ORIGINAL ARTICLE / *ARTICLE ORIGINAL*

Pathology / *Pathologie*

COMPARATIVE EVALUATION OF THE EFFICACY OF TOPICAL OZONATED OLIVE OIL AND TOPICAL CHLOROHEXIDINE GLUCONATE IN THE MANAGEMENT OF RECURRENT APHTOUS STOMATITIS

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Introduction: Aphthous ulcers are painful and may significantly impact dental hygiene, speech, and eating. the objectives of treatment are to lessen discomfort and to improve healing. Many symptomatic treatment modalities are used for aphthous ulcerations. Topically chlorhexidine gluconate is used most commonly in these ulcerations.

Aims: The study aimed to compare the efficacy of topical ozonated olive oil and topical chlorhexidine gluconate in the management of recurrent aphthous stomatitis.

Methods: This randomized single-blinded study was done with 20 participants who were split into the chlorhexidine gluconate group and the ozonated olive oil group. Treatment response was assessed by measures of pain reduction, erythema reduction, and ulcer duration on the 2nd, 4th, and 6th day. SPSS version 21 was used to conduct the statistical analysis.

Results: The ozonated oil group indicated a significant decrease in pain and erythema on day 2 and day 4. There was no pain and erythema on day 6 in the ozonated olive oil group.

Conclusions: Applying ozonized olive oil to aphthous ulcers results in decreased pain levels and improved ulcer healing by minimizing the erythema, or period required for healing.

Clinical Significance: An additional study with specific parameters like dose and application time is needed to establish ozonated olive oil as a useful alternative therapy strategy for aphthous ulcerations.

Keywords: chlorhexidine gluconate, ozonated olive oil, recurrent aphthous stomatitis (RAS), erythema, pain

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Conflicts of interest:
The authors declare no conflicts of interest.

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ÉVALUATION DE L'EFFICACITÉ DE L'APPLICATION TOPIQUE DE L'HUILE D'OLIVE OZONÉE COMPARÉ AU GLUCONATE DE CHLOROHEXIDINE DANS LA GESTION DE LA STOMATITE APHTOUSE RÉCURRENTE

Introduction: Les ulcères aphteux sont douloureux et peuvent avoir un impact significatif sur l'hygiène dentaire, la parole et l'alimentation. Les objectifs du traitement sont de diminuer l'inconfort et d'améliorer la guérison. De nombreuses modalités de traitement symptomatique sont utilisées pour les ulcérations aphteuses. Le gluconate de chlorhexidine est utilisé localement le plus souvent dans ces ulcérations.

Objectifs: L'étude visait à comparer l'efficacité de l'huile d'olive ozonée topique et du gluconate de chlorhexidine topique dans la prise en charge de la stomatite aphteuse récurrente.

Méthodes: Cette étude randomisée en simple aveugle a été réalisée auprès de 20 participants répartis dans le groupe gluconate de chlorhexidine et le groupe huile d'olive ozonée. La réponse au traitement a été évaluée par des mesures de réduction de la douleur, de réduction de l'érythème et de la durée de l'ulcère aux 2ème, 4ème et 6ème jours. SPSS version 21 a été utilisé pour effectuer l'analyse statistique.

Résultats: Le groupe huile ozonée a indiqué une diminution significative de la douleur et de l'érythème aux jours 2 et 4. Il n'y avait aucune douleur ni érythème au jour 6 dans le groupe huile d'olive ozonée.

Conclusions: L'application d'huile d'olive ozonisée sur les ulcères aphteux entraîne une diminution des niveaux de douleur et une amélioration de la guérison de l'ulcère en minimisant l'érythème ou la période requise pour la guérison.

Signification clinique: Une étude supplémentaire avec des paramètres spécifiques tels que la dose et le temps d'application est nécessaire pour établir l'huile d'olive ozonée comme une stratégie thérapeutique alternative utile pour les ulcérations aphteuses.

Mots clés: gluconate de chlorhexidine, huile d'olive ozonée, stomatite aphteuse récurrente (SRA), érythème, douleur

Introduction

Aphthous stomatitis is also known as canker sores or aphthae. Recurrent aphthous stomatitis (RAS), frequently manifests as superficial, oval, painful ulcers with a pseudomembranous base that is yellowish-gray and has an erythematous halo [1, 2]. These uncomfortable lesions may have a significant impact on dental hygiene, speech, and eating. Hence, the lesions may have an even greater influence on living quality than only the discomfort they cause [3-5]. Even though the lesion normally heals on its own, the pain from the aphthae causes severe morbidity.

