BMC Oral Health

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Tinidazole mouth rinse for the treatment of oral lichen planus: an observational pilot study

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Abstract

Background Given the limited treatment options available for oral lichen planus (OLP), a study was undertaken to obtain preliminary information on the therapeutic efficacy of tinidazole mouth rinse in patients with OLP.

Methods A prospective, open-label pilot study was conducted to assess the efficacy of thrice-daily tinidazole mouth rinse for one week in OLP patients ($n=27$). Reticulation/erythema/ulceration (REU) scores and visual analog scale (VAS) scores were used to measure lesions at baseline and after one week of treatment. Mucosal samples were collected, and the abundance of *Fusobacterium nucleatum* was quantified using RT-PCR. Statistical analysis using t-test, Wilcoxon signed rank test and Pearson correlation test.

Results After treatment, VAS scores significantly decreased in both reticular ($P=0.03$) and erosive OLP patients ($P=0.003$). However, REU scores significantly decreased only in erosive OLP patients ($P=0.002$). The relative abundance of *Fusobacterium nucleatum* on the damaged mucosa surface significantly decreased in all OLP patients ($P=0.01$). In erosive OLP patients, the triamcinolone group showed a significantly greater improvement in VAS scores compared to the tinidazole group ($P=0.01$). However, there was no statistically significant correlation between the relative abundance of *Fusobacterium nucleatum* and REU scores in OLP patients ($r=0.0754$, $P=0.61$).

Conclusion Tinidazole mouth rinse showed potential in reducing disease severity in OLP patients and was well-tolerated, suggesting its viability as a local therapeutic option. However, randomized controlled studies are warranted to confirm these preliminary findings.

Keywords Oral lichen planus, Tinidazole mouth rinse, *Fusobacterium nucleatum*

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Introduction

Oral lichen planus (OLP) is an immune-mediated chronic inflammatory disease affecting various oral mucosal sites. The clinical presentations of OLP are diverse, including reticular, atrophic, ulcerative, and plaque-like lesions [1, 2]. The global pooled prevalence of OLP was 1.01% [3]. Although factors such as genetics, emotional stress, immunology, infections, and hormonal levels have been proposed as potential contributors, the precise etiology of LP remains unknown [4]. The semi-quantitative reticulation/erythema/ulceration (REU) scoring system has been widely recognized and used to assess the severity of OLP [5]. Topical corticosteroids are the first-line treatment for OLP, however, some patients do not respond to corticosteroids [6].

In recent years, microbial infections have attracted much attention in the pathogenesis of OLP. Several recent studies have found significant differences in the diversity and composition of microbial communities in the saliva and tissue samples of OLP patients compared to healthy subjects [7–9]. Notably, our previous research established a correlation between the increased abundance of *Fusobacterium nucleatum*, a gram-negative anaerobic bacterium, and OLP [10]. A clinical study has shown that metronidazole can be used as an alternative therapy for LP and is a safe drug to be considered [11]. Recently, a retrospective cohort study indicated that a significant portion of OLP patients experienced symptom improvement following treatment with metronidazole [12]. The mouth rinse makes contact with hard-to-reach crevices and surfaces at the far end of the mouth, preventing new lesions from developing [13]. However, the clinical efficacy of mouth rinse containing nitroimidazole drugs was never investigated in clinical trials.

Tinidazole, a type of nitroimidazole, exhibits selective activity against anaerobic bacteria. Its extended half-life and fewer adverse reactions compared to metronidazole make it an attractive therapeutic choice [14]. We conducted a prospective clinical trial to evaluate the short-term efficacy of tinidazole mouth rinse in alleviating the symptoms of OLP. Additionally, we analyzed the changes in the abundance of *Fusobacterium nucleatum* before and after treatment and investigated whether these changes significantly correlated with the treatment efficacy for OLP.

