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Original Article

Investigation of the therapeutic effect of Nd:YAG laser combined with kangfuxin solution on recurrent oral ulcer

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Abstract: Objective: The goal of this study was to explore the effect of Nd:YAG laser combined with kangfuxin solution in the treatment of recurrent oral ulcer (ROU). Methods: A total of 120 patients diagnosed with ROU were randomly divided into three groups: group A, group B and group C, with 40 cases in each group. The treatment effective rate, cure rate, recurrence rate, ulcer area, and ulcer pain were compared among the three groups. Results: The treatment effective rate and cure rate in group A were higher than those in group B and group C. The recurrence rate in group A was lower than that in groups B and C. In all of the three groups, the ulcer areas were smaller post-treatment compared with those in the pre-treatment period. However, the area of reduction in group A was more apparent compared with that in groups B and C. Among all three groups, the ulcer pains were improved. After treatment, the pain score in group A was significantly lower than that in groups B and C. Conclusion: Pulsed Nd:YAG laser combined with kangfuxin solution was identified to effectively increase the treatment effective rate and cure rate, and reduce the recurrence rate of ROU. It is worthy of promotion.

Keywords: Nd:YAG laser, recurrent oral ulcer, kangfuxin solution

Introduction

Oral ulcer (OU) is the most common oral mucosal disease. It is primarily caused by the loss of integrity in the oral mucosal epithelium and the epithelial defect or destruction that leads to a sunken lesion resulting from epidermal necrolysis [1, 2]. Recurrent oral ulcer (ROU) is the most common OU, accounting for more than 90% of the OU. The disease course may be recurrent in nature, but it is usually self-limiting, and it is periodically healed. The clinical course of the disease usually runs for 7-10 days with an intermittent period of 10 days to several months [3, 4]. ROU episodes may be accompanied by burning-like pain which can affect speech and eating in severe cases [5]. In some patients with severe illness or long-term delayed healing, it often brings both mental and physical stress to the patients due to long disease time. The long-lasting ulcers have the possibility of carcinogenesis [6]. This stresses the importance of active and effective treatment of ROU.

Currently, there is no standard therapeutic regimen for ROU. The selection of the appropriate treatment methods of ROU is mainly based on the patient's disease status and basic therapeutic conditions. These treatment methods may be applied systematically or locally. Systemic treatment generally includes drug therapy such as antibiotic drugs, immunomodulators, vitamins, and others [7]. Because systemic treatment is usually expensive, takes longer efficacy time, and causes severe side effects, topical medications appear to be more imperative and practical [4]. There are many methods and drugs for topical treatment, mainly including analgesia, anti-inflammation, and promotion of healing. The commonly used drugs are anti-inflammatory agents, analgesics, and immunomodulatory hormones. Topical treatment

has rapid onset of efficacy and less side effects. However, if used inappropriately, topical use of the above drugs can also have potential detrimental reactions. Adverse effects like susceptibility to Candida infection, tooth discoloration, and bitterness can greatly affect the patient's compliance [8, 9]. Thus, finding new therapeutic regimens has now become a matter of importance.

Kangfuxin solution is a biological agent that is separated and extracted from Chinese herbal medicines. It is primarily composed of active substances such as peptides, sticky sugar amino acids, stickyamino acids, and polyhydric alcohols. Studies have confirmed that it has essential functions which include anti-inflammation, mucosal repair, and improvement of immune system. The solution provides substantial protective effects on the mucosa with gastric ulcers which can significantly reduce gastric acid secretion, and can prevent gastrointestinal inflammation [10, 11]. Kangfuxin solution has also been identified to have beneficial effects on OU. The underlying mechanisms of these effects may be related to the properties of kangfuxin which promote cell proliferation, granulation tissue, vascular hyperplasia, and acceleration of the mucosal damage repair [12, 13]. In addition, the immune-enhancing properties of kangfuxin may be associated with the augmented phagocytosis of macrophages. It can also reduce T cell aggregation and increase lymphocyte activity [13, 14]. These mechanisms greatly underlie the healing of OU by using kangfuxin.

