ORIGINAL RESEARCH

Clinical Effect of Vitamin E Combined with Recombinant Human Epidermal Growth Factor on the Recurrent Oral Ulcer and Effects of Serum Superoxide Dismutase, IL-10, and TNF-α

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ABSTRACT

Objective • To examine the therapeutic effects of vitamin E combined with recombinant human epidermal growth factor on recurrent oral ulcers as well as on the levels of serum superoxide dismutase (SOD), interleukin-10 (IL-10), and tumor necrosis factor- (TNF-α), to provide evidence to facilitate medical management.

Method • From June 2021 to May 2022, 84 patients with recurrent oral ulcers assessed and treated in our hospital were assigned to the control group and observation group with 42 cases in each group. Vitamin E was administered to the control group, while recombinant human epidermal growth factor and vitamin E were administered to the observation group. The clinical efficacy, serum SOD level, inflammatory factor level (IL-10, TNF-α), immune function index, clinical symptom improvement, pain disappearance time, healing time of ulcer surface, and adverse reactions were examined.

Results • Clinical efficacy of the observation group (92.86%) was considerably greater than the control group (73.81%), ($P < .05$). Following treatment, the observation group had comparatively higher levels of serum SOD and significantly decreased TNF-α and IL-10 concentrations compared to the control group ($P < .05$). Similarly, post-treatment, the observation group had substantially higher CD3+, CD4+, and CD4+/CD8+ concentrations and lower CD8+ concentrations compared to the normal control ($P < .05$). In contrast to the control group, the observation group's pain degree score, ulcer diameter, duration for pain relief, and ulcer surface healing time duration were reduced substantially ($P < .05$). Notably, the incidence of adverse reactions was fairly similar in both groups ($P > .05$).

Conclusion • Vitamin E combined with recombinant human epidermal growth factor has a significant clinical effect on recurrent oral ulcers, can achieve rapid improvement of symptoms in patients, and is relatively safe to be used as a clinical therapy. (*Altern Ther Health Med.* 2024;30(4):113-117)

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INTRODUCTION

Oral ulcer is a relatively common oral disease in clinical practice, with an incidence of 10%-25%, and young women are prone to it.[1] The ulcers are usually located in the oral mucosa such as the tongue, lip, soft palate, etc., with a low degree of keratosis, and the ulcers are usually round or oval.[2] The ulcer surface pain is the main symptom of the disease which impacts diet and speech. At the same time, this disease is prone to relapse, and its recurrence seriously affects patients' mental state and quality of life.[3] The pathophysiology of this disorder is yet unknown. From our current understanding, it could be caused by a deficiency in trace elements, dysfunction of some oral bacteria, low immune system, and microcirculation issues.[4] Since it is very difficult to treat recurrent oral ulcers, it is necessary to explore an effective and safe treatment method.

Vitamin E has antioxidant effects which can inhibit the peroxidation of unsaturated fatty acids in the oral mucosa, remove the cytotoxic effect of peroxides on the ulcerative surface, improve the oral lipid metabolism, promote the proliferation of small vessels on the ulcerative surface, improve the cell vitality of the ulcerative surface, and contribute to the healing of the ulcerative surface.[5] Vitamin E is known to regulate redox balance in the body due to its high concentration among the lipid-soluble vitamin groups and exists ubiquitously in the whole body. The recombinant human epidermal growth factor can promote wound repair and healing and has been widely used in healing wound and burn.[6]

This study aims to analyze the clinical efficacy of vitamin E combined with recombinant human epidermal growth

factor on recurrent oral ulcers as well as on the levels of serum superoxide dismutase (SOD), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α), to provide evidence to facilitate medical management and the clinical development of a safe and effective treatment program.

DATA AND METHODS

Baseline Data

42 cases in each group were chosen from a total of 84 patients with recurrent oral ulcers who were identified and treated at the stomatology department of our hospital between June 2021 and May 2022. Control group: 18 males and 24 females; the average age was (38.74 ± 5.32) years, ranging from 18 to 64 years. The course of the disease ranged from 1 to 7 years, with an average of (2.84 ± 0.76) years. Severity: I degree 19 cases, II degrees 13 cases, and III degrees 10 cases. Observation group: 17 males and 25 females; the average age was (38.79 ± 5.30) years. The course of the disease ranged from 1 to 7 years, with an average of (2.88 ± 0.74) years. Severity: I degree 19 cases, II degrees 12 cases, and III degrees 11 cases.