This disease entity is caused by multifactorial etiologies, which include inherited, environmental, infections caused by various bacteria, deficiencies of iron and vitamin B, etc. [6]. Despite this, research has revealed that taking iron or vitamin supplements does not decrease ulcer symptoms. It has been demonstrated that there is no link between microorganisms and aphthous ulceration [7]. As a result, the objectives of treatment are to lessen discomfort and to improve healing.

Many symptomatic treatment modalities are used for aphthous ulcerations. Antiseptics and analgesic medications constitute the initial line of treatment. One of the bisguanide antiseptics is chlorhexidine, which has a broad spectrum of anti-microbial activity in addition to being safe, effective, and adequate [4-9]. Chlorhexidine is offered in a variety of products, including chips, mouthwash, dental varnish, and bioadhesive gels [4, 8-9]. It is appropriate to advise chlorhexidine 0.2% rinse to all patients with aphthous ulcerations to reduce the risk of superinfection. Chlorhexidine is also effective at removing and stopping biofilms' growth, which is frequently present in oral plaque [10].

Ozone therapy has drawn a great deal of attention in the field of medicine, due to its potent oxidizing properties, antibacterial activity, ability to promote blood circulation and the immune system, and analgesic properties [11-13]. Ozone works by achieving infection control and accelerating healing [12-18]. Topically application of ozone to the diseased cutaneous and mucosal regions is effective [2]. As ozone is unstable, it is used in the form of ozonated oil which makes it stable. Olive oil is viscous and used to extend the shelf life of ozone [19, 20]. The atypical cutaneous and mucosal regions are treated with ozonated oil [5, 6]. There are not many studies looking at ozonated oil's potential as a treatment for recurrent aphthous ulcers. To treat oral illnesses, ozonated oil has been applied with superior outcomes [21, 22]. Therefore, the study aimed to evaluate the efficacy of topical ozonized olive oil and topical chlorhexidine gluconate in the management of RAS.

Materials and Methods

We conducted a study in Sharad Pawar Dental College and Hospital, DMIHER-DU in the Department of Oral Medicine, from December 2022 to February 2023. Ethical approval was taken from the institutional ethical committee of Datta Meghe Institution of Medical Sciences [IBR number: DMIMS (DU)/IEC/2022/1157]. After a diagnosis of aphthous ulcer, each patient was informed about the study, and consent was taken.

Inclusion criteria

Individuals in the age group 10-70 years, having one or more recurrent ulcers were selected. Based on the patient's medical history and the clinical symptoms of a round, shallow ulcer with a regular border and an erythematous halo around it in the mucosa, the diagnosis of recurrent aphthous ulcer was made.

Exclusion criteria

The following patients were excluded from the study: Patients suffering from systemic disorders, patients already receiving treatment for aphthous ulcers, patients presenting with chronic non-healing ulcers, patients suffering from oral sub mucous fibrosis, pregnant women or lactating mothers, patients having a known history of serious drug hypersensitivities, patients having no habits like tobacco and beetle nut chewing, smoking and alcohol intake.

Therapeutic regimen

Patients were advised local application of prescribed treatment, three to five times each day until the lesion healed completely. Patients were counseled and trained for the prescribed medication application. After drying and isolation of the ulcer area, application of the chlorohexidine gluconate or ozonated olive oil to the ulcers with a cotton-tipped applicator was advised. Patients were advised not to drink or eat anything for 30 minutes after the prescribed medication was applied. Subjects were evaluated for characteristics such as intensity of pain before and after application, ulcer healing, and commencement of size decrease following application on successive treatment days. Two investigators were involved in the examination of ulcers during the study.