Methods

Study design and treatment with study drug

It was a prospective, open-label, self-controlled pilot study. Tinidazole mouth rinse (Zhejiang Hacon Pharmaceutical Co., Zhejiang, China) was uniformly dispensed to OLP patients by the pharmacy of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine and equipped with a 10mL container. Twenty-seven eligible participants were enrolled in the clinical trial. The selection of the sample size was determined by feasibility considerations rather than formal power calculations, which is suitable for the exploratory nature of the study. Participants were instructed to use the mouth rinse as directed in the leaflet, which specified a tinidazole concentration of 8 mg/ml. They should rinse their mouth with 5 ml of this solution three times a day, swishing for 1 min each time, for a duration of 1 week, followed by a follow-up after one week. (Fig. 1). Concurrent use of other medication effective against OLP was prohibited during treatment and follow-up periods.

Enrollment of participants

The OLP patients who visited to the Department of Oral Medicine, School of Stomatology, Shanghai Jiao Tong University, from May 2019 to May 2020 were recruited. OLP participants were diagnosed by two experienced oral medicine professionals and confirmed by histopathological examination. Fifteen reticular OLP patients and thirteen erosive patients were included in the study. The diagnosis of OLP is based on the World Health Organization criteria (1978) and modified by Van Der Meij and Van Der Waal: [15](1) presence of bilateral symmetric lesions; (2) presence of lace-like network of slightly raised gray-white lines (reticular, annular or linear pattern), with atrophies or erosions or ulcerations. Patients range in age from 18 to 65. Reticular OLP patients refer to those with fine white lines or striae and no erosive lesions, while those with erosive lesions are erosive OLP patients.

The exclusion criteria were as follows: (a) a history of allergies to nitroimidazoles; (b) received any treatment for OLP in the previous 3 months; (c) positive for bleeding on probing; (d) visible untreated caries or lesions; (e) pregnancy or lactation; (f) severe systemic disease; (g) smoking history; (h) used prescription drugs including antibiotics or glucocorticoids for 3 months. All participants provided written informed consent before enrollment. This study was approved by the Ethics Committee of the Shanghai Ninth People's Hospital affiliated with Shanghai Jiao Tong University School of Medicine.

Clinical assessment and sample collection

The visual analogue scale (VAS) score is a subjective scale used to express different degrees of pain experienced by a person and to quantify pain symptoms. A score of 0 means no pain, and a score of 10 means the most severe pain that is unbearable. The REU scoring system described previously was used to assess the clinical signs in this trial [5]. Briefly, the oral cavity was divided into 10 areas, and the severity of lesion at the above 10 sites was evaluated based on the presence or absence of reticular/hyperkeratotic/white popular (R) lesions, as well as