Our study was approved by the institutional review board of the hospital and was conducted in accordance with the ethical principles.

Inclusion and exclusion criteria

Inclusion criteria: (1) complete medical record; (2) Age range from 18 to 64 years; (3) The clinical symptoms and oral examination confirmed that the diagnosis of recurrent oral ulcers met the requirements in oral mucosa: (i) the lesions were mainly located in the mucosa such as tongue, lip, and buccal and soft palate, with different sizes and shapes; (ii) yellow, red, concave, and pain symptoms; (iii) it has the characteristics of recurrence, periodicity, and self-limiting; (iv) a history of recurrent oral ulcer > 6 months; (v) occurs at least once every 3 months; (4) The duration of the disease was < 3d; (5) Knows the research content and agreed to participate.

Exclusion criteria: (1) Serious diseases of major organs; (2) Severe infection; (3) Diseases of the blood system; (4) Immune dysfunction; (5) Mental illness; (6) Pregnant and lactating women; (7) There are contraindications for study drugs; (8) Poor compliance.

Treatment methods

Control group: Vitamin E treatment. Prick two soft capsules of vitamin E (Jilin Huagang Pharmaceutical Co., LTD., National medicine license number H22022956) and make a paste. Use a sterilized cotton swab to dip in the appropriate amount and apply it on the ulcer surface. Do not drink or eat for 10 minutes after application, 3-4 times/day.

Observation group: Vitamin E combined with recombinant human epidermal growth factor treatment. The vitamin E treatment method was the same as the control group. Recombinant human epidermal growth factor treatment methods: patients with the degree I were treated with cotton tablets dipped in recombinant human epidermal growth factor gel (Guilin Huanowei Gene Pharmaceutical Co., LTD., National medicine approval number S20020112), and applied on the ulcer surface, twice a day; For degree II and III patients, spray 5000U/mL liquid into the mouth, after meals and before bed, twice a day. Do not drink or eat for 30 minutes after medication.

Both groups were treated for 7 days, during which patients were instructed to eat a light diet, avoid irritation of oral mucosa, and pay attention to oral hygiene.

Observation Indicators

The clinical efficacy, serum SOD level, inflammatory factor level, immune function index, improvement of clinical symptoms, pain disappearance time, healing time of ulcer surface, and adverse reactions of the two groups were statistically evaluated.[2] (1) Clinical effect: after treatment, it can be divided into: (i) Obvious effect: symptoms disappear, the oral ulcer surface heals, and the mucosal congestion in the area near the ulcer disappears; (ii) Effective: the symptoms were improved, the healing area of oral ulcer surface was > 60%, and the mucosal congestion near the ulcer area was reduced. (iii) Ineffective: symptoms did not improve significantly, the healing area of the oral ulcer was < 60% and the mucosal congestion in the area near the ulcer was not significantly reduced. Total effective rate = (number of effective cases + number of effective cases)/total cases ×100%.[7] (2) Serum SOD level: measured before and after treatment, fasting blood was collected in the morning, and an enzyme-linked immunosorbent assay was used. The kit was derived from Shanghai Huyu Biotechnology Co., LTD., and the instructions were followed.[8] (3) Before and after therapy, the levels of inflammatory substances like IL-10 and TNF-α were assessed. Early in the morning, fasting blood was drawn and an enzyme-linked immunosorbent assay was performed. The kit was obtained from Shanghai Huyu Biotechnology Co., LTD., and the instructions were followed.[9] (4) Indicators of immune function: CD3+, CD4+, CD8+, and CD4+/CD8+ were measured before and after treatment, blood samples were collected on an empty stomach in the morning, and automatic flow cytometry was used for detection.[10] (5) Improvement of clinical symptoms, including pain degree and ulcer diameter, were evaluated before and after treatment. Pain degree: a visual analog scoring method was adopted, with a total score of 10, and the lower the score, the better.[11] (6) Time of pain disappearance and healing time of ulcer surface. (7) Adverse reactions: During the medication period, observations were recorded, including gastrointestinal reactions, vertigo, and rash, and the total incidence was calculated.

Data Statistics

SPSS 22.0 software was used, and the counting and measurement data were expressed as % and ($\bar{x} \pm s$) respectively. χ^2 and t tests were performed. For multiple comparisons, data were analyzed via analysis of variance (ANOVA). The computational significance was established at $P < .05$.

