Advanced Dental Journal
Volume 2 (2020) | Issue 1| Pages 1-11 10.21608/adjc.2020.22381.1047

Original Article

Evaluation of Topical Pomegranate Extracts in Management of Oral Lichen Planus: A Randomized Clinical Trial

Mai Zakaria[1], Ataa Said [2], Amal Abd EL-Kader[3], Basma Mostafa[4]

[1]Oral Medicine and Periodontology Dep., Faculty of Dentistry, Cairo University, Egypt
[2]Pharmacognosy Dep., Pharmaceutical Sciences Division, National Research Centre, Cairo, Egypt
[3]Chemical Engineering and Pilot Plant Dep. National Research Centre, Cairo, Egypt
[4]Surgery and Oral Medicine Dep., Oral and Dental Research Division, National Research Centre, Cairo, Egypt

E-mail: mai.zakaria@dentistry.cu.edu.eg

Received: 7-1-2020
Accepted For Publishing: 18-1-2020

Abstract

Background: The current study aimed to evaluate the effect of using topical pomegranate extracts gel versus topical steroid gel as a control in management of atrophic oral lichen planus (OLP).
Materials and methods: Forty-two patients presenting clinically with atrophic OLP were involved in the study. They were randomly divided into three equivalent groups to be managed with topical corticosteroid gel as control (Group 1, Group C), topical pomegranate seed extract gel (Group 2, Group S) and topical pomegranate peel extract gel (Group 3, Group P). Assessment of pain, sign scores and oral health impact profile- 14 (OHIP- 14) were carried out in each group before and after the used management protocols.
Results: The results showed a significant decrease in sign; pain scores and OHIP-14 values which were recorded in group S and group P.
Conclusion: Provided data in this contemplate using topical pomegranate seeds and peel extracts gel offer a new promising natural, safe and effective management of OLP.

Key words: extracts, peel, OHIP-14, oral lichen planus, pain, Punica granatum L.

Introduction

Lichen planus is a widespread chronic mucocutaneous disorder of uncertain origin. It has been documented that oral lichen planus (OLP) involved 0.1-4% of the population worldwide [1]. OLP can be detected mostly in the fifth and sixth decades of life with a twice prevalence in females in comparison to males [2, 3]. The exact etiology and pathogenesis of OLP are indistinctive including T-cell mediated immune response associated with deterioration of the basal cell layer of the epithelium and invasion of both T-helper and T-cytotoxic lymphocytes subepithelially [4]. Six clinical forms of OLP lesions are detected comprising the plaque-like, papular, reticular, bullous, erosive and atrophic ulcerative sores, characterized with chronicity [5]. White keratotic forms of it are asymptomatic without the need for treatment. Meanwhile red sores are painful with burning sensation which requires treatment. Red sores are considered owing to the potentially malignant disorders according to the WHO with risk for malignant transformation to squamous cell carcinoma frequently arising in 0.4-2% of cases

[6]. OLP is usually detected bilaterally on the buccal mucosa in a symmetrical manner, less common on the tongue, mucosa of the lips and gingiva [5].

Multiple different therapeutic approaches have been provided in management of OLP. As there is an amendment in disease activity, the use of a single and absolute therapeutic treatment approach is challenging. Current treatment modalities are principally aimed to improve the symptoms of pain and ulcerations of the mucosa. The existing treatments are still incapable to treat the illness entirely due to its nature characterized by refraction. Methods utilized in management of OLP involve both topical and systemic use of various treatment modalities. Corticosteroids are essentially used in systemic or intralesional way nevertheless with commonly unacceptable results [7].

Corticosteroids are the common treatment for OLP associated with symptoms until now; though, its continued usage show numerous unwanted side effects such as mucosal tissues atrophy associated with pain, overgrowth of candida, suppression of the adrenal gland, raise in the blood pressure, gastrointestinal distress and increase in blood glucose level. Effective treatment modality with least side effects still seems to be necessary concerning the occurrence of topical steroids resistance which becomes inconvenient in some patients [8].

As a consequence of the reported adverse effects of corticosteroids, different natural plant extracts have been suggested. Punica granatum L which belongs to family Punicaceae, commonly identified as "Pomegranate" is one of the frequently utilized extract of plant origin in a diversity of medical conditions. Pomegranates have been identified for hundreds of years for their numerous benefits for health, comprising their antibacterial, antimicrobial, antifungal, anti-inflammatory, antioxidant, anti-carcinogenic and immunomodulatory activities. In accordance with these properties, it has been documented that pomegranates and their extracts may be used as natural treatment modality [9].