Data collection and outcomes

All of the data needed for the study was collected during the subject's initial session. This information contains demographics, general examination, and previous history. Aphthous ulceration was identified during a normal oral examination. The history and clinical symptoms were used to make the diagnosis of aphthous ulcer. Clinically, the ulcers were assessed based on pain size and erythema as described by the patient, as well as an overall assessment of these clinical aspects. On the 2nd, 4th, and 6th days of treatment, the evaluations were repeated till the ulcer was completely healed. Pain intensity was measured by making use of a visual analog scale (VAS) of 0-10, where 0 represents no pain and 10 represents the most severe pain. In this study, Bhat S Suraksha D's

methodology is used for grading erythema. The degree of erythema was measured on a 4-point scale with a range of 0 to 3, according to Bhat S Suraksha D's methodology [23] as shown in Table 1. Total healing duration was assessed in the total number of days required for healing.

Table 1: Criteria for erythema (Bhat S Suraksha D)

Score	Findings
1	No erythema
2	Light pink/ red
3	Red but not dark in color

Statistical Analysis

SPSS version 21 was used to conduct the statistical analysis. The current study included both descriptive and inferential statistical analysis. The significance of the results for measurement data was evaluated at the 5% level of significance and provided as mean ± SD.

Results

Demographic assessment

In Group I, the mean age of the individuals is 32.10 ± 15.96, while in Group II, it is 30.10 ± 12.93 as shown in Table 2 and Figure 1. In the present study, in Group I, 50% of the subjects were female and 50% were male. 20% of men and 80% female were present in Group II as shown in Table 3.

Assessment of pain score

For patients in Group 1, the mean pain score on the first day (at baseline), is 7.80 ± 0.91. On days 2, 4, and 6, the mean pain scores are 5.60 ±1.07, 3.20 ±1.032, and 0.20 ± 0.42, respectively. For patients in Group 2, the mean pain score at baseline, or on the first day is 7.10 ± 1.28. The mean pain scores on days 2, 4, and 6 after therapy are 3.30 ± 1.05, 0.90 ± 1.66, and 0 respectively. No pain was present on the 6th day in this group. Comparing Group 2 to Group 1, these statistics indicate a significant decrease in pain as shown in Table 4.

Table 2: Age distribution of Group 1 and Group 2

Age in year	Group 1		Group 2	
	N	%	N	%
Below 20	4	40%	4	40%
21-30	2	20%	2	20%
31-40	1	10%	2	20%
More than 41	3	30%	2	20%
Mean ± SD	32.10 ± 15.96		30.10 ± 12.93	

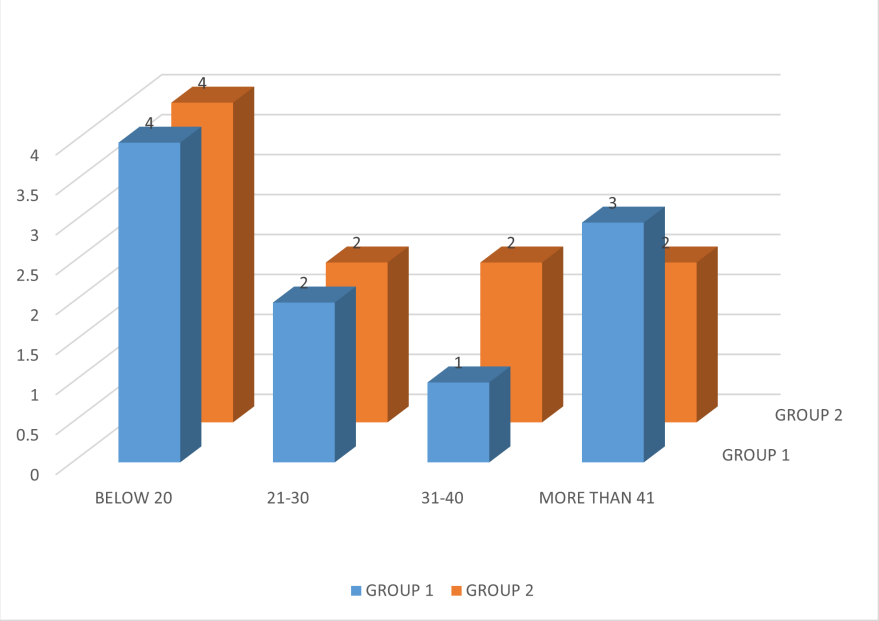

Figure 1. Graph showing the age distribution of Group 1 and Group 2

Table 3: Gender distribution of Group 1 and Group 2.