RESULTS

Comparison of clinical efficacy between the two groups after treatment

The baseline data for the control and the observation groups in terms of general characteristics showed no discernible difference ($P > .05$). The study revealed that the observation group has considerably higher clinical efficacy than the control group ($P < .05$). The clinical efficacy of the control group was 73.81% while that of the observation group was 39.86% (Table 1).

Comparison of serum SOD levels between the two groups before and after treatment

Before therapy, the serum SOD levels in the control group (237.19 ± 36.36 U/L) and the observation group (241.26 ± 35.11U/L) were comparable ($P = .302$). After treatment, the observation group's serum SOD level was 294.13 ± 40.27 U/L, which had increased more than that of the comparison group (260.12 ± 38.50 U/L), and this difference was statistically significant ($P = .000$), as shown in Table 2.

Comparison of the levels of inflammatory factors before and after treatment between the two groups

Before treatment, there was no statistically significant difference in the levels of IL-10 and TNF-α between the two groups ($P > .05$). After treatment, the observation group's IL-10 and TNF-α concentrations significantly decreased compared to the control group, and this variation was statistically meaningful ($P < .05$), as shown in Table 3.

Comparison of immune function indexes between the two groups before and after treatment

Before treatment, there was no discernible difference in the concentrations of CD3+, CD4+, CD8+, or CD4+/CD8+ between the two groups ($P > .05$). After treatment, the observation group's levels of CD3+, CD4+, and CD4+/CD8+ were greater compared to the control group, while the concentrations of CD8+ in the former were reduced compared to the latter. These variations were statistically significant ($P < .05$), as shown in Table 4.

Comparison of the improvement of clinical symptoms between the two groups before and after treatment

Before treatment, there was no discernible difference between the two groups in terms of pain intensity score or ulcer diameter ($P > .05$). However, the observation group's ulcer diameter and pain degree score significantly reduced following the therapy compared to the control group, and this variation was statistically significant ($P < .05$), as shown in Table 5.

Comparison of pain disappearance time and healing time of the ulcer surface between the two groups

The time of pain disappearance and the healing time of the ulcer surface were compared between the two groups. The observation group experienced faster pain relief and ulcer surface healing than the normal control, and this variation was statistically meaningful ($P < .05$), as shown in Table 6.

Table 1. Comparison of Clinical Efficacy Between the Two Groups of Patients [n (%)] After Treatment

Grouping	Number of patients	Obvious effect	Effective	Ineffective	Clinical efficacy
Control group	42	19	12	11	31 (73.81)
Observation group	42	26	13	3	39 (92.86)
χ^2 value	-	-	-	-	5.486
P value	-	-	-	-	.019

Table 2. Comparison of Serum SOD Levels ($\bar{x} \pm s$, U/L) Between the Two Groups Before and After Treatment

Grouping	Number of examples	Before treatment	After treatment
Control group	42	237.19 ± 36.36	260.12 ± 38.50
Observation group	42	241.26 ± 35.11	294.13 ± 40.27
t test	-	0.522	3.956
P value	-	.302	.000

Table 3. Comparison of Inflammatory Factor Levels ($\bar{x} \pm s$) Between the Two Groups Before and After Treatment

Grouping	Number of examples	IL-10 (ng/L)		TNF-α (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	42	18.35 ± 3.22	14.38 ± 2.51	16.36 ± 4.18	13.37 ± 3.17
Observation group	42	18.40 ± 3.24	11.79 ± 2.10	16.40 ± 4.16	10.38 ± 2.59
t value	-	0.071	5.129	0.044	4.734
P value	-	.472	.000	.483	.000

Table 4. Comparison of Immune Function Indexes ($\bar{x} \pm s$) Between the Two Groups Before and After Treatment

Grouping	Number of examples	CD3+ (%)		CD4+ (%)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	42	50.61 ± 5.53	55.23 ± 6.16	38.03 ± 4.78	42.33 ± 4.96
Observation group	42	50.57 ± 5.48	59.54 ± 6.89	37.90 ± 4.80	46.60 ± 5.29
t value	-	0.033	3.022	0.124	3.816
P value	-	.487	.002	.451	.000