Diverse parts of the Punica granatum L, comprising flowers, leaves, fruits, and trunks have tannins for instance ellagic acid, gallic acid, and flavonoids. Tannin complexes in pomegranate are frequently utilized in the management of injuries and acceleration of wound healing owing to its astringent activity [10].

Flavonoid constituents of pomegranate have profound antioxidant properties and aid in the immune system regulation. The probable beneficial activities of pomegranate in the medical filed are widespread and comprise management of inflammations, malignancy, cardiovascular disorders, diabetes, chronic periodontitis, recurrent aphthous stomatitis (RAS) and recurrent intraoral herpes (RIOH) [9, 11-13].

To the authors' knowledge pomegranate extracts were not yet used in management of OLP. Accordingly, this study aimed to evaluate the beneficial effect of topical pomegranate extracts gel in management of OLP in comparison to topical steroid gel as a control.

Materials and Methods

Ethical approval

The current trial was conducted in accordance with the World Medical Association guidelines of ethics (Declaration of Helsinki, 1978, as revised in 2008) for studies including human contributors. The contemplate protocol was accepted by the Ethical Committee of the National Research Centre (NRC), Cairo, Egypt and was registered in code no 19 0 38. Also in the Clinical Trials.gov the registration code was NCT04193748. In advance to starting the study, all the participants signed an informed consent afterward full explanation of the study steps.

Sample size calculation

By the means of G*power software the appropriate sample size was calculated according to the results of the previously conducted study by Thomas et al., [14]. Considering that $\alpha = 0.05$; power at 0.8; allocation ratio (1:1:1) and the effect size = 1.12. Hence, the sample size was 42 patients to evade any reduction that might happen due to withdrawal of patients.

Topical pomegranate extracts preparation

The preparation of the pomegranate extracts was conducted in the Phamacognosy Department, Pharmaceutical Sciences Division, NRC, Egypt. The peel and seeds of the pomegranate were separated. The peel was mixed in the mixer with the least amount of water then filtered through filter paper Whamman no. 1 and evaporated by distillation flask in the rotary evaporator at 55 ^{0}C and heated to one-third of its original volume under reduced pressure till exhaustion to yield a dry powder. As for the seeds, the same was done but without adding any drops of water. Both of them were separately made in the gel form for topical application on the OLP lesions orally in a concentration of 4% after adding carboxy methyl cellulose sodium salt [15].

Measurement of potential cytotoxicity of pomegranate extracts

Potential cytotoxicity of both pomegranate seeds and peel extracts prepared gels was confirmed according to earlier study described by Skehan et al. [16] , conducted in the Clinical Pharmacy Department at the National Cancer Institute, Egypt.

Patients

This study was a randomized controlled clinical trial including a total number of 42 patients with atrophic OLP, who attended the Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University. According to the modified WHO criteria [17], the diagnosis of OLP was carried out subsequent to thorough clinical examination using incandescent light and sterile diagnostic instruments.

Inclusion and exclusion criteria

The study inclusion criteria were patients of both sexes, ranging from 18 to 60 years old with atrophic type OLP and signed the informed consent.

Pregnant or lactating women, smokers and patients using steroids either topically or systemically during the previous two months were omitted from the study. Patients consuming lichenoid reaction-inducing drugs, patients with hepatitis C virus (HCV) antibodies, systemic diseases that may participate in the existence of OLP such as uncontrolled diabetes and hypertension were excluded in this study. Patients with lesions in relation to amalgam filling were also not involved. Patients with previous history of allergy to pomegranate were also not included.

Study design

The involved 42 patients were randomly allocated by means of preoperative envelope drawing, to be managed in the diverse study groups. The patients were divided equally into three groups. In group 1 (Group C; n = 14) patients received topical steroid gel as a control. Group 2 (Group S; n = 14) involved patients that received topical pomegranate seed extract gel. The group 3 patients (Group P; n=14) patients received topical pomegranate peel extract gel.

Topical steroid therapy was done using commercially available gel (triamcinolone acetonide 0.1%, Kenacort-A Orabase®, Turkey). Pharmaceutically prepared topical pomegranate seeds and peel were used in group S and group P respectively. In all the study groups all the patients were instructed to use the prescribed topical treatment four times per day for four weeks. Patients were not allowed to eat or drink for at least 1 hour after the application of the gel. The patients were instructed to stop the treatment immediately if any unwanted side effects occurred and contact the investigators. The patients were instructed not to use any treatment for the lesions other than the prescribed one. The patients couldn't be masked about the prescribed treatment due to the obvious color difference between the commercially available topical corticosteroids gel and topical pomegranate extracts ones.

