



THE EFFECTIVENESS OF TOPICAL AVOCADO IN THE TREATMENT OF MINOR RECURRENT APHTHOUS ULCERATION: A RANDOMIZED CONTROLLED CLINICAL TRIAL

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ABSTRACT

Objective: Recurrent aphthous ulceration (RAU) is a common condition, Different treatment modalities have been suggested to either eradicate or reduce the duration of ulcer recurrences. **Aim** of this research was to determine the effectiveness of topically applied 0.5% avocado gel in the treatment of (RAU). **Subjects and method:** Sixty patients in the ulcerative stage of RAU were divided at random among two groups. Group I: Patients received topical 0.5% avocado gel three times daily for seven days. Group II: Patients received topical placebo gel three times daily for seven days. The patients were examined at the time of initial visit before treatment administration and on the fourth and the seventh day of treatment. **Results:** The results showed that topical 0.5% avocado gel were more effective than placebo gel in the management of minor recurrent aphthous RAU ulceration as it reduces the pain after its application more than the placebo gel alone. Patients on 0.5% topical avocado gel therapy revealed less degree of erythema, decrease in ulcer size and healing period than patients on the placebo therapy. **Conclusion:** Topical avocado gel may be considered a reasonable treatment of minor RAU as it reduces pain, erythema and ulcers size and accelerates its healing.

KEYWORDS: Recurrent aphthous ulcer, Avocado gel, treatment

INTRODUCTION

Recurrent aphthous ulcer (RAU) is a widespread oral health problem. Which interferes with normal life activities by affecting eating and swallowing⁽¹⁾.

Tumor necrosis factor alpha and other cytokines trigger epithelial cell death and ulceration in the pathogenesis of RAU, which is caused by the activation of a cell-mediated immune response mediated mostly by T- lymphocytes⁽²⁾.

Some patients with mild RAU may be more likely to develop symptoms if they consume certain foods or beverages, including chocolate, tea, coffee,

peanuts, almonds, strawberries, cheese, tomatoes, and wheat flour. Additionally, recent studies have shown a correlation between elevated serum levels of anti-milk cow's protein immunoglobulin A(IgA), IgG, and IgE antibodies and recurrent aphthous ulcers^(3,4).

Self-limited, painful, shallow, round or oval ulcers with a yellow-gray pseudo-membrane, surrounded by slight elevated borders with an erythematous halo reflecting superficial vasculitis and foci of extravasated erythrocytes are the common characteristic features of minor RAU lesions^(5,6).

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Drugs like as anti-inflammatories, corticosteroids, analgesics, and antimicrobials are used to treat RAS, and lately topical mucosal protectants have been created to temporarily provide a physical barrier over the ulcers, safeguarding them from oral damage and trauma ^(7,8).

Different topical gels containing hyaluronic acid, jojoba oil and aloe vera resulted in a considerable decrease in healing time and pain alleviation, with no adverse effects observed, which is encouraging ^(9,10,11).

Quitting smoking has been linked to fewer episodes of oral aphthous ulcers. Evidence from experiments shows that nicotine has a powerful and efficient anti-inflammatory activity on keratinocytes, which may explain why the number of lesions and the time between recurrences seem to decrease while the patient is smoking as opposed to when they are not ^(12,13).

Avocados have a high concentration of oil, making its processing and manufacture a potentially lucrative business ⁽¹⁴⁾.

Avocado oil pressed from ripe avocados is rich in oleic acid, making it a nutritious and risk-free dietary choice. It also contains vitamin E, which acts as an antioxidant and prolongs the oil's shelf life ⁽¹⁵⁾.

Polyunsaturated fatty acids (PUFAs), linolenic acids, monounsaturated fatty acids, oleic acid, beta-carotene, lecithin, minerals, and vitamins A, C, D, and E are all found in abundance in avocado oil, which is derived from the pulp of the fruit ^(16,17). Avocado oil has been utilised for a variety of skin conditions, including scarring, stretch marks, scleroderma, and psoriasis ^(18,19).

Several studies have shown that eating avocados may help protect the skin by speeding the healing process after an injury and decreasing sun damage to the skin ^(20,21).

With that in mind, the purpose of this research was to assess the effectiveness of a 0.5% avocado gel for the topical treatment of mild (RAU).

SUBJECTS AND METHODS

Ethical approval

The present study followed the ethical standards set out by the World Medical Association (Declaration of Helsinki, 1978, as updated in 2008) for clinical trials involving human participants. Code number (25)/10-2022 indicates that the Future University in Egypt's (FUE.REC) Research Ethics Committee approved the protocol under consideration. All participants provided an informed consent after receiving a thorough description of the study's procedures before participation began.