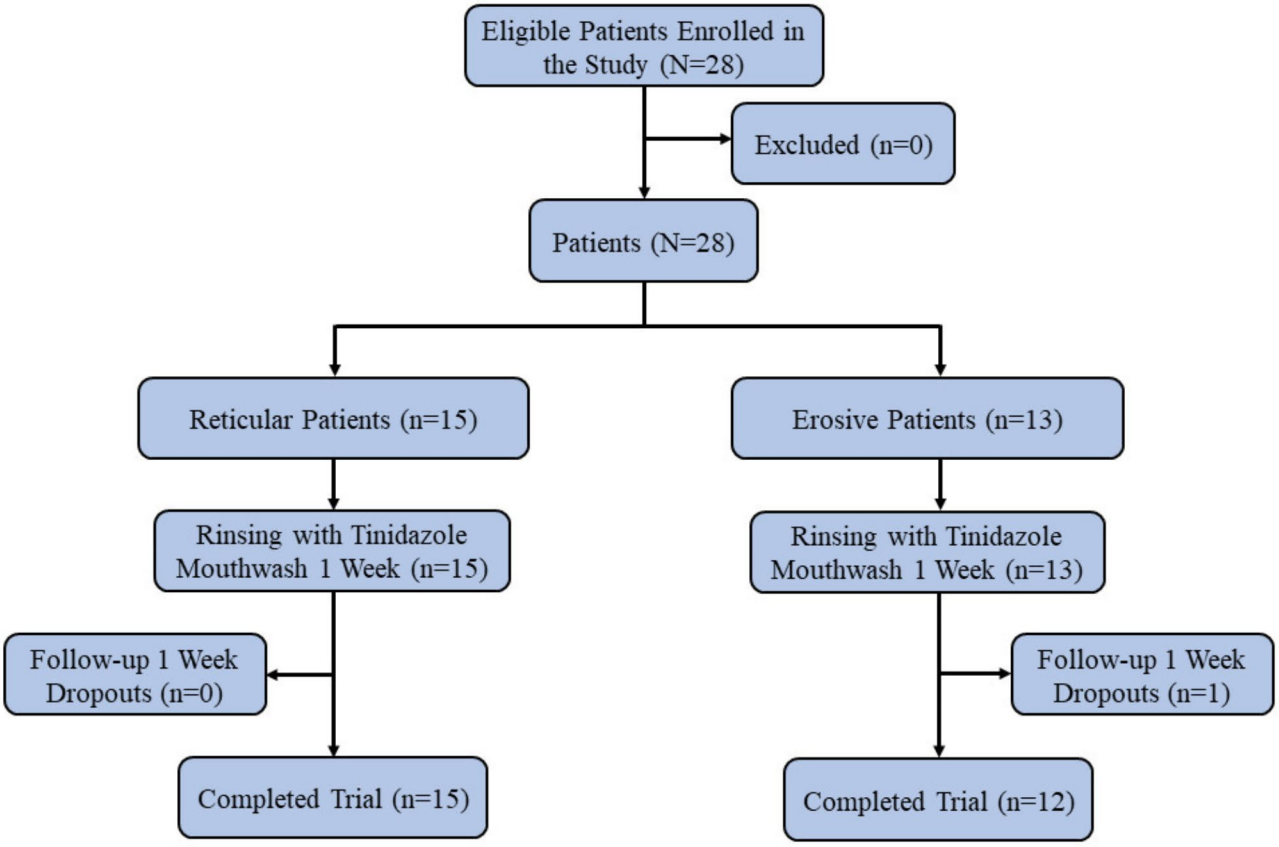

Fig. 1 Study flowchart

the area of erosive/erythematous (E) and ulcerative (U) lesions as follows: reticular/hyperkeratotic/white popular were scored from 0 to 1 (0=no white striations, 1=presence of white striations or keratotic papules); erosive/erythematous areas were scored from 0 to 3 by area of involvement (0=no lesion, 1=lesions less than 1 cm [2], 2=lesions from 1 to 3 cm [2], 3=lesions greater than 3 cm [2]); ulcerative areas were scored from 0 to 3 by area of involvement (0=no lesion, 1=lesions less than 1 cm [2], 2=lesions from 1 to 3 cm [2], 3=lesions greater than 3 cm [2]).The final weighted REU score was a summation of reticular score, erythematous score (weighted 1.5), and ulcerative score (weighted 2.0) for all 10 sites. The observers used a periodontal probes (Hu Friedy®, Chicago, USA) to calculate the size of the damaged area. At the start of the study and 1 week later, treatment was evaluated according to the approach previously described by Carozzo and Gandolfo (complete remission: disappearance of all ulcerative lesions with/without remaining mild striae; partial response: improvement without complete healing of the ulcerative lesions; no response: worsening or absence of any improvement of the lesions) [16]. All outcomes were recorded by another independent examiner.

Each subject gently gargled with water for 1 min before collecting the oral cotton swab sample, samples from mucosa were collected between 8:00 and 11:00 am by rotating a swab (Qiagen, Dusseldorf, Germany) pressed to the buccal mucosa of OLP patients [10, 17]. All mucosal samples were collected by the same experienced investigator. The swabs were then stored at -80℃ and total sample genomic DNA was extracted immediately for further analysis. In addition, any adverse reactions experienced by the participants were recorded.

We used the triamcinolone acetonide group from our current clinical study on OLP as a control. The inclusion and exclusion criteria for both studies were consistent. In the control group, a total of 8 patients with erosive OLP were treated with 0.1% triamcinolone acetonide dental paste (Bright Future Pharmaceutical Laboratories Ltd., Hong Kong, China) three times daily for 1 week. VAS and REU scores were recorded before and after treatment.