Gender	GROUP 1		GROUP 2	
	N	%	N	%
Male	5	50%	2	20%
Female	5	50%	8	80%

Table 4: Assessment of pain score for Group 1 and Group 2.

TIME INTERVAL	**Group 1** Mean VAS ± SD	Difference from baseline	p-value
1st day (baseline)	7.80 ± 0.91	-	-
2nd day	5.60 ± 1.07	2.1±019	0.004*
4th day	3.20 ± 1.032	1.97±023	0.001*
6th day	0.20 ± 0.42	1.12±0.17	0.004*
TIME INTERVAL	**Group 2** Mean VAS ±SD	Difference from baseline	p-value
1st day (baseline)	7.10 ± 1.28	-	-
2nd day	3.30 ± 1.05	3.36±1.16	0.002*
4th day	0.90 ± 1.66	2.19±0.95	0.084
6th day	0.0	-	-

*Statistically significant at $p<0.05$

Assessment of erythema

The patients in Group 1 had an average erythema score of 2.90 ± 0.31 on the first day (baseline). The mean erythema scores in Group 1, on days 2, 4, and 6 were, respectively, 2.40 0.51; 1.30 0.48; and 0.10 0.31. The patients in Group 2 have a mean erythema score of 2.90 ± 0.31 on the first day (baseline). The mean erythema scores for Group 2, on days 2, 4, and 6 after therapy are 1.40 0.69, 0.50 0.70, and 0, respectively. There is a significant reduction of erythema levels on days 2nd and 4th and no erythema present on the 6th day in this group as shown in Table 5.

Assessment of healing duration

The mean of days for healing the ulcer in group 1 was 5.2 days. For group 2, it was 3.8 days. In group 2, there is a significant reduction in the healing duration of aphthous ulcers in the present study as shown in Figure 2.

Inference of the study

Applying ozonized olive oil to aphthous ulcers resulted in a decrease in pain levels and improved ulcer healing by minimizing the erythema. Additional research with precise parameters like dosage and application duration is needed to establish that ozonized olive oil can be used as a helpful alternative treatment modality in aphthous ulceration.

Table 5: Assessment of erythema for Group 1 and Group 2.

Time interval	**Group 1** Mean Erythema ± SD	Difference from baseline	p-value
1st day (baseline)	2.90 ± 0.31	-	-
2nd day	2.40 ± 0.51	0.55±0.11	0.002*
4th day	1.30 ± 0.48	1.01±0.21	0.056
6th day	0.10 ± 0.31	0.72±0.09	0.071
Time interval	**Group 2** Mean Erythema ± SD	Difference from baseline	p-value
1st day (baseline)	2.90 ± 0.31	-	-
2nd day	1.40 ± 0.69	1.58±1.23	0.078
4th day	0.50 ± 0.70	0.98±0.22	0.004*
6th day	0.0	-	-

*Statistically significant at p<0.05

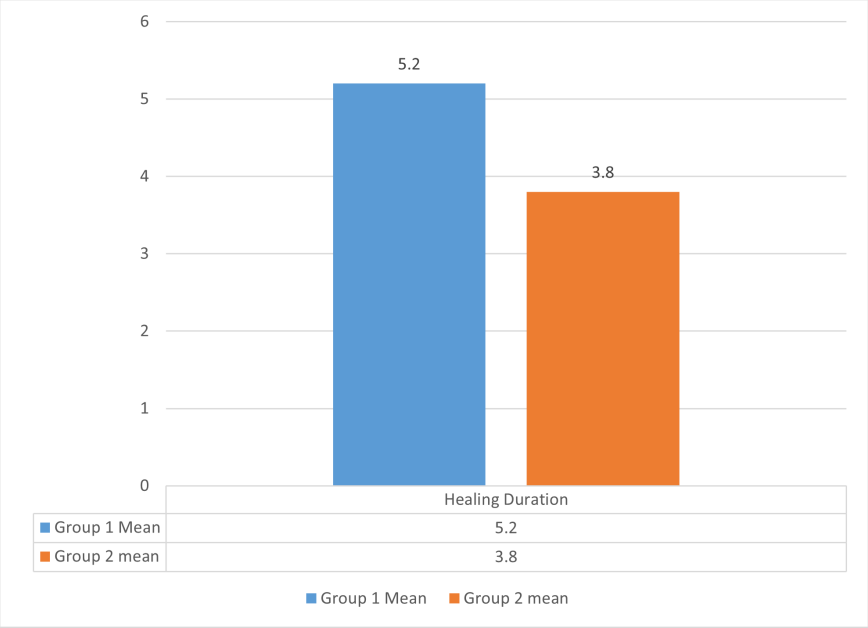

Figure 2. Graph showing healing duration in days.