Sample size calculation

To determine the minimal number of patients for this clinical trial, a power analysis was conducted. With an alpha level of 0.05 and a Beta (β) level of 0.05 (i.e. power = 80%), the appropriate sample size was calculated to be 60 participants in each group to avoid a potential loss of revenue as a result of a patient dropping out.

Steps of gel preparation:

In order to extract the oil from ripe avocados, the pulp was scooped out and ground into a paste using a manual grinder after being peeled with a peeler and having the seeds removed. After transferring the paste to a beaker, we heated it to between 75 and 80 degrees Celsius in a water bath and let it sit there for three days to allow the water to evaporate. After the water was removed, the avocado paste was squeezed through muslin fabric to extract its oil, which was then centrifuged to separate the remaining solids. Finally, glycerin and propylene glycol were added, and the resulting liquid was heated to produce the final product.

In the present study the avocado was made in the gel form for topical application on minor RAU orally after adding carboxy methyl cellulose sodium salt then the mixture was condensed by rotary evaporator with 70 rpm and 50 degrees Celsius to achieve sufficient viscosity with 5 % concentration.

The placebo gel contained the same carboxy methylcellulose without the avocado oil ⁽²⁵⁾.

Selection of patients

Sixty people who visited the outpatient clinic of the Oral Medicine, Diagnosis and Periodontology department at the Faculty of Oral and Dental Medicine at Future University in Egypt participated in the research.

Inclusion criteria

Patients included in this study were suffering from painful minor RAU with free medical history and no systemic diseases.

Exclusion criteria

Patients were excluded from this study if they had the following :

1. Systemic diseases as cyclic neutropenia ,ulcerative colitis, endocrinopathies as diabetes mellitus and impaired thyroid function, recurrent intraoral herpes simplex virus , long-term infection as well as acute viral disease.
2. Drug administration as nonsteroidal anti-inflammatory drug, chemotherapeutic drugs and any drugs that might potentially alter the parameters of the investigation.
3. Those who have a history of possible sensitivity to mouth wash or tooth paste.
4. Patients with RAS-related disorders and illnesses as (e.g. Behcet's syndrome , Reiter's syndrome, Coeliac disease , Crohn's disease)
5. Patients used either systemic or topical medicine to treat their present ulcer.
6. Pregnant females.
7. Smokers.
8. Patients with recurrent aphthous ulcers older than 4 days and patients who received any other treatment for the last 4 weeks.

Case history

History of psychological stress, family history of RAS, some precipitating factors as trauma, menstruation, allergy to certain foods , upper respiratory tract infection, smoking and previous treatment was recorded .

Clinical examination:

Intraoral examination

Patients with RAU were examined for number of ulcers present and their site,size and depth .The oral mucosa was examined for scars of previous ulcers and areas of erythema indicating newly developing ulcers . Sharp cusps or broken down teeth were palpated as they may predispose for or delay healing of an ulcer .

Extraoral examination:

Skin and eyes were examined to exclude any mucocutaneous diseases also the regional lymph nodes were examined .

Sixty patients at the beginning of the ulcerative stage of minor RAU were randomly divided equally into two groups:

Group I: included thirty patients who received topical (0.5% avocado gel) 3 times daily after meals for 7 days.

Group II: included thirty patients who received topical placebo gel 3 times daily after meals for 7 days.

Using a clean finger, apply 2.5 ml (half a measuring spoon) of the gel to the afflicted area(s). Do not swallow the gel right away; instead, keep it in your mouth for as long as you can.

All the patients were provided with sufficient amounts of treatment in graduated eppendorf tubes and the patients were instructed to use the same kind of toothpastes and to refrain from using any other dental hygiene products except dental floss and tooth picks.

The participants were instructed to complete one diary sheet per day until their ulcers healed, and the investigator oversaw the initial application of the treatment. He also gave the patients verbal and written instructions on how to apply the treatment. Every day they were followed on WhatsApp and at the end of the treatment the amount of gel left was recorded to track their compliance.

Patients were asked to give their comments about the ease of application of the treatment used, any unpleasant feeling or taste and any irritation occurred after treatment application.

Measurement of clinical data:

The patients were examined at the time of initial visit before treatment administration and on the fourth day and the seventh day by the same investigator to record both subjective and objective parameters. Subjective parameters include pain measured by horizontal visual analogue scale (VAS) and healing period.

The visual analogue scale (VAS) is a 10-centimeter horizontal line with zero representing no pain and ten representing the worst possible pain. Pain is quantified by marking a vertical line at a point that corresponds to the evaluation of the pain and then measuring the line's deviation from zero⁽²²⁾.