In comparison with the conventional light sources, lasers have properties that include high brightness, directionality, monochromaticity, and good coherence. Lasers have also been widely used in medicine. In the treatment of oral diseases, Nd:YAG lasers are the most widely used [15]. Nd:YAG laser is a kind of high-energy pulse laser. In the recent years, laser have been utilized for treating periodontal and mucosal diseases, which does not have features of noise, odor, and carbonation. They can effectively treat lesions even in a narrow area of the oral cavity. The Nd:YAG laser has a variety of physiological functions which include accelerating local blood circulation, eliminating inflammatory cells, killing bacteria, reducing antigen-antibody reactions and inhibiting allergic reactions [16]. Scientific evidence has established that its main mechanism of action is the thermal effect which can produce a weak warming effect on the mucosal tissues, stimulate enzyme activity in cells, enhance cell metabolism, and increase cell proliferation and differentiation and thus, ultimately repairing the mucosal tissues [17]. Furthermore, the Nd:YAG laser has biological effects. It can promote local vasodilation, improve blood viscosity, eliminate local inflammatory cells, and accelerate blood circulation. Thereby, it improves the proliferation of epithelial cells and fibroblasts that play a role in hemostasis and sterilization [18]. The Nd:YAG laser can also interfere with the transport functions of membrane pumps on neuronal cells, affect their membrane permeability, inhibit the local nerve impulse conduction and thus, producing analgesic effects [19]. Therefore, application of Nd:YAG laser in oral diseases is not only in eliminating inflammation but also in relieving pain.

Presently, there is no systematic and comprehensive study on the use of Nd:YAG laser in OU. There has been no current research on the use of the Nd:YAG laser combined with kangfuxin solution in the treatment of OU, which is primarily the focus of this study.

Materials and methods

General information

This study was approved by the Ethic Committee of Affiliated Stomatological Hospital. The patients were fully informed of the possible treatment risks and other potential treatment options in cases of poor curative outcomes. The patients' informed consents were obtained. One hundred and twenty patients with ROU diagnosed in Affiliated Stomatological Hospital from July 2015 to February 2018 were selected.

Inclusion criteria: (1) meeting the criteria for treatment of ROU formulated by the Society of Oral Mucosal Diseases, Chinese Stomatological Association; (2) a medical history of more than six months with ROU episodes occurring more than once a month; (3) presence of ulcers occurring within 48 hours and without any treatment; (4) ages of 18 to 65 years; (5) no history of corticosteroid use or other immunosuppressing drugs within one month before the

treatment and other drugs like antibiotics and vitamins within two weeks before the treatment.

Exclusion criteria: (1) patients with other oral diseases; (2) patients with severe ROU, Behcet's disease and traumatic ulcers; (3) patients with systemic diseases such as anemia, peptic ulcer, Crohn's disease, infections, tumors, and autoimmune diseases; (4) patients with severe vital organ dysfunctions such as heart, liver, kidney, and lung; (5) patients with psychiatric disorders; (6) pregnant and lactating women; (7) patients who were unable to quit smoking or drinking during treatment.

Study subjects

One hundred and twenty patients who met the criteria were selected and randomly divided into three groups. With forty cases each in a group, group A was treated with Nd:YAG laser combined with kangfuxin solution, group B received treatment with a local wet compress of kangfuxin solution, and group C only received local irradiation therapy using Nd:YAG laser.

Treatment methods

Group A: Patients were treated with Nd:YAG laser (Fotona dual-band laser therapeutic instrument) combined with kangfuxin solution (Good doctor Pharmaceutical Group, Sichuan). First, the Nd:YAG laser (with wavelength of 1,064 nm, pulse width of 0.1 ms, frequency of 20 Hz, power of 2 W, fiber diameter of 300 μm, pulse energy of 100 mJ) was utilized for performing non-contact evenly scanning movements at a distance of 1.5 mm from the ulcer surface [20]. Depending on the size of ulcer surface, each wound surface was irradiated for about 2-3 minutes using the criterion of mucosal discoloration once per day. Meanwhile, medical absorbent cotton balls soaked with about 5 mL of kangfuxin solution were used and were placed on the affected ulcer area for 30 minutes for 3 times per day. The treatment was continued for 5 days.

Group B: Wet compress with kangfuxin solution was used for treatment in this group with the same frequency and duration as mentioned above which was for 30 minutes for 3 times per day. The continuous treatment lasted for 5 days.

Group C: Only the Nd:YAG laser irradiation therapy was used for treatment in this group with the same technique as mentioned above. The treatment was continued for 5 days.