Discussion

Being the most prevalent oral condition, aphthous ulcerations affect 20% of the population at least once or twice in their lifetime [23-24]. Patients who experience recurrent aphthous ulceration may experience severe pain, especially when several ulcers develop at once. Since there is no specific scientific test to confirm the diagnosis of RAS, the clinical appearance of the lesion is truly used to make the diagnosis. However, a complete clinical history and examination aid in identifying any secondary causes [2]. Treatment options for aphthous ulceration are primarily palliative and focused on alleviating symptoms to improve the patient's oral health because the specific etiology of the condition is not well understood [25]. Ozone therapy is one such medical therapy that is entirely focused on reducing ulcer size and comforting the patient. There have been few reports in the literature on using ozone as a treatment for recurrent leg ulcers. The oldest report was from 1957, while Thwaites and Dean reported in 1985 that ozone had a positive impact on leg ulcer healing [26]. Iman M.S., et al. evaluated the effectiveness of topical ozone therapy in traumatic ulcer healing in rat tongue ulcers. They discovered that ozone had a robust antibacterial impact and a good therapeutic effect in encouraging and speeding the clinical and histological healing of traumatic ulcers [27].

Ozone is considered one of the greatest bactericidal, antiviral, and antifungal medications due to its wide range of inherent therapeutic qualities. This kind of ozone is being empirically used in clinical settings to treat chronic wounds such as trophic ulcers, ischemic ulcers, and diabetic wounds [28-29] With specialized machinery called ozonizers, oxygen is subjected to silent electrical discharges to create ozone. It cannot be preserved since

its half-life is limited and is very reactive and unstable. Ozone is successfully and effectively used as ozonized sesame oil. It has a life period that is estimated in years and is therefore dissolved on an oil basis. Ozonated oils have been used to treat aphthous ulceration due to their antibacterial, immune-stimulating, analgesic, anti-hypoxic, and detoxicating effects [30].

Ozonated oil consists of ozone and unsaturated fatty acids, among the latter, it can be classified into three types: ω-9 series of unsaturated fatty acids represented by oleic acid in tea oil, ω-6 series of unsaturated fatty acids represented by sub-acid in vegetable oils and ω-3 series of unsaturated fatty acids represented by eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) in fish oil. Direct ozonation of vegetable oils with unsaturated fatty acids produces the 1,2,4-trioxolane molecule, which is the active form of ozone in these substrates. When a humid wound or an ulcer is treated, the trioxolane ring within the vegetable ozonated matrices swiftly creates certain molecules responsible for the healing process. Furthermore, it is in charge of antibacterial and antimycotic treatments. Furthermore, the oil itself functions as a moisturizer and protectant, especially for patients with compromised skin barrier function. More importantly, it is storable and portable in daily life, allowing it to fulfill the high demand of more patients [31].

Ozonated oils have been utilized for a variety of medicinal purposes, with the release of reactive oxygen species (ROS) and the existence of ozonides (ozonated oil derivatives) assumed to be involved in their mechanism of action. Ozonated oils are antibacterial against a wide variety of pathogens, including bacteria, viruses, and fungi. The reactive oxygen species produced by ozonated oils are thought to play a role in disrupting these microorganisms' cell membranes, resulting in their inactivation [32]. When used topically, ozonated oils may have anti-inflammatory qualities that can help relieve inflammation and pain. They are thought to influence the release of pro-inflammatory mediators [33]. Ozonated oils are supposed to increase oxygen flow to tissues, potentially improving the body's healing ability. This can help with wound healing and tissue repair [33]. While ozone is an oxidant, ozonated oils may have antioxidant properties due to the presence of ozonides and their potential to scavenge free radicals [34]. Ozonated oils are thought to promote cellular oxygen usage, potentially improving overall cell function and energy generation [35]. While some scientific evidence supports the potential benefits of ozonated oils, additional research is needed to completely understand their mechanisms of action and therapeutic uses. Before utilizing ozonated oils for medical or therapeutic purposes, always consult with a healthcare practitioner.