Clinical evaluation

All patients in the study groups were evaluated using the sign scoring scale described by Thongprasom et al., 1992 [18]. As follows: 5 = (white striae with an erosive area > 1 cm2), 4= (white striae with an erosive area < 1 cm2), 3= (white striae with an atrophic area > 1 cm2), 2= (white striae with an atrophic area < 1 cm2), 1= (mild white striae only), and 0= (no lesions, normal mucosa).

Assessment of pain in all cases of the three groups was carried out using visual analog scale (VAS)

involving a straight line of 10-cm among ends, with 0 indicating no pain and 10 for intolerable pain was performed [19].

Oral health impact profile- 14 (OHIP- 14) questionnaire as explained by Slade in 1997 [20] was conducted to evaluate the oral health related quality of life (OHRQoL) in all the study participants. It measures the seven dimensions of OHRQoL where each dimension was evaluated through two questions. The answer for each question was designed in a five-point measure. Where 0=never, 1=hardly ever, 2=occasionally, 3=fairly often and 4=very often. Inside each dimension, the answer was multiplied by certain weight to induce each sub-score analysis. The sum of the seven dimensions produced the total OHIP-14.The validated Arabic version of the questionnaire was used [21].

The assessment of the sign score, pain score and OHIP-14 was done by one of the study authors who was masked about the treatment modality used every week as follow up from the baseline data of the first visit before starting the prescribed treatment in all the study groups for 4 weeks which was the study duration.

Statistical methods

Data were coded using SPSS version 25 (IBM Corp., Armonk, NY, USA) by a statistician who was masked about the treatment used in each study group. Data was summarized using mean and standard deviation (mean ± SD) values for categorical data. Comparisons between groups were done using ANOVA with post hoc test or non-parametric Kruskal-Wallis test and Mann-Whitney test were used according to normality. For comparison of serial measurements within each group repeated measures ANOVA was used or non-parametric Friedman test was utilized according to normality. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was done instead when the expected frequency is < 5. P-values < 0.05 were considered statistically significant.

Results

The present study was carried out on 42 patients (16 males and 26 females), ranging from18 to 60 years (mean 54.67 ± 7.41 years), where they completed the study duration without any dropping outs.

In the present contemplate both topical pomegranate extracts gel used did not induce any undesirable tissue responses or complications. However, one patient in group C after topical steroid gel usage developed oral candidiasis in the last follow up visit.

In the three study groups, no statistically significant difference was recorded between mean age (p = 0.82) and sex distributions (p = 0.9) as detailed in Table 1.

The baseline data of sign score (p= 0.885), pain score (p= 0.98) and OHIP-14 (p= 0.99) showed no significant difference between the three groups as presented in table 2.

In each of the three groups comparisons of the sign score, pain score and OHIP-14 results at baseline and during the trial intervals at 1, 2, 3 and 4 weeks within the same group showed that a statistically significant difference was recorded (Table 3).

As regards the mean ± SD values of sign scores after 4 weeks, the lowest value was recorded in group S (1.14 ± 0.36), while the highest one was recorded in group C (1.71 ± 0.47) where there was a significant difference between the three groups (p=0.002). Tukey's post hoc test showed a non-significant difference between group S and group P (Table 2, figure 1).

Considering the mean ± SD values of pain scores after 4 weeks, the lowest value was noted in group S (0.5 ± 0.65), while the highest one was seen in group C (1.64 b ± 0.84) where there was a significant difference between the three groups (p= 0.001). Tukey's post hoc test showed a non-significant difference between group S and group P (Table 2, figure 2).

Table 1: Demographic findings in the study groups

Groups		Group C (group 1)	Group S (group 2)	Group P (group 3)	P value
		Count (%)	**Count (%)**	**Count (%)**	
Sex	**M**	6 (42.9%)	5 (35.7%)	5 (35.7%)	0.904^{ns}
	F	8 (57.1%)	9 (64.3%)	9 (64.3%)	
Age (Mean ± SD)		45.86 ± 6.21	44.29 ±7.94	44.36 ± 8.08	0.821^{ns}

Significance at $p < 0.05$; ns = non-significant.