Detection of relative expression of *Fusobacterium nucleatum* in buccal mucosa of OLP patients before and after treatment with tinidazole mouth rinse by RT-PCR

Genomic DNA isolation and amplification were conducted as described in our previous study [10]. Briefly, mucosal samples were processed for genomic DNA extraction using the QIAamp® UCP Pathogen Mini Kits (Qiagen, Hilden, Germany), following the provided

Table 1 Baseline characteristics and clinical response of all study subjects

Variables	Reticular OLP ($n=15$)	Erosive OLP ($n=12$)	*P* value
Age (y) (Mean ± SEM)	49.93 ± 3.36	57.75 ± 3.31	0.11[a]
Male/Female	7/8	2/10	0.10[b]
Disease duration (mo)	7.77 ± 10.41	8.58 ± 9.92	0.89[c]
REU scores (Mean ± SEM)	5.143 ± 0.653	11.460 ± 1.620	0.001[c]
VAS scores (Mean ± SEM)	2.571 ± 0.477	5.167 ± 0.534	<0.001[a]

[a]unpaired t test; [b]Fisher's exact test; [c]Mann-Whitney test

instructions meticulously. The concentration and quality of the extracted DNA were assessed using 1% agarose gel electrophoresis and a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA), respectively. Real-time quantitative polymerase chain reaction (RT-PCR) was performed in triplicate with specific primers using SYBR® Premix Ex Taq (Takara), following the standard quantitative PCR protocol. The primer sequences and the method for detecting *Fusobacterium nucleatum* were described in our previous study [10]. The primer sequences were as follows: *Fusobacterium nucleatum: (F) 5'*-CAACCATTACTTTAACTCT ACCATGTTCA-*3' and (R) 5'*-GTTGACTTTACAGAA GGAGATTATGTAAAAATC-*3'.* PCR results were analyzed and expressed as relative gene expression, with fold changes calculated using the $2^{-\Delta\Delta CT}$ method.

Statistical analysis

Twenty-seven participants finished the trial. Statistical analyses were performed using Prism software version 9.3.0 (GraphPad Software, San Diego, CA, USA). The paired t-test and Wilcoxon matched-pairs signed rank test were used to analyze the changes of VAS scores, REU scores and the relative expression of *Fusobacterium nucleatum* before and after treatment. An independent t-test was used to calculate the significance of changes in VAS and REU scores. The Pearson correlation test was used to analyze the correlation between changes in *Fusobacterium nucleatum* abundance and REU scores. In all cases, the threshold for significance was 5%.

Results

A total of 28 participants, including 15 with reticular OLP and 13 with erosive OLP, were initially enrolled in this trial. One patient with erosive OLP was excluded due to experiencing nausea during treatment, resulting in 27 participants who successfully completed the study.

Baseline analysis

The clinical information for all subjects was presented in Table 1. At baseline, there were no statistically significant differences between the reticular and erosive OLP groups in terms of age, gender or disease duration ($P=0.11$ and $P=0.10$, respectively).

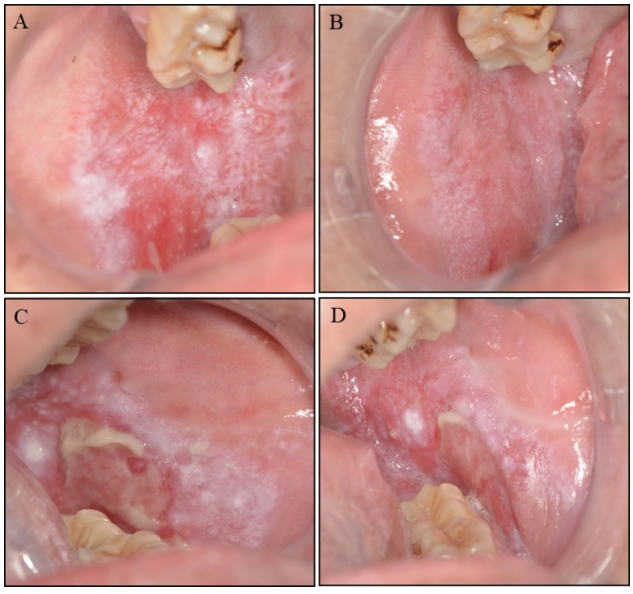

Fig. 2 Clinical manifestations of erosive OLP lesions in subjects at baseline on the right cheek (**A**) and left cheek (**C**), as well as at day 7 on the right cheek (**B**) and left cheek (**D**)

Efficacy of tinidazole mouth rinse in patients with oral lichen planus

After 1 week of treatment with tinidazole mouth rinse, the response rate was 66.67% for reticular OLP and 83.33% for erosive OLP. Significant improvement in OLP lesions was observed during treatment and follow-up (Fig. 2). However, no statistically significant difference was found between the two groups ($P=0.40$) (Table 2). Notably, REU values returned to pre-treatment levels in 2 patients in the erosive OLP group at 1 week after treatment. Nevertheless, there was also no statistically significant difference in response rates between the reticular and erosive OLP groups ($P>0.99$) (Table 2).