Chlorhexidine is one of the drugs that are most usually given to patients who complain of mouth ulcers [36]. Antibiotics and analgesic medications, such as 0.2 percent chlorhexidine in rinses or topical gel, three times a day, are the first-line therapy alternatives for as long as the lesions last [37]. In research by Miles DA et al., they compared the efficiency of topical chlorhexidine for pain control to triamcinolone acetonide, a drug used to treat aphthous stomatitis. Triamcinolone acetonide and chlorhexidine gluconate did not exhibit any significant variations [38].

In the current study, group 1's mean age was 32.10 years, while group 2's mean age was 31.10 years as shown in table 2. In the study, more patients were seen below 20 years of age with female predominance as shown in Table 3 and Figure 1.

Patients in the current study who received treatment with ozonated oil experienced much less pain, erythema, and improved ulcer healing during the study than the group receiving chlorohexidine gluconate. Figure 3 represents a patient with aphthous ulcerations treated with ozonated olive oil. In comparison with Group 1, there was a significant reduction in VAS score, and erythema levels on the 2nd and 4th day of evaluation in Group 2. Table 4 represents VAS scores for Group 1 and Group 2. On day 6, there was no pain and erythema observed in both Group 2 compared to Group 1. Group 2 showed a considerable reduction in pain and erythema. Table 5 represents erythema for Group 1 and Group 2. The ozonated oil group experienced this reduction more quickly, highlighting the therapeutic benefits of ozone. Our findings are similar to those reported by Dharmavaram AT et al., who investigated the efficacy of sesame oil and ozonated oil in the treatment of recurring aphthous ulcers. This study demonstrated that, when compared to sesame oil, ozonated oil is the preferred method of treating ulcer pain and ulcer size [2].

Ozonated oil was used to treat recurrent aphthous stomatitis in three randomized controlled trials and two non-randomized controlled trials, and it was compared to other therapies such as multivitamins and 0.2% chlorohexidine mouthwashes, sodium perborate alkaline mouthwashes and 0.2% chlorohexidine mouthwashes, and finally a comparative study with metronidazole gel, with a follow-up duration of 7 to 14 days, an application interval of 2 to 4 times per day, and a healing time was 5 to 7 days. When Ozonated oil was used as therapy, the recovery time was reduced in all cases. There were just two studies that found statistically significant differences. There were no recorded side effects [39]. Similarly in our study, healing duration was comparatively less in the ozonated oil group (Figure 2).

To evaluate the differences in efficacy between the two topical oil treatments, Ayesha Thabusum Dharmavaram, et al. completed a study with a sample size of 30 to investigate the efficacy of ozonated oil in the treatment of recurrent