Size (cross-sectional area) of the ulcer and erythema as an inflammatory indication were objective measures.

The greatest diameter of the ulcers were measured using a calibrated periodontal probe, and the values were multiplied to estimate the ulcers' cross-sectional area⁽²³⁾.

A 4-point scale was used to assess the level of erythema. that ranges from 1 representing no erythema to 4 which represents severe erythema⁽²⁴⁾.

- 1= no erythema.
- 2= Mild erythema (Light pink/red) .
- 3= Moderate erythema (Red but not dark in color) .

- 4= Severe erythema (Very red,dark in color).

The investigator who did these measurements and the patients were blinded about the treatment that was used.

Statistical Methods

The mean, standard deviation, and standard error were employed in the statistical presentation and analysis of the current research, and the student t-test was used to compare the two groups' quantitative data.

$P \leq 0.05$ was used as the significance threshold in this investigation. With IBM® SPSS® Statistics Version 20 for Windows, a statistical analysis was carried out.

RESULTS

Sixty patients agreed to take part in the research. All patients completed the required follow-up, allowing for statistical analysis of the data.

There were 14 men and 16 women among the patients in Group I, whereas there were 12 men and 18 women in Group II.

Group I had an average age of 28.34, whereas Group II had a mean age of 27.87, and there was no statistically significant difference between the groups when it came to the distribution of either age or sex.

1- Changes in pain scores:

Table 1 and **Fig.1** show the changes in the mean value of pain at different periods, **First** the results revealed that pain scores before treatment in the first group ranged from 5-10 with mean value $(6.93) \pm 1.47$ and in the second group ranged from 5-10 with mean value $(6.98) \pm 1.50$ with no significant difference between the two groups (**P value > 0.05**), **then** on the 4th day it ranged from 0-3 with mean value $(0.70) \pm 0.8$ in the 1st group, while in 2nd group it ranged from 3-7 with mean value $(4.1) \pm 1.0$ with statistically significant difference (**P value < 0.001***).

Finally on the 7th day the pain in the 1st group was 0 in all cases and in the 2nd group ranged from 0-2 with mean value (0.20) with no statistically significant difference (**P value > 0.05**).

TABLE (1) Comparison of pain scores between the two groups before treatment and on 4th & 7th day of treatment

	Pain before treatment		T-test	
	Range	Mean±SD	t	P-value
Group I	5.0-10.0	6.93±1.47	-0.094	0.92
Group II	5.0-10.0	6.98±1.50		

	Pain on 4th day		T-test	
	Range	Mean±SD	t	P-value
Group I	0.0-3.0	0.70±0.8	-12.64	<0.001*
Group II	3.0-7.0	4.10±1.0		

	Pain on 7th day		T-test	
	Range	Mean±SD	t	P-value
Group I	0.0-0.0	0.00±0.00	-2.000	0.05*
Group II	0.0-2.0	0.20±0.50		

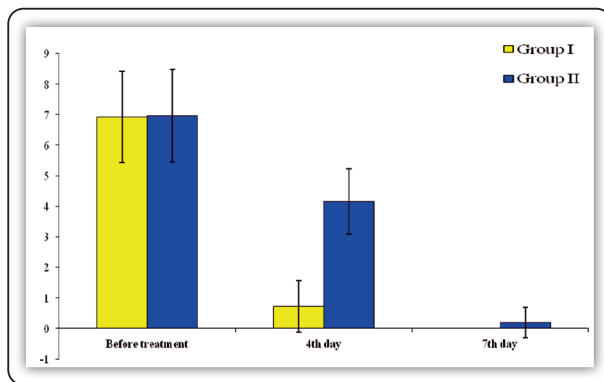


FIG (1) Histogram representing the comparison of pain scores between the two groups before treatment and on 4th & 7th day of treatment

2- Changes in erythema scores:

Table 2 and **Fig 2** summarize the changes in the mean value of erythema at different periods, **First** the results revealed that erythema scores before treatment in the first group ranged from 3-4 with mean value (3.26) ± 0.4 while in the second group

ranged from 3-4 with mean value (3.54) ± 0.5 with no significant difference between the two groups (**P value > 0.05**), then on the 4th day it ranged from 1-2 with mean value (1.160) ± 0.38 in the 1st group and ranged from 2-4 with mean value (2.35) ± 0.55 in the 2nd group with statistically significant difference (**P value <0.001***), **Finally** on the 7th day the erythema in the 1st group was 1 in all cases and in the 2nd group it ranged from 1-2 with mean value (1.12) ± 0.33 with no significant difference between the two groups (**P value > 0.05**).