In addition, compared to baseline, VAS values were significantly decreased in reticular, erosive and all OLP patients after using tinidazole mouth rinse, with statistically significant differences observed ($P=0.03$,0.003 and $P<0.001$) (Fig. 3A, B and C). However, REU scores showed a significant decrease only in the erosive OLP patients and all OLP patients ($P=0.002$ and 0.001) (Fig. 3D, E and F).

Compared to before treatment, both VAS and REU scores of patients with erosive OLP were significantly

Table 2 Clinical efficacy of tinidazole mouth rinse in the treatment of OLP

Variables	1 week of treatment			1 week after treatment		
	R-OLP (*n* = 15))	E-OLP (*n* = 13)	*P*-value*	*R*-OLP (*n* = 15))	E-OLP (*n* = 13)	*P*-value*
Complete Remission	0	0		0	0	
Partial response	10	10		10	8	
No response	5	2		5	4	
Response rate	66.67%	83.33%	0.40	66.67%	66.67%	> 0.99
Adverse reactions	0	1		0	1	

R-OLP, reticular OLP; E-OLP, erosive OLP; *Fisher's exact test

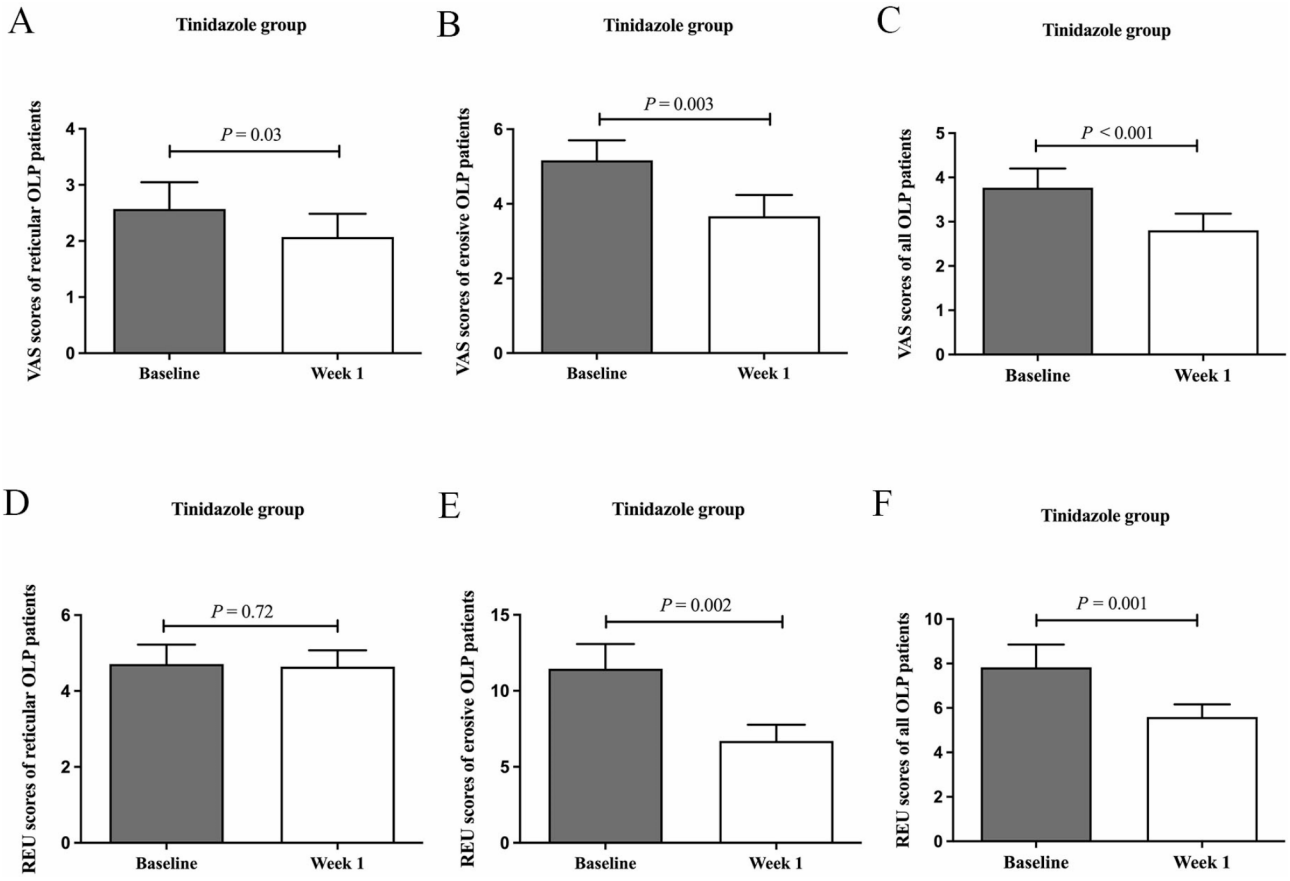

Fig. 3 VAS scores and REU scores in the reticular OLP group, erosive OLP group and OLP groups before and after treatment with tinidazole mouth rinse. (**A**) VAS scores of reticular OLP patients. (**B**) VAS scores of erosive OLP patients. (**C**) VAS scores of all OLP patients. (**D**) REU scores of reticular OLP patients. (**E**) REU scores of erosive OLP patients. (**F**) REU scores of all OLP patients

reduced after using triamcinolone acetonide dental paste ($P<0.001$ and $P=0.01$) (Fig. 4A and B). After 1 week of treatment, the improvement in VAS scores was significantly greater in the triamcinolone group compared to the tinidazole group ($P=0.01$), whereas the difference in REU score improvement between the two groups was not statistically significant ($P=0.13$) (Fig. 4C and D).

Abundance of *Fusobacterium nucleatum* on the surface of damaged mucosa in patients with oral lichen planus

After using tinidazole mouth rinse, the relative abundance of *Fusobacterium nucleatum* on the damaged mucosal surface significantly decreased in reticular OLP patients and in all OLP patients ($P=0.04$ and 0.01, respectively) (Fig. 5A and C). However, no significant change was observed in erosive OLP patients ($P=0.13$) (Fig. 5B). Additionally, no statistically significant correlation was found between the relative abundance of *Fusobacterium nucleatum* and REU scores in all OLP patients ($r=0.0754$, $P=0.61$) (Fig. 5D).

Discussion

Therapies for OLP primarily focus on symptom management, as a definitive cure remains elusive. Oral or topical corticosteroids are the primary clinical approaches for treating patients with symptomatic OLP [1]. However,