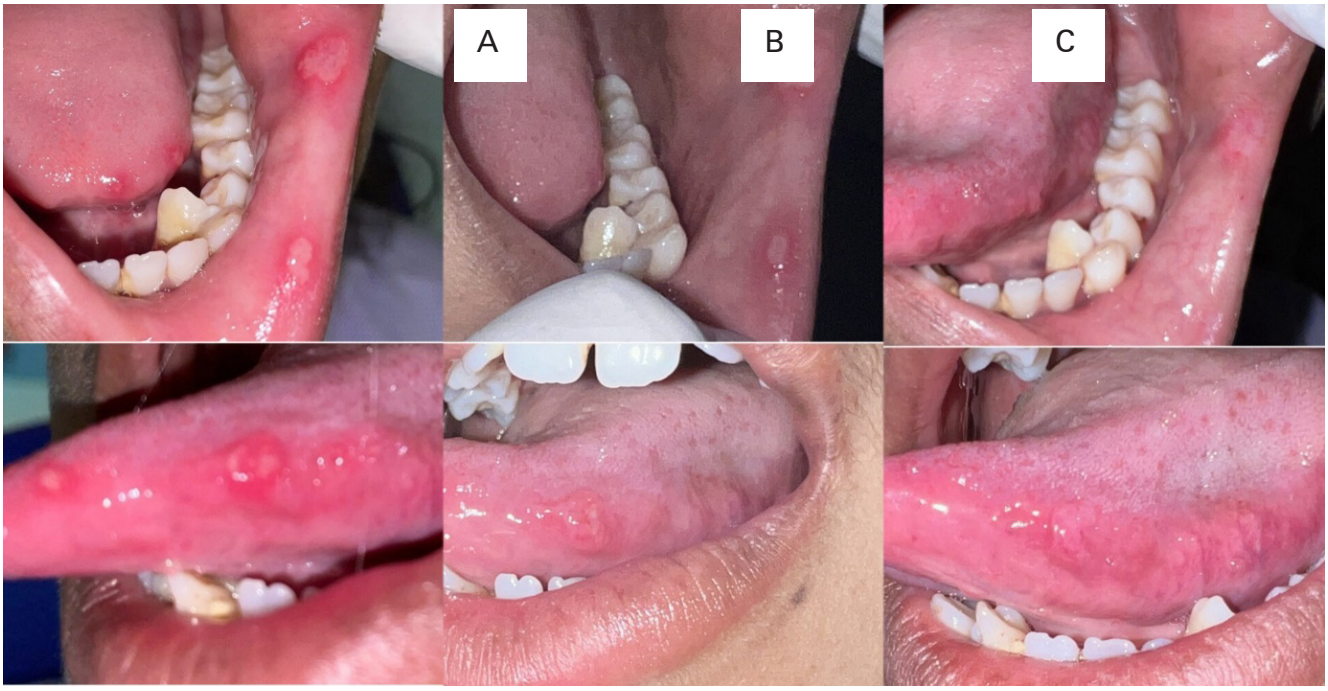

Figure 3. Patient with aphthous ulcerations on the lower left labial mucosa and left lateral border of tongue; treated with ozonated olive oil. Follow-up photos on day 1 (Baseline), 2, and 4 respectively are shown in A, B, C.

aphthous ulcers and to compare with sessame oil. When compared to sesame oil, the study demonstrated that ozonated oil was the better option for treating ulcers by totally reducing their pain and size [2]. Similar results were observed in the present study.

The therapeutic efficacy of ozonized oil in treating aphthous ulcerations has not been extensively studied. Because topical ozone has a wide range of antibacterial, immune-stimulating, and analgesic properties, Richard Logan has documented the medicinal purpose of the application of topical ozone to the ulcer using the Healozone appliance, which provided an efficient way to produce the elimination of clinical symptoms [40].

Use of ozonated oil in other oral conditions: Ozone treatment is very promising since it is non-invasive, has strong disinfection properties that particularly lower bacterial counts, and has few side effects. It enables us to shorten treatment times and ease patient discomfort, improving compliance [41]. Herpes labialis, oral candidiasis, oral lichen planus, and angular cheilitis can all be treated with topical ozone treatment, a less invasive approach, without any negative side effects [19]. With a sample size of 50 patients, Kumar T et al. conducted research to assess the effectiveness of ozonized olive oil in treating oral lesions and diseases, including aphthous ulcerations, herpes labialis, oral candidiasis, oral lichen planus, and angular cheilitis. According to the study, topical ozone therapy can also provide beneficial benefits without any toxicity or adverse effects, even if gaseous ozone therapy is more effective [19].

CONCLUSION

Applying ozonized olive oil to aphthous ulcers results in decreased pain levels and improved ulcer healing by minimizing the erythema, or period required for healing of this lesion. Ozonized oil provides an alternative approach to treating recurring aphthous ulcers because of the variety of natural qualities it possesses that are advantageous to the patient and make it simple and affordable to use.

Limitation of the study: The current study's limitations remain to be its smaller sample size.

Future directions of the study: To establish ozonated olive oil as an effective therapy option for recurrent aphthous ulcers, a larger sample size must be used in the study. To establish ozonized oil as a beneficial alternative treatment modality in oral medicine, additional research with precise parameters like dosage and application duration is required.

Funding Acknowledgements: None

Acknowledgements

We acknowledge ADC Inclusive Dentozoneindia, who had helped in this study.

Author contribution statement

Dr. Prasanna R. Sonar and Dr. Aarati S. Panchbhai carried out the study. Dr. Prasanna R. Sonar wrote the manuscript with support from Dr. Aarati S. Panchbhai and Dr. Anil Govindrao Ghom. Dr. Sudhir Dole conceived the original idea.

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