 10% ethanol as an Optimum formulation with sustained release up to 48 hours and a reasonable sol gel transition phase.

Statistical analysis:

Statistical analysis was done using SAS 9.4 Software (SAS Institute Inc., Cary, NC, USA). Means and standard deviations (SD) were calculated for all continuous variables (periodontal parameters: CAL, PD, BOP, GI, PI) at the baseline, fourth week, eighth week, and twelfth week and 6 months. Repeated linear mixed-effects models (PROC MIXED in SAS) were used to examine the changes in all periodontal parameters over the five-time points within each group and between groups. An unstructured covariance matrix was used, residual plots were visually reviewed to check model fit, and extreme outliers were eliminated using the restricted likelihood distance. A Tukey-Kramer 8 correction was applied to all pairwise comparisons. One-way ANOVA was used to examine group differences in PD reduction and CAL. A p-value of 0.05 was considered statistically significant.

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