Looking to the total mean ± SD values of OHIP-14 after 4 weeks, the lowest value was showed in group S (2.75 ± 0.63), while the highest one was presented in group C (5.81 ± 0.66) where there was a significant difference between the three groups ($p< 0.001$). Tukey's post hoc test showed a non-significant difference between group S and group P (Table 2, figure 3).

Table 2: Comparisons between the three groups regarding sign score, pain score and OHIP-14 at baseline and after 4 weeks.

Groups	**Group C (group 1)**	**Group S (group 2)**	**Group P (group 3)**	**P value**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Sign score (Baseline)	2.79 ± 0.43	2.79 ± 0.43	2.71 ± 0.47	0.885^{ns}
Sign score (After 4 w)	1.71^{b} ± 0.47	1.14^{a} ± 0.36	1.21^{a} ± 0.43	0.002*
Pain score (Baseline)	6.86 ± 1.29	6.93 ±1.07	6.86 ± 0.86	0.980^{ns}
Pain score (After 4 w)	1.64^{b} ± 0.84	0.5^{a} ± 0.65	0.64^{a} ± 0.63	0.001*
OHIP-14 (Baseline)	15.64 ± 1.13	15.64 ±1.18	15.7 ± 1.17	0.987^{ns}
OHIP-14 (After 4 w)	5.81^{b} ± 0.66	2.75^{a} ± 0.63	2.88^{a} ± 0.79	< 0.001*

Significance at $p < 0.05$; SD= standard deviation; *=significant; ns=non-significant. Mean values having the same superscript letter are not different significantly.

Table 3: Comparison of sign score, pain score and OHIP-14 values over time (1, 2, 3 and 4 weeks) from baseline in each study group

Groups		Group C (group 1)		Group S (group 2)		Group P (group 3)	
		Mean ± SD	*p*- value	Mean ±SD	*p*-value	Mean ±SD	*p*-value
Sign Score	Baseline	2.79±0.43		2.79±0.43		2.71±0.47	
	After 1 w	2.57±0.51		2.64±0.5		2.50±0.52	
	After 2 w	2.29±0.47	<0.001*	1.93±0.27	<0.001*	1.86±0.36	<0.001*
	After 3 w	2±0.39		1.57±0.51		1.64±0.50	
	After 4 w	1.71±0.47		1.14±0.36		1.21±0.43	
Pain Score	Baseline	6.86±1.29		6.93±1.07		6.86±0.86	
	After 1 w	5.64±1.28		5.21±1.12		5±0.96	
	After 2 w	4.57±1.34	<0.001*	3.71±0.83	<0.001*	3.64±0.74	<0.001*
	After 3 w	3.36±1.01		2±0.68		1.86±0.66	
	After 4 w	1.64±0.84		0.5±0.65		0.64±0.63	
OHIP-14	Baseline	15.64±1.13		15.64±1.18		15.7±1.17	
	After 1 w	13.78±0.96		11.35±0.95		11.27±0.97	
	After 2 w	10.49±1.03	<0.001*	7.63±0.99	<0.001*	7.55±1.11	<0.001*
	After 3 w	8.19±0.99		4.87±0.83		4.94±0.88	
	After 4 w	5.81±0.66		2.75±0.63		2.88±0.79	

Significance at $p < 0.05$; SD= standard deviation; *=significant; ns=non-significant. Mean values having the same superscript letter are not different significantly.

.

