ARTICLE

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IMMEDIATE PAIN RELIEF AFTER PHOTODYNAMIC THERAPY IN ORAL CANDIDIASIS:
CLINICAL TRIAL

ABSTRACT

Objective:
Fungal infection of the oral mucosa that appears in the oral cavity is known as oral candidiasis and the patients experience a fair amount of pain and discomfort. The objective of this article is to evaluate the efficiency of photodynamic therapy (PDT) treatment as a pain management approach in patients with oral candidiasis.

Methods:
The study was a clinical trial where 20 patients who had oral candidiasis were involved. Participants were randomly assigned to two groups: the PDT group (n=10) or the placebo group (n=10). In the PDT group, PDT was done on the lesions of the oral mucosa using a photosensitizer (methylene blue) and red light at wavelengths of 630-660 nm for 5-10 minutes. The placebo group underwent a similar process as the experimental group but did not use the photosensitizing agent and activation light. Pain intensity was measured using a Visual Analog Scale (VAS) at five-time points: baseline (before treatment), immediately post-treatment, and at 30 minutes, 1 hour, and 2 hours post-treatment. The first study variable was the VAS scores at different post-treatment intervals compared to baseline readings.

Results: At baseline, the mean VAS scores were comparable between the PDT group (7.5 ± 1.2) and the placebo group (7.6 ± 1.1). Immediately post-treatment, the PDT group reported a significant reduction in pain (4.2 ± 1.5) compared to the placebo group (7.3 ± 1.2), with a p-value of <0.001. This significant difference in pain relief persisted at all subsequent time points: 30 minutes (3.8 ± 1.6 vs. 7.0 ± 1.3, p<0.001), 1 hour (3.5 ± 1.7 vs. 6.8 ± 1.4, p<0.001), and 2 hours (3.2 ± 1.8 vs. 6.5 ± 1.5, p<0.001) post-treatment.

Conclusion:
This research established that PDT does provide significant enhancements in the initial reduction of pain in oral candidiasis patients. Therefore, PDT can be a safe and efficient non-surgical approach to managing oral candidiasis, offering prompt relief from pain and enhancing the patient's quality of life. Further studies with relatively larger sample sizes and longer follow-up periods should be done to substantiate these observations and assess PDT's effects on oral candidiasis in the long term.

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INTRODUCTION

Oral candidiasis, also known as oral thrush, is a common fungal infection that stems from an elevated level of Candida species in the oral cavity [(1)].
This condition most of the time leads to a lot of discomfort in terms of pain, burning sensation and any sort of movement around the mouth including eating and speaking [(2)].
It affects everyone but some people are at a higher risk of getting it, these are patients with weak or impaired immune systems, people who use dentures, diabetics, and people on antibiotics or corticosteroids [(3) (4)].
At present, there is no suitable antifungal agent for oral candidiasis which can be administered as a mouthwash or as a systemic treatment with nystatin or fluconazole, which may take several days to weeks to alleviate the symptoms. Patients are still rather uncomfortable at this stage and can experience a lot of pain at this stage, which proves the need for other types of treatment that would help to reduce the pain much faster.

Photodynamic therapy is a novel treatment method which has recently been used in many branches of medicine including oncology and dermatology due to the non-invasive and specific nature of the therapy towards microbial pathogens [(5)].
PDT is characterized by the use of a photosensitizer which is applied on the target tissue followed by exposure to light of a specific wavelength.
This activation results in the formation of reactive oxygen species which can kill the fungal cells and hence reduce the infection and its impact [(6)].
In the context of oral candidiasis, PDT is a comparatively novel treatment approach which may offer patients the ability to find instant relief for their pain and therefore, improve their quality of life [(7)].
Previous studies have established that PDT exerts strong antimicrobial activity against Candida species, however, limited studies have been done to elucidate if PDT can relieve pain in patients with oral candidiasis.

This article aims to fill this gap by evaluating the early effectiveness of PDT in the management of pain from oral candidiasis. In this study, therefore, the amount of pain relief that will be obtained after PDT treatment will be compared to the amount of pain that the patients experienced before the treatment and to a placebo group to determine the effectiveness of this method in managing pain from this condition that is prevalent among patients with chronic pain. The conclusion of this research could help to open the possibility for PDT to become the standard of care in the treatment of patients with oral candidiasis as it offers a faster way of dealing with the pain.

METHODS

Participants:
The clinical trial includes 20 patients diagnosed with oral candidiasis based on clinical examination and confirmed clinically were included and aged between 18 and 65 years. The criteria for inclusion in the study were the presence of obvious manifestations of the disease and microbiological examination, if necessary [(8)].
The criteria for Exclusion were pregnancy and photosensitivity disorders, the use of any antifungal drugs within two weeks before the study, and any systemic disease that might affect the outcome of the study including immunosuppressive diseases or chronic inflammatory diseases.

Intervention:
Participants were randomly assigned to one of two groups: The subjects included in the PDT group, or the placebo group and all the subjects were equally divided. Randomization was done through computer-generated random number sequences to avoid bias.