TABLE (2) Comparison of erythema between two groups before and on 4th & 7th day of treatment

	Erythema before treatment		T-test	
	Range	Mean±SD	t	P-value
Group I	3.0-4.0	3.26±0.4	-1.75	0.086
Group II	3.0-4.0	3.54±0.5		

	Erythema on 4th day		T-test	
	Range	Mean±SD	t	P-value
Group I	1.0-2.0	1.16±0.38	-8.81	<0.001*
Group II	2.0-4.0	2.35±0.55		

	Erythema on 7th day		T-test	
	Range	Mean±SD	t	P-value
Group I	1.0-1.0	1.00±0.00	-1.809	0.077
Group II	1.0-2.0	1.12±0.33		

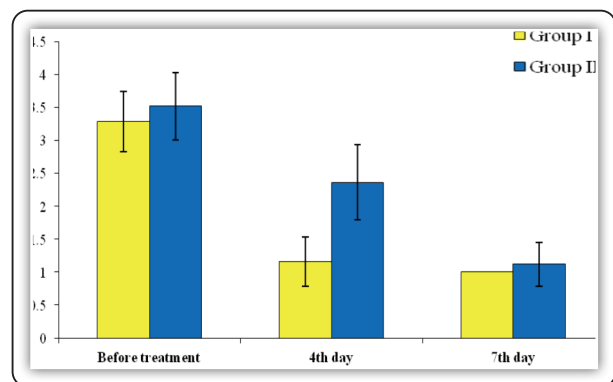


FIG (2) Histogram showing the comparison of erythema scores between the two groups before treatment and on 4th & 7th day of treatment

3- Changes in ulcer size:

Table 3 and **Fig 3** show the changes in the mean value of ulcer sizes at different periods, **First** the results revealed that Minor RAU sizes in the 1st group before treatment ranged from 4-16 mm² with mean value (7.93) ± 2.6 while in the 2nd group ranged from 4-16 mm² with mean value (7.76) ± 3.01, with no significant difference between the two groups (**P value > 0.05**), **then** on the 4th day the ulcer sizes in the 1st group reduced and ranged from 3-9 mm² with mean value (4.93) ± 1.79 while in the 2nd group ranged from 3-12 mm² with mean value (6.50) ± 2.54 with statistically significant difference (**P value < 0.05**), **Finally** the ulcer sizes in the 1st group was 0 mm² all cases while in 2nd group it ranged from 0-2 mm² with mean value (0.34) ± 0.64 with statistically significant difference between the two groups (**P value < 0.05**).

TABLE (3) Comparison of ulcers size in the two groups before treatment and on 4th & 7th day of treatment

	Size before treatment		T-test	
	Range	Mean±SD	t	P-value
Group I	4.0-16.0	7.93±2.60	0.196	0.84
Group II	4.0-16.0	7.76±3.01		
	Size on 4 th day		T-test	
	Range	Mean±SD	t	P-value
Group I	3.0-9.0	4.93±1.79	-2.40	0.02*
Group II	3.0-12.0	6.50±2.54		
	Size on 7 th day		T-test	
	Range	Mean±SD	t	P-value
Group I	0.0-0.0	0.00±0.00	-2.55	0.01*
Group II	0.0-2.0	0.34±0.64		

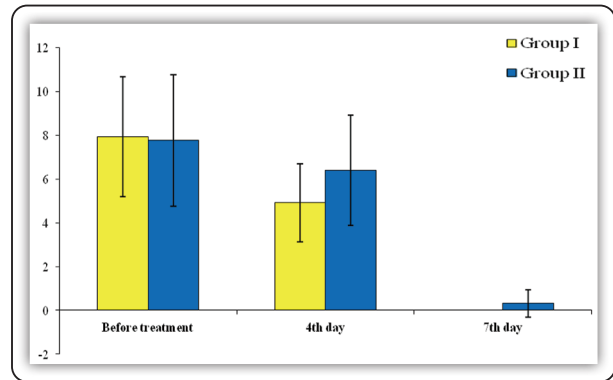


FIG (3) Histogram showing comparison of ulcers size in the two groups before treatment and on 4th & 7th day of treatment

4- Comparison of healing period:

Table 4 and **Fig 4** show the difference of healing periods in the avocado gel group (1st group) which ranged from 2-6 days with mean value (4.23) ± 0.91 while the healing periods in the placebo group (2nd group) ranged from 5-8 with mean value (6.32) ± 0.79 with statistically significant difference between the two groups (**P value < 0.001***).