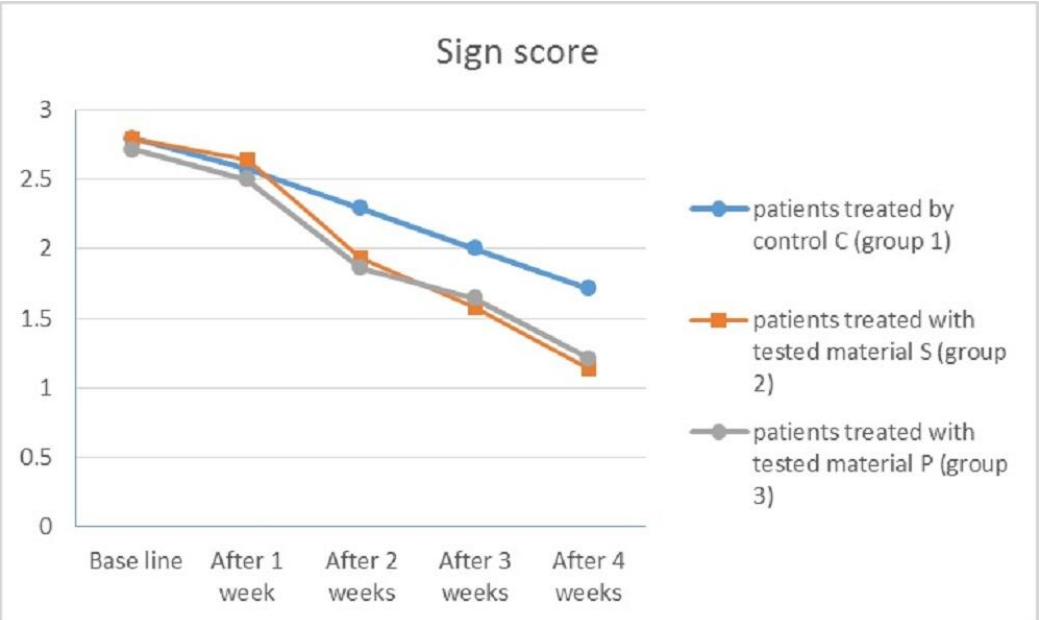

Figure 1: Showing mean sign score values over time in the three groups.

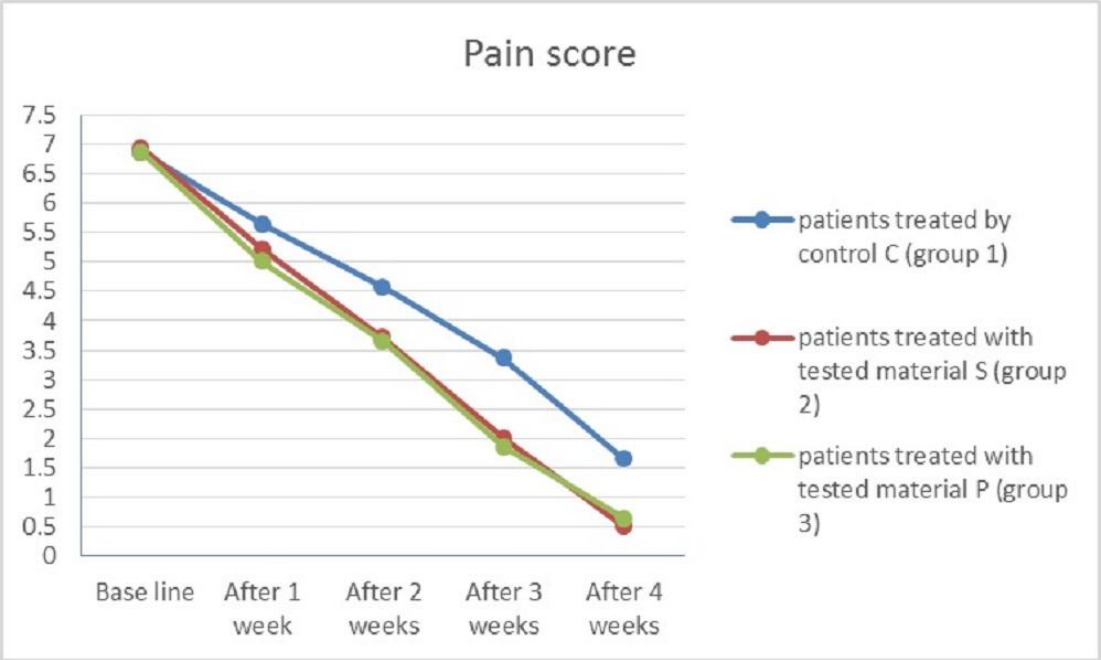

Figure 2: Showing mean pain score values over time in the three groups.