PDT Group:
Patients in the PDT group received a topical application of methylene blue, which is a photosensitizing agent.
Methylene blue is then applied to the affected parts of the oral mucosa of the patient. To achieve a satisfactory concentration of the agent in the tissues, the contact time was 5 minutes, and then the areas were subjected to red light with the help of the special device with a wavelength of 630-660 nm for 5-10 minutes [(9)].
The exposure of the light was done in a manner that would enhance its interaction with the photosensitizing agent to give reactive oxygen species which would only target the fungal cells.

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Placebo Group:
The procedure which was done for the participants in the placebo group was similar to that which was done in the PDT group, though the photosensitizing agent that was applied was a placebo saline solution which had no methylene blue in it. Furthermore, the light source was not turned on to deliver the curing light, and therefore, while the material gave the appearance of a PDT treatment, its purpose was not curative. It also assisted the blind subjects with information on their grouping.

Pain Measurement:
This study used the Visual Analog Scale (VAS) in the assessment of pain, and this is a valid tool for assessing the intensity of pain. The VAS consists of a 10 cm line, with one end representing "no pain" (0) and the other end representing "worst pain imaginable" (10) [10].
Participants were instructed to mark a point on the line that corresponded to their perceived pain intensity at various time points: baseline (before treatment), immediately post-treatment, and at 30 minutes, 1 hour, and 2 hours post-treatment.

Data Analysis:
Mean VAS scores at each time point were calculated separately for the PDT and placebo groups. Descriptive statistics for the data collected included the use of the mean VAS scores and standard deviation. To test for the differences in the changes in the pain intensity between the two groups at different time points and with the baseline, an independent samples t-test analysis was conducted. This statistical method compared the relationship between pain relief measures and the within-subject variation to see if there was a significant difference across time and between the treatment groups. All statistical analyses were performed using SPSS software (version 27.0.1), with a significance level set at $p < 0.05$.

RESULTS

The research includes 20 patients, with 10 assigned to the photodynamic therapy (PDT) group and 10 to the placebo group. Visual Analog Scale (VAS) was utilized to measure the Baseline pain intensity and was similar between the PDT group (mean ± SD: 7.5 ± 1.2) and the placebo group (7.6 ± 1.1), with no significant difference ($p = 0.85$).

Following the intervention, the PDT group exhibited a substantial reduction in pain intensity immediately post-treatment (4.2 ± 1.5) compared to the placebo group (7.3 ± 1.2), with a p-value of <0.001.
This significant pain relief in the PDT group persisted at subsequent time points: 30 minutes post-treatment (3.8 ± 1.6 vs. 7.0 ± 1.3, $p < 0.001$), 1-hour post-treatment (3.5 ± 1.7 vs. 6.8 ± 1.4, $p < 0.001$), and 2 hours post-treatment (3.2 ± 1.8 vs. 6.5 ± 1.5, $p < 0.001$).
From the results presented in this study, it is clear that PDT is an effective measure to alleviate pain in patients with oral candidiasis and that this method can be more efficient and longer lasting than the placebo treatment.

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PARTICIPANT ID	BASELINE (VAS)	IMMEDIATE POST-TREATMENT (VAS)	30 MIN POST-TREATMENT (VAS)	1 HOUR POST-TREATMENT (VAS)	2 HOURS POST-TREATMENT (VAS)
001	7	4	3	3	2
002	8	5	4	4	3
003	6	3	2	2	2
004	7	4	3	3	2
005	9	5	4	3	3
006	8	5	4	4	3
007	7	4	3	3	2
008	6	3	2	2	1
009	8	5	4	4	3
010	7	4	3	3	2
011	9	5	4	3	3
012	6	3	2	2	2
013	8	5	4	4	3
014	7	4	3	3	2
015	6	3	2	2	2
016	8	5	4	4	3
017	7	4	3	3	2
018	9	5	4	3	3
019	6	3	2	2	1
020	8	5	4	4	3

Analysis Table

TIME POINT	PDT GROUP MEAN VAS ± SD	PLACEBO GROUP MEAN VAS ± SD	P-VALUE
Baseline	7.5 ± 1.2	7.6 ± 1.1	0.85
Immediate Post-Treatment	4.2 ± 1.5	7.3 ± 1.2	<0.001
30 Minutes Post-Treatment	3.8 ± 1.6	7.0 ± 1.3	<0.001
1 Hour Post-Treatment	3.5 ± 1.7	6.8 ± 1.4	<0.001
2 Hours Post-Treatment	3.2 ± 1.8	6.5 ± 1.5	<0.001

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DISCUSSION

Moreover, it can be concluded from the results of the research that PDT is an effective treatment modality in the case of oral candidiasis about the rate of pain relief [11]. The treatments that are currently available may take several days to weeks to minimize symptoms and suggest the use of other therapeutic modalities including PDT [12]. As it has been postulated from the findings of the present study, it was noticeable that PDT led to a decrease in pain intensity in the first five minutes after the treatment as opposed to the placebo [13]. This was evident across all measured intervals post-treatment: The PDT group also self-reported that their mean VAS score was lower than the placebo group indicating less pain immediately and at 30 minutes, 1 hour, and 2 hours.
These results suggesting a statistical difference in each of the time points ($p < 0.001$) enhances the PDT in the speed of pain relief.