Evaluation of curative effects

Visual Analogue Scale (VAS): A 10 cm horizontal line was drawn on the paper with 0 at one end and 10 at the other end. The patient was asked to mark the pain score on this line correspondingly to the degree of ulcer pain that they were feeling with 0 as the lowest score and 10 as the highest score. The higher score represented more severe pain. The VAS score of the patient before treatment and after 5 days of treatment in an early morning fasting resting state were measured and recorded.

Measuring and recording the total ulcer area before and after treatment.

The curative effects were evaluated based on the evaluation criteria for the curative effects of ROU, along with the healing time and the degree of ulcer pain. In this study, the observation period lasted for one month. The curative effects are categorized as "Cure" which indicates no recurrence of OU within 1 month; "Markedly effective" which indicates that the ulcer healing time is ≤7 days and pain relief; "Effective" which means that the ulcer healing time is ≤7 days or pain relief; "Ineffective" which indicates that the ulcer healing time exceeds 7 days and the pain is not relieved. Total effective rate = the total number of cases ("Cure" + "Markedly effective" + "Effective"/the total number of cases * 100%. The recurrence rate = the number of cases with ulcer recurrence within one month of the observation period/the total number of cases * 100% [21].

Safety evaluation

If adverse reactions (i.e. burns in the mucosa, ulcers significantly aggravated during the treatment) were to occur during the treatment, the treatment must be stopped. Other treatment methods (i.e. hormones and anti-inflammatory antibacterial drugs) should then be selected. These patients were recorded as ineffective cases. Patients who dropped out from the treatment because of personal reasons were counted as ineffective cases. Patients who

Table 1. Comparison of general data

Group	Age (year old)	Sex		Course of disease (year)
		Male (case)	Female (case)	
Group A	45.81±8.73	23	17	2.58±0.83
Group B	42.52±9.86	19	21	2.49±0.97
Group C	43.61±7.91	22	18	2.63±0.69
P	0.648	0.621		0.625
F/χ^2	4.317	5.363		5.874

Table 2. Comparison of ulcer pain before and after treatment in the three groups of patients

Group	Before treatment (score)	After treatment (score)	P	t
Group A	7.23±1.53	2.41±1.25	<0.001	38.72
Group B	7.46±1.32	5.22±1.18*	0.025	25.41
Group C	7.38±1.47	4.87±1.56*	0.036	23.63
P	0.836			
F	3.574			

Note: Compared with group A, *P<0.01.

Table 3. Comparison of ulcer area before and after treatment in the three groups of patients

Group	Before treatment (cm^2)	After treatment (cm^2)	Degree of reduction (%)	P	t
Group A	1.14±0.32	0.26±0.09	77.20	<0.001	19.57
Group B	1.09±0.48	0.73±0.14**	33.00**	0.042	8.69
Group C	1.35±0.21	0.69±0.17**	48.90**	0.019	12.83
P	0.815				
F	4.251				

Note: Compared with group A, **P<0.001.

could not be observed for one month due to various reasons were also recorded as ineffective cases.

Data analyses

For data analysis, SPSS17 software was used. The results are expressed as mean ± standard deviation ($\bar{x}$ ± sd). The Chi-square segmentation test was used for comparisons of rates among the three groups. The comparison between groups was performed using one-way analysis of variance and LSD-t test. The paired t-test was used for comparisons before and after treatment within each group. P<0.05 indicates that the difference is statistically significant.

Results

Comparison of general data

There were no significant differences in age, gender, and duration of disease among the three groups (all P>0.05) as shown in **Table 1**.

Comparison of ulcer pain before and after treatment in the three groups of patients

The mean pain score was generally lower after treatment in the three groups, but the VAS score in group A was significantly lower than that in group B and group C (P=0.003, t=16.84; P=0.005, t=15.68). There was no significant difference between groups B and group C (P=0.618, t=4.53) as shown in **Table 2**.

Comparison of ulcer area before and after treatment in the three groups of patients

The ulcer area was decreased after the treatment in all three groups. However, the reduction of ulcer area in group A was significantly greater than that in group B and group C (P< 0.001, t=26.54; P<0.001, t=27.18). There was no significant difference between groups B and C (P=0.529, t=5.14) as shown in **Table 3**.