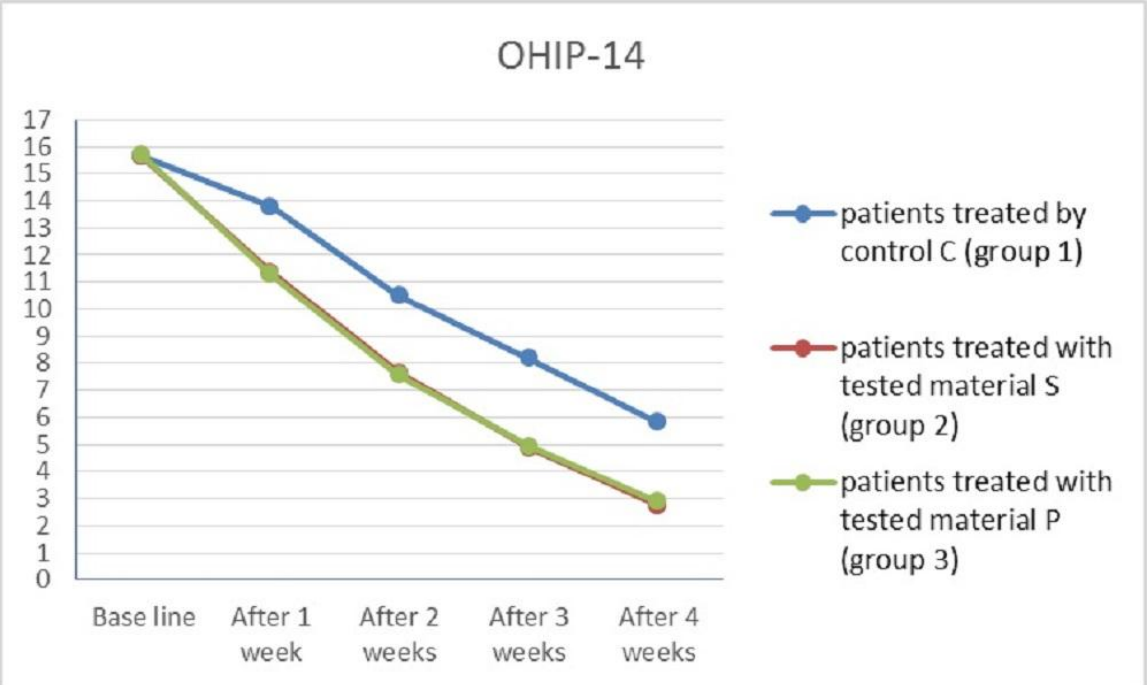

Figure 3: Showing mean OHIP-14 values over time in the three groups.

Discussion

Lichen planus (LP) is an inflammatory disorder characterized by chronicity that involves the skin, mucous membranes, or both of them. It is described by periods of remission and

exacerbation. It is the furthermost well-known disease of dermatological origin that influences the oral mucosa [22]. OLP occurs in a prevalence that ranges between 0.2 and 5% around the world. The precise cause of OLP is still unclear [23].

Complete healing following OLP management has not been achieved until now due to the nature of the disorder which is characterized by chronicity and refraction [24].

The usage of corticosteroids has been recommended for OLP owing to its inflammatory and immunological characters; hence topical, systemic and intralesional corticosteroids are used. Corticosteroids are recognized as a painkilling and analgesic treatment instead of being therapeutic drug in the OLP management [25].

Topically applied steroids are known to be the first profound treatment of choice for symptomatic OLP management with hopeful results in respect to pain and burning sensation decrease. Numerous patients experienced several adversative reactions with this treatment option such as candidiasis and mucosal atrophy as formerly recognized [26].

Natural-origin drugs are considered to be safe and effective replacement therapy for many disorders [27]. As a result, the current study was conducted to assess the effectiveness of pharmaceutically prepared topical pomegranate extracts gel compared to commercially available topical steroid gel as a control in management of OLP concerning sign score, grade of pain and OHRQoL in this randomized clinical trial.

To the authors' knowledge, no previous trials have been carried out utilizing pomegranate extracts in the management of OLP; therefore results of the current study cannot be related to former studies and is basically dedicated to explain the current results.

In the present study, the results revealed a decrease in the sign score, pain score and OHIP-14 values along the different observational times within each study group which was statistically significant. Comparing the three study groups showed a significant difference, however no significant was detected between group S and group P.

Punica granatum belonging to the Punicaceae family, mostly referred to as "Pomegranate" have been known since hundreds of years for their many health benefits, including antimicrobial, antifungal, anti- inflammatory, and antioxidant activities. It has been pointed out that pomegranates and their extracts can be a natural replacement therapy in management of many medical conditions [28]. These activities can be related to ellagic acid and ellagitannins, mainly punicalagins, punicalins, and gallagic acid. Moreover, it has recognized that anthocyanins and certain fatty acid profile add to the described properties. The combination of these compounds has synergistic properties that are significantly higher than the activity of individual compounds.

The significant results in the sign and pain scores in group S and Group P may be explained by the following mechanisms.