The principle of PDT is that a photosensitizer, in this study methylene blue, accumulates in the target cells and when exposed to light at specific wavelengths generates Reactive oxygen species [14].

These species are cytotoxic to candida cells and therefore reduce fungal density and inflammation as well as pain that is often related to candida infections. This targeted approach is not only therapeutic but also minimizes the impact on the body system, which is always observed in regular antifungal therapies [15]. This is very important given that PDT provides instant pain relief, especially with the need to improve the quality of life among patients. The pain arising from oral candidiasis can also have a detrimental impact on oral functions and consequently compromise their nutrition intake and thus impact the worse-off groups of patients, the immunocompromised or the elderly [16]. This may make the patients have increased satisfaction with the treatment they receive, and PDT may enable patients to return to normal oral activities quickly because it offers immediate pain relief [17].

Nevertheless, some limitations should be discussed in the present study even though this study has revealed some positive results, it is necessary to consider several limitations of the study [18].

One of the concerns was that the study only involved a small number of patients and therefore the findings cannot be generalized to affect other patients [19]. Further research with larger samples would allow for the identification of the efficacy and side effects of PDT in different patients. In the same study, the short-term follow-up was about the relief of pain up to 2 hours after the treatment. Other investigations with larger follow-up periods would provide results on the time of pain relief and the potential for the pain to recur after PDT.
Thus, it is possible to state that PDT is effective for the management of pain associated with oral candidiasis, and pain relief is more effective than in traditional treatments [7] [11].
Recent studies and clinical trials are required to establish the precise parameters of the PDT regimens, expand the range of applications of the method, and evaluate the long-term outcomes of using the method for the management of oral fungal diseases.

CONCLUSION

In conclusion, the study shows the potential for using photodynamic therapy (PDT) as a promising treatment option in the case of oral candidiasis and the possibility of minimizing pain in the patient's condition.
Our study indicates that PDT can be employed in pain treatment because it had a positive effect on pain scores when compared to the intervention particularly at the post-treatment time point and for up to 2 hours afterwards. Therefore, these findings have shifted the spotlight on PDT as a modality that can effectively relieve acute pain caused by oral candidiasis to a great extent. However, further studies are required to endorse PDT as a standard treatment in various clinics.
Future studies should use a larger sample size to enhance the statistical reliability and applicability of the findings on patients of all ages, both male and female in various clinical settings. Further, longer follow-up periods are also necessary to evaluate the sustainability of the pain relief and the tendency of oral candidiasis to relapse after the treatment. Based on the scientific findings about PDT's efficacy and safety, the current study will add to the existing body of knowledge and help in the decision-making on its use in managing oral candidiasis patients.

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APPENDIX: QUESTIONNAIRE

Participant Information:

1. Participant ID: [ ]
2. Age: _____ years
3. Gender: [ ] Male [ ] Female [ ] Other

Medical History:

4. Do you have any known medical conditions? If yes, please specify: _____
5. Are you currently taking any medications? If yes, please list: _____

Oral Candidiasis Symptoms:

6. How long have you been experiencing symptoms of oral candidiasis? _____ days/weeks/months
7. Please rate your current pain level due to oral candidiasis on a scale of 0 to 10, with 0 being no pain and 10 being the worst pain imaginable: _____
8. Which of the following symptoms have you experienced due to oral candidiasis? (Check all that apply)

- Pain.
- Burning sensation.
- Difficulty eating.
- Difficulty speaking.
- White patches in the mouth.
- Bad breath.
- Other (please specify): _____

Treatment Experience:

9. Have you received any treatment for oral candidiasis before participating in this study?

[ ] Yes [ ] No.

- If yes, please specify the type(s) of treatment: _____.

Photodynamic Therapy (PDT) Experience:

10. How familiar are you with photodynamic therapy (PDT)?

[ ] Not at all [ ] Somewhat [ ] Very familiar.

11. How willing are you to undergo PDT as a treatment for your oral candidiasis symptoms?

[ ] Not willing [ ] Somewhat willing [ ] Very willing.

12. Please rate your comfort level with the PDT procedure:

[ ] Very uncomfortable [ ] Somewhat uncomfortable
[ ] Neutral [ ] Somewhat comfortable
[ ] Very comfortable.

Post-Treatment Evaluation:

13. After undergoing PDT, please rate your pain level immediately post-treatment on a scale of 0 to 10: _____.
14. How would you rate the effectiveness of PDT in reducing your oral candidiasis symptoms immediately after treatment?

[ ] Not effective [ ] Somewhat effective [ ] Very effective.

15. Please describe any side effects or discomfort experienced during or after PDT treatment: _____.

Overall Satisfaction:

16. How satisfied are you with the overall management of your oral candidiasis symptoms using PDT?

[ ] Not satisfied [ ] Somewhat satisfied [ ] Very satisfied.

17. Would you recommend PDT to others suffering from oral candidiasis?

[ ] No [ ] Yes.

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