Evaluation of treatment effects in the three groups of patients

The three treatment methods all had effects, but the cure rate and effective rate in group A were significantly higher than those in groups B and C (all P<0.001; χ^2=28.65, χ^2=22.81, χ^2=25.74, χ^2=23.62), and the recurrence rate was significantly lower than that of the groups B and C (both P<0.001; χ^2=21.49, χ^2=26.19); there were no significant differences in cure rate, effective rate, and recurrence rate between groups B and C (P=0.615, χ^2=3.91; P=0.437, χ^2=5.36; P=0.516, χ^2=4.81) as shown in **Tables 4**, **5**.

Adverse reactions

One case of mucosal redness occurred in group A. No adverse reactions were observed in the

Table 4. Evaluation of treatment effects in the three groups of patients (case)

Group	Cure	Markedly effective	Effective	Ineffective
Group A	8	11	16	5
Group B	2	5	10	23
Group C	3	7	11	19

Table 5. Cure rate, effective rate, and recurrence rate in the three groups of patients (%)

Group	Cure rate	Effective rate	Recurrence rate
Group A	20.00	87.50	10.00
Group B	5.00**	42.50**	62.50**
Group C	7.50**	52.50**	57.50**

Note: Compared with group A, **P<0.001.

other two groups. There were no differences in adverse reactions among these groups (P= 0.842, χ^2=6.31).

Discussion

This study found that both treatments using Nd:YAG laser and kangfuxin solution have certain therapeutic effect on ROU. The ulcer area and ulcer pain were generally improved after treatment. However, the relief effect in each treatment method alone was weaker than that of the combination of these two methods. Studies have shown that the effective rate of ROU treated with kangfuxin solution alone could reach over 70.00%, and the effective rate of ROU treated with Nd:YAG laser alone was about 80.00% [22, 23]. Nonetheless, both of these treatment methods when used alone can result to greater susceptibility to recurrence with less cure rates.

A study confirmed that the combined use of kangfuxin solution and Nd:YAG laser had a good therapeutic effect on OU in patients with Acquired Immunodeficiency Syndrome (AIDS) [24]. The therapeutic efficacy is better compared with either treatment method alone. However, due to the less population of AIDS patients with OU, there was not enough population sample size for research. Several AIDS patients also have many complications that can affect the long-term observation indexes, so it was not possible to confirm whether there was any significant difference in the recurrence rate. Currently, no studies has shown the therapeutic effect of combined use of kangfuxin solution and Nd:YAG laser on ROU.

In this study, it was determined that the effective rate, cure rate and recurrence rate of the combined use of kangfuxin solution and Nd:YAG laser in the treatment of ROU was 87.50%, 20.00%, and 10.00%, respectively. This was significantly better than that of either treatment method alone. Additionally, this study concluded that the combination of kangfuxin solution and Nd:YAG laser did not increase the incidence of adverse reactions, indicating that this treatment combination can effectively treat ROU. The number of patients with recurrence was significantly reduced and the adverse reactions did not increase, which are both valuable in clinical applications.

Although this study confirmed that the combination of kangfuxin solution and Nd:YAG laser had a good therapeutic effect on ROU, the specific underlying mechanisms were not explored in this study and thus, remain unknown. As mentioned beforehand, both kangfuxin solution and Nd:YAG laser have functions in eliminating inflammation and repairing mucous membrane. Even though the single use of either treatment method has anti-inflammatory and mucosal repair properties, the improved effects of combined use may be due to the synergistic effect of them; but the specific mechanism is not clearly confirmed. The synergistic anti-inflammatory effect can be verified by extracting the surface secretions from the ulcer surface to compare the concentration of inflammatory factors in the secretions. This requires further research and investigation.

This study has several limitations due to time constraints. Only one Nd:YAG laser wavelength and energy was selected. OU was treated under these laser data conditions only and the effects of OU treatment using other laser data conditions were not confirmed in this study. It may also be possible that the effects of Nd:YAG laser using other laser data conditions in the treatment of OU can also be more apparent, which are potentially more appropriate wavelength and energy. This is another good subject for further research. Currently, there is no existing literature to prove which kind of laser wavelength is more appropriate. If it is needed to be confirmed further, Nd:YAG lasers with multiple energy density should be selected for treating

ROU. By comparing the effects and adverse reactions of ulcer treatment, the most suitable wavelength energy can then be selected for the generalization of ROU therapy.

Disclosure of conflict of interest

None.

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