The key component of fatty acids pomegranate, pu nicic acid, is known to be a powerful anti-inflammatory material with the ability to decrease the development of prostaglandin that is principally associated with pain. Pomegranate constituents for instance ellagic acid can diminish interleukin-8 and nitric oxide production. Additionally, pomegranate extract has the ability of preventing cyclooxygenase, lipoxygenase, and matrix metalloproteinases enzymes, which are the important enzymes in the development of several inflammatory mediators and initiation of tissue damage. In addition to the above-mentioned mechanisms, pomegranates can exert an immunoregulatory role on macrophages, T and B lymphocytes. Pomegranate extracts can act as scavenger for free radicals and reduce macrophage oxidative stress and lipid peroxidation by its antioxidant property as formerly recognized [29].

This is in line with the previous trial that used muco-adhesive pomegranate gel in the treatment of minor RAS which found that the pomegranate group was the lowest regarding the degree of pain and duration of wound healing [13]. In addition to the former randomized clinical study findings demonstrated that using pomegranate peel extract gel associated with significant decrease in pain score, ulcer size and healing period [12].

The antimicrobial property of pomegranates in the form of antibacterial, antiviral, and antifungal actions which may explain the absence of fungal infection by candida albicans that has not occurred in group S or group P compared to group C where one case developed oral candidiasis at the end of the study. This is due to the existence of ellagitannin and punicalagin, which can inhibit bacterial adherence, diminish total protein associated with plaque forming bacteria presence, reducing the actions correlated to cell injury, and intensifying ceruloplasmin activity, which have a defensive role against oral oxidative stress [10]. This finding is in accordance with the results of randomized clinical trial using pomegranate extract as a topical anti-fungal drug for the management of candidosis related to denture stomatitis which revealed that it was as profound as miconazole, as a gold standard treatment. Pomegranate peel extract gel was effective versus Streptococcus mutans, S. sanguisand S. mitis through regulating their adhesion probability to the oral mucosa [30].

The significant decrease of total OHIP-14 values in group S and group P in comparison with group C may be attributed to the usage of topically applied pomegranates agents which enhanced collagen, DNA, and protein production along with improving contraction rate and tensile strength. As well as high levels of polyphenolic and tannin in the pomegranate extracts which accelerated wound healing through stimulation of production and movement of fibroblasts augmenting angiogenesis [27]. This is with an earlier clinical investigation which concluded that using pomegranate peel extract as a mouth wash was effective in decreasing pain and enhance wound healing in patients with RIOH [9].

Conclusion

Topical Pomegranate extracts in the gel form may be used as a novel, profound, cost- effective and safe treatment modality for atrophic OLP management. They were associated with better results in decreasing the sign and pain scores with improved OHRQoL.

Funding

This research is self-funded

Conflict of Interest

The authors declare no conflict of interest

References

1. Zakaria M, Khashaba O. Diagnostic accuracy of the mean platelet volume in oral lichen Planus. Journal of the Arab Society for Medical Research. 2019;14:52–56.

2. Kini, R., Nagaranta, D.V., Saha, A. Therapeutic management of Oral Lichen Planus: a review for the clinicians. World J Dent. 2011; 2: 249-253.

3. Mostafa B, Ahmed E. Prevalence of oral lichen planus among a sample of the Egyptian population. J Clin Exp Dent. 2015; 7:e7-12.

4. Gupta, S., Ghosh, S., Gupta, S. Interventions for the management of oral lichen planus: a review of the conventional and novel therapies. Oral Diseases. 2017; 23:1029-1042.

5. Mostafa B, Zakaria M. Evaluation of combined topical ozone and steroid therapy in management of oral lichen planus. Open Access Maced J Med Sci. 2018; 6:879-884.

6. Dissemond, J. Oral lichen planus: an overview. Dermatol Treat. 2004; 15:136-140.

7. Alrashdan, M.S., Cirillo, N. & McCullough, M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539–551.

8. Sansriti Tiwari, Alok Avinash , Shashank Katiyar, A., Aarthi Iyer, Suyog Jain. Dental

applications of ozone therapy: A review of Literature. The Saudi Journal for Dental Research. 2017; 8:105-111.

9. Zakaria M, Mostafa B. Comparing pomegranate extract and chlorhexidine mouth washes in treatment of recurrent intraoral herpes
Journal of The Arab Society for Medical Research. 2018;13:53–59.
10.Vučić V, Grabež M, Trchounian A, Arsić A. Composition and Potential Health Benefits of Pomegranate: A Review. Curr Pharm Des. 2019; 25:1817-1827.
11. Jurenka J. Therapeutic applications of pomegranate (*Punica granatum L.*): a review. Altern Med Rev. 2008; 13:128-44.