Grouping	CD8+ (%)		CD4+/CD8+	
	Before treatment	After treatment	Before treatment	After treatment
Control group	29.96 ± 4.22	27.35 ± 4.96	1.09 ± 0.41	1.25 ± 0.47
Observation group	30.00 ± 4.19	25.47 ± 4.32	1.06 ± 0.37	1.46 ± 0.52
t value	0.044	1.852	0.352	1.942
P value	.483	.034	.363	.028

Table 5. Comparison of Clinical Improvement ($\bar{x} \pm s$) Between the Two Groups Before and After Treatment

Grouping	Number of examples	Pain level (points)		Ulcer diameter (mm)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	42	3.25 ± 0.82	2.04 ± 0.65	2.54 ± 0.76	1.62 ± 0.41
Observation group	42	3.29 ± 0.80	1.43 ± 0.40	2.57 ± 0.74	1.05 ± 0.35
t value	-	0.226	5.180	0.183	6.853
P value	-	.411	.000	.428	.000

Table 6. Comparison of Pain Disappearance Time and Ulcer Surface Healing Time Between the Two Groups ($\bar{x} \pm s$, days)

Grouping	Number of examples	Time for the pain to disappear	Ulcer surface healing time
Control group	42	3.54 ± 0.67	4.85 ± 1.06
Observation group	42	2.72 ± 0.55	3.17 ± 0.79
t value	-	6.131	8.236
P value	-	.000	.000

Table 7. Comparison of Adverse Reactions in the Two Groups [n (%)]

Grouping	Number of examples	Gastrointestinal reactions	vertigo	rash	Total incidence
Control group	42	1	1	0	2 (4.76)
Observation group	42	1	1	1	3 (7.14)
χ^2 value	-	-	-	-	.213
P value	-	-	-	-	.645

Comparison of adverse reactions between the two groups

Among the two groups, there was no discernible variation in the overall frequency of adverse responses ($P > .05$). The total incidence rate of the control group was 4.76%, which was significantly lower than that of the observation group (7.14%), as summarized in Table 7.

DISCUSSION

The recurrent oral ulcer is a chronic inflammatory disease treated in the department of stomatology. The surface of the ulcer is often covered by a fibrin pseudo-membrane, and the lesion site can be single or multiple with shallow depth but the pain is obvious, which is often aggravated by eating food.[12] This disease throughout the year, regardless of age or race.[13] The general form of the disease is a superficial yellow or white membrane, adjacent to the mucous membrane hyperemia. Although the disease is self-healing and can subside by itself within 1 to 2 weeks, it is prone to repeated onset and often presents burning pain when it recurs, which will seriously affect eating and cause speech dysfunction.[14] Clinical studies have found that patients often feel local burning 2~48 hours before the appearance of oral ulcers. However, the etiology of this disease has not been clarified, and it is currently believed to be caused by the combined influence and action of multiple factors.[15] At the early stage of this disease, dense lymphatic and monocyte infiltration will occur in lamina propria and adjacent epithelium and around blood vessels, followed by the infiltration of prokaryotic leukocytes and plasma cells. After epitheliolysis, capillaries will be congested, small blood vessel walls will become thick, the lumen will be blocked, and small localized necrotic areas will appear.[16]

At present, the main objective of clinical treatment of this disease is to quickly relieve patients' pain and promote the healing of ulcer surfaces.[17] Vitamin E is insoluble in water, has good stability to heat and acid, has no odor, and is easier for patients to accept. It is used locally on the oral ulcer wound, which can effectively improve oral lipid metabolism, promote peripheral blood vessel dilation, accelerate the proliferation of small blood vessels on the ulcer wound, and improve the cell activity on the ulcer surface. Vitamin E will also be synthesized with cell deoxyribonucleic acid, can stabilize cell membrane, protect T lymphocytes and red blood cells against free radical oxidation, so that the oral ulcer site is not infected by bacteria, and thus accelerate wound healing. In addition, the Vitamin E can also inhibit the growth of oral *Helicobacter pylori*, and help to control the inflammatory response. The recombinant human epidermal growth factor is an endogenous growth factor, which can exert a certain influence on the cell cycle of target cells, promote cell division and reproduction, and stimulate epidermal cells, which can accelerate the reproduction and repair of wounds. Biologically, Vitamin E is produced using deoxyribonucleic acid biological recombination technology, which has a significant effect on mucosal wound repair. In the treatment of oral ulcers, the Vitamin E can speed up the time of pain disappearance, promote the healing of the oral ulcers, improve the expression and distribution of cell growth factors, reduce inflammation, and enhance immune function. The combined application of vitamin E and recombinant human epidermal growth factor can exert their synergistic effects to better control inflammation and promote wound healing. In this study, the effects of vitamin E alone and vitamin E combined with recombinant human epidermal growth factor treatment were compared. The results showed that the clinical efficacy of the observation group (92.86%) was considerably higher than the normal group (73.81%), ($P < .05$), indicating that the combined treatment could obtain significantly higher curative effect and contribute to the control of patients' disease, thus favoring the combined application of the two drugs which can achieve the therapeutic effect of "1+1>2".