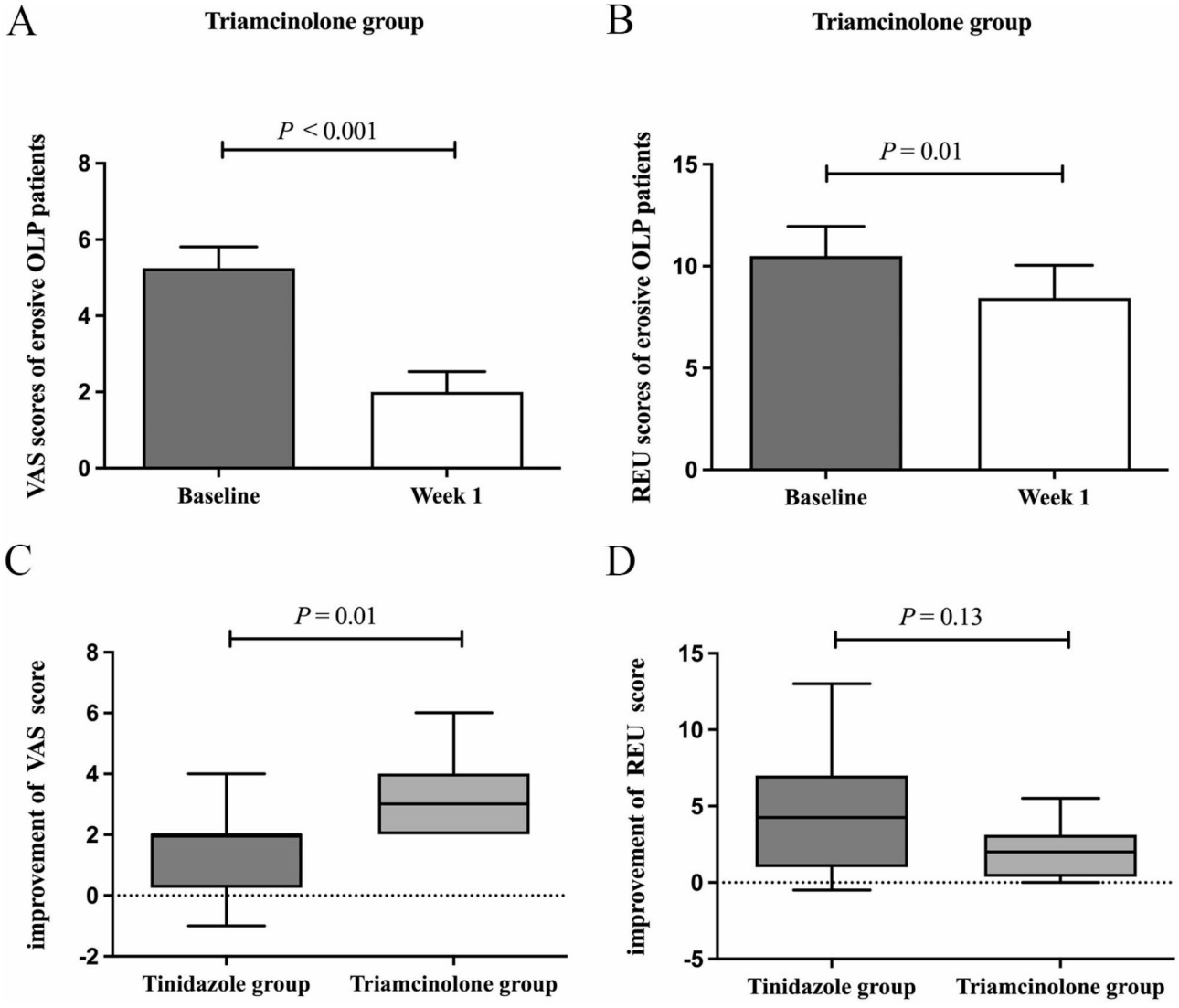

Fig. 4 VAS scores and REU scores of erosive oral lichen planus patients before and after triamcinolone therapy, and comparison of improvement in REU/VAS scores between triamcinolone and tinidazole groups. (**A**) VAS scores of erosive OLP patients. (**B**) REU scores of erosive OLP patients. (**C**) Comparison of improvement in VAS scores between triamcinolone and tinidazole groups. (**D**) Comparison of improvement in REU scores between triamcinolone and tinidazole groups

due to the adverse reactions, the clinical use of corticosteroids is limited. Calcineurin inhibitors and immunosuppressive agents are also commonly used in the treatment of OLP, however, their toxicity and possible carcinogenic effects restrict their application [18]. Consequently, treating symptomatic OLP, particularly erosive OLP, remains challenging, highlighting the critical need for alternative, cost-effective therapeutic options [19]. Our preliminary findings suggest that tinidazole mouth rinse may be effective in alleviating symptoms in OLP patients.

Although the specific pathogenesis of OLP remains unknown, it is generally believed that the disease may be caused by a combination of extrinsic and intrinsic factors in the body, which may include bacteria, viruses, and drugs [20]. With the development of molecular biology and high-throughput sequencing technology, researchers have gained new insights into the role of host microbiota, which has spurred interest in treatments targeting microbial communities [21]. Recent studies suggest that the host microbiota can influence the function and differentiation of host epithelial cells, macrophages, and helper T cells, thus playing an important role in regulating host immune responses [22, 23]. Despite this, current evidence does not support classifying OLP as a disease caused by specific microorganisms. However, alterations in the oral microbiota may lead to ecological dysregulation that contributes to the disease's development. In addition, the effects of many drugs used for treatment on the microbiome can lead to worsening of the condition, which also means that the treatment process of the