12. Darakhshan S, Malmir M, Bagheri F, Safaei M, Sharifi R, Sadeghi M, et al. The effects of pomegranate peel extract on recurrent aphthous stomatitis. Curr. Issues Pharm. Med. Sci.2019; 32: 115-120.
13. Tavangar A, Aslani A, Nikbakht N. Comparative Study of Punica granatum Gel and Triadent Oral Paste Effect on Recurrent Aphthous Stomatitis, a Double Blind Clinical Trial. J Dent Shiraz Univ Med Sci. 2019; 20: 184-189.
14.Thomas A E,Varma B, Kurup S, Jose R, Chandy M Z, Kumar S P, et al. Evaluation of Efficacy of 1% Curcuminoids as Local Application in Management of Oral Lichen Planus – Interventional Study.Journal of Clinical and Diagnostic Research. 2017; 11:89-93.

15.Bhadbhade SJ, Acharya AB, Rodrigues SV, Thakur SL. The antiplaque efficacy of pomegranate. Quintessence Int (Berl). 2011; 42:2936.
16. Skehan P, Storeng R, Scudiero D, Monks A, McMahon J, Vistica D, et al.New coloremetric cytotoxicity assay for anti-cancer drug screening. J Natl Cancer Inst. 1990; 82:1107–1112.
17. Rad M, Hashemipoor MA, Mojtahedi A, Zarei MR, Chamani G, Kakoei S, Izadi N. Correlation between clinical and histopathologic diagnoses of oral lichen planus based on modified WHO diagnostic criteria. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 107:796–800.

18. Thongprasom, K., Luangjarmekorn, L, Sererat, T., Taweesap, W. Relative efficacy of fluocinolone acetonide compared with triamcinolone acetonide in treatment of oral lichen planus. J Oral Pathol Med. 1992; 21 :456-458.

19. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990; 13:227–236.

20. Slade G.D. Derivation and validation of a short-form oral health impact profile. Community Dent. Oral Epidemiology. 1997; 25: 284-290.

21. Osman S.M., Khalifa N. And Alhajj M.N. Validation and comparison of the Arabic versions of GOHAI and OHIP-14 in patients with and without denture experience. BMC oral health. 2018; 18:157.

22. Spanemberg JC, Rivera-Campillo M-E., Otero-Rey E-M., Estrugo-Devesa A, Jané-Salas E, López-López J. Oral lichen planus and its relationship with systemic diseases. A review of evidence. J Clin Exp Dent. 2018; 10:e938–e944.

23. Gorouhi F, Davari P, Fazel N. Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. Sci World J. 2014; 10:742826.
24. Thongprasom K, Dhanuthai K. Steroid in the treatment of lichen planus: a review. J Oral Sci. 2008; 50:377-385.
25. Amirchaghmaghi M, Delavarian Z, Iranshahi M, Shakeri MT, Mosannen Mozafari P, Mohammadpour AH, Farazi F, Iranshahy M. A randomized placebo-controlled double blind clinical trial of quercetin for treatment of oral lichen planus. J Dent Res Dent Clin Dent Prospects. 2015; 9:23-28.

26. Kia SJ, Shirazian S, Mansourian A, Khodadadi FL, Ashnagar S. Comparative efficacy of topical curcumin and triamcinolone for oral lichen planus: a randomized, controlled clinical trial. J Dent. 2015; 12:789-796.

27. Farzaei MH, Farzaei F, Gooshe M, Abbasabadi Z, Rezaei N, Abdolghaffari AH. Potentially effective natural drugs in treatment for the most common rheumatic disorder: osteoarthritis. Rheumatol Int. 2015; 35:799–814.

28. Ismail T, Sestili P, Akhtar S. Pomegranate peel and fruit extracts: a review of potential anti-inflammatory and antiinfective effects. J Ethnopharmacol 2012; 143:397–405.

29. Prasad D, Kunnaiah R. Punica granatum: a review on its potential role in treating periodontal disease. J Indian Soc Periodontol. 2014; 18:428–432.

30. Vasconcelos LC, Sampaio MC, Sampaio FC, Higino JS. Use of Punica granatum as an antifungal agent against candidosis associated with denture stomatitis. Mycoses. 2003; 46:192-6