It has been reported that the serum SOD level of patients with recurrent oral ulcers is lower than that of healthy people while the SOD level in saliva is higher than that of healthy people. It is suggested that the antioxidant balance in patients with recurrent oral ulcers is disturbed, which may be one of the factors affecting the occurrence of the disease. The analysis of data revealed that the serum SOD levels of the observation group after treatment were higher than the normal control, suggesting that the observation group has improved antioxidant activity. This indicates that the combination of drugs can further enhance the antioxidant capacity of the body, which helps to improve the body's immunity. Inflammation is the main pathological basis of this disease.[18] Inflammatory cytokines (such as IL-10, TNF-α, etc.) play a significant role in immune regulation, damage repair, and other aspects.[19] According to clinical investigations, patients with recurrent oral ulcers had higher serum levels of IL-10 and TNF-α than normal individuals. Therefore, lowering levels of inflammatory cytokines could help patients better manage their disease. According to the findings of the study, IL-10 and TNF-α levels in the observation group following treatment were decreased compared to the normal control, indicating that the inflammatory response of patients in the observation group was better improved, indicating that combined treatment could more effectively inhibit the inflammatory response in the body. The underlying mechanism is possibly directly related to the anti-inflammatory effect of recombinant human epidermal growth factor. Studies have shown that patients with this disease often show abnormal changes in T cell subsets, in which CD4+ and CD8+T lymphocytes play a significant regulatory role.[20] CD4+/CD8+ is the main reference index for clinical evaluation of immune regulation ability. In the

population of recurrent oral ulcers, there is often a trend of decreasing CD4+ cells, increasing CD8+ cells, and decreasing CD4+/CD8+ levels. Therefore, it is thought that the occurrence and progression of the disease may be linked to aberrant cellular immunological activity. Consequently, it is essential to raise the patient's immunological response indexes. After treatment, levels of CD3+, CD4+, and CD4+/CD8+ elevated while CD8+ declined in both groups. However, the changes in the observation group were noticeably more than the control group. This suggests that the immune function indexes of patients in both groups had been improved; however, the improvement was more significant in the observation group. These results indicate that vitamin E combined with recombinant human epidermal growth factor therapy can improve the immune function of patients, enhance the body's immunity, and promote the faster healing of oral ulcers.

Local pain is a common symptom of a recurrent oral ulcer. Reduced negative emotions and increased comfort are two benefits of pain relief for patients. This study investigated how patients' pain changed before and after therapy. The outcomes showed that although patients in the control group and the observation group experienced less pain overall, the observation group's experience of pain was milder, suggesting that combined treatment can achieve better pain relief for patients. The findings further supported the benefits of combination therapy for pain reduction by demonstrating that the observation group's duration of pain elimination was quicker compared to the control group. The ulcer diameter of the observation group after treatment was less than the control group, and the ulcer surface healed more quickly in the observation group. These results indicate that the observation group's wound healing was more efficient and quicker, thus supporting the fact that combined treatment could promote wound healing and accelerate ulcer healing.

The total incidence of adverse reactions in both groups was comparable from the standpoint of safety analysis, indicating that both therapies were equally safe. Thus, this indicates that the addition of recombinant human epidermal growth factor in the treatment of recurrent oral ulcers would not cause an increase in adverse reactions, implying that the safety of this drug is good.

CONCLUSION

In summary, it is concluded that vitamin E combined with recombinant human epidermal growth factor has a significant clinical effect on the recurrent oral ulcer, and can achieve rapid improvement of symptoms in patients. In addition to high clinical efficacy, the combined therapy is relatively safe, thus being popularized and used as a clinical therapy.

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AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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