TABLE (4) Comparison of healing perids in the two groups

	Healing period		T-test	
	Range	Mean±SD	t	P-value
Group I	2.0-6.0	4.23±0.91	-7.14	<0.001*
Group II	5.0-8.0	6.32±0.79		

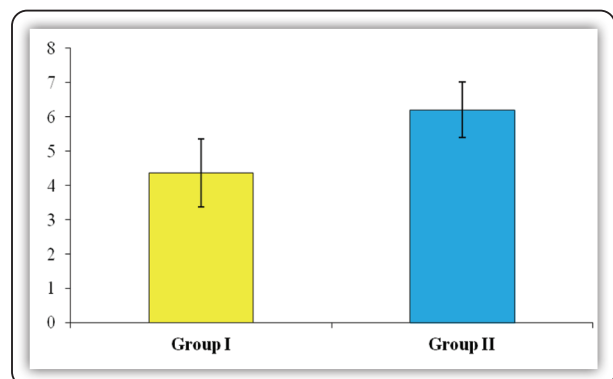


FIG (4) Histogram representing comparison of healing periods in the two groups

DISCUSSION

Diagnosing and treating RAS is a prevalent issue in both general and specialty oral practice due to RAU's prevalence; these ulcers often first appear in infancy and lessen in severity and frequency as patients mature⁽²⁶⁾.

Recent years there have seen a rise in the popularity of using different and contrasting herbal drugs to promote tissue regeneration and wound healing^(27,28).

Encouraged by the effect of avocado oil in wound healing by increasing the collagen synthesis, reducing the number of inflammatory cells and reducing pain, furthermore recent studies have approved the anti-ulcer activity of avocado oil in addition to its antioxidant and anti-inflammatory effects^(29,30).

The aim of this study was to evaluate the efficacy of topically applied 0.5% avocado gel in the treatment of minor (RAU).

The results of the present investigation showed that 0.5 topical avocado gel therapy was very effective in reducing pain, erythema, size of minor RAU ulcers and healing period than placebo treatment.

On comparing the mean pain score of both 0.5 avocado gel and placebo gel it was found that topical avocado gel therapy reduced pain in the 4th day of treatment better than placebo gel at (P value < 0.001*) and in the 7th day of treatment at (P value < 0.05) which may be due to the high percentage of linoleic acid and different vitamins in avocado oil and These substances play crucial roles as antioxidants, protecting against free radicals that cause toxicity, slow tissue repair, and discomfort⁽¹⁷⁾.

In the present study on comparing the mean of erythema scores between the first group used 0.5 avocado gel treatment and the second group on placebo gel, the avocado gel reduced erythema in the 4th day of treatment better than placebo gel at (P value < 0.001*) and in 7th day at (P value < 0.07). These results show that pain scores run parallel with the scores of erythema as severe erythema is

always associated with the presence of severe pain and this process continues until erythema fades away and at this stage there is transition from severe pain to moderate or mild pain.

These findings are in accordance with Shamsah⁽³¹⁾ who reported a statistically significant reduction of pain and acceleration of healing following treatment with topical avocado gel on traumatic oral ulceration.

In the present study on comparing the mean of the healing period of both 0.5 avocado gel and placebo gel it was found that topical 0.5 avocado gel therapy reduce the healing period of minor RAU better than the placebo gel at (P value < 0.001*).

Concerning the ulcer size outcomes, the avocado gel treatment has better results than placebo gel as it reduced the ulcers size in the 4th day of treatment at (P value < 0.02) and in the 7th day at (P value < 0.01).

Reduction of pain, erythema and ulcer diameter in the placebo group may be explained by three possible reasons. First, the placebo gel may have formed a protective film to cover the ulcer and therefore produced some curative effect. Second, minor RAU are a self-limiting disease which can get relief without any treatment. Finally, the psychiatric factors have been known as etiologic factors and the subjects might be consoled by the feeling of being treated.

The results of this study may be useful in establishing new effective, safe topical therapy for treatment of patients suffering from minor recurrent aphthous ulcerations.

CONCLUSIONS

Considering the adverse side effects of topical corticosteroids, topical antibiotics and inability of local analgesics to enhance healing of minor RAU, it can be concluded that topical avocado gel may offer a good alternative safe and effective therapy to other topical agents including corticosteroids, antibiotics and analgesics.

LIMITATION

Some limitations, such as the frequency of recurrence and sample size should be noted when analyzing the results gained from this study. In order to confirm these results, larger and longer-term randomised controlled clinical trials are required and drawbacks of employing avocado gel for RAS treatment. Additional studies also are required to determine the histopathologic examination on its effect on ulcer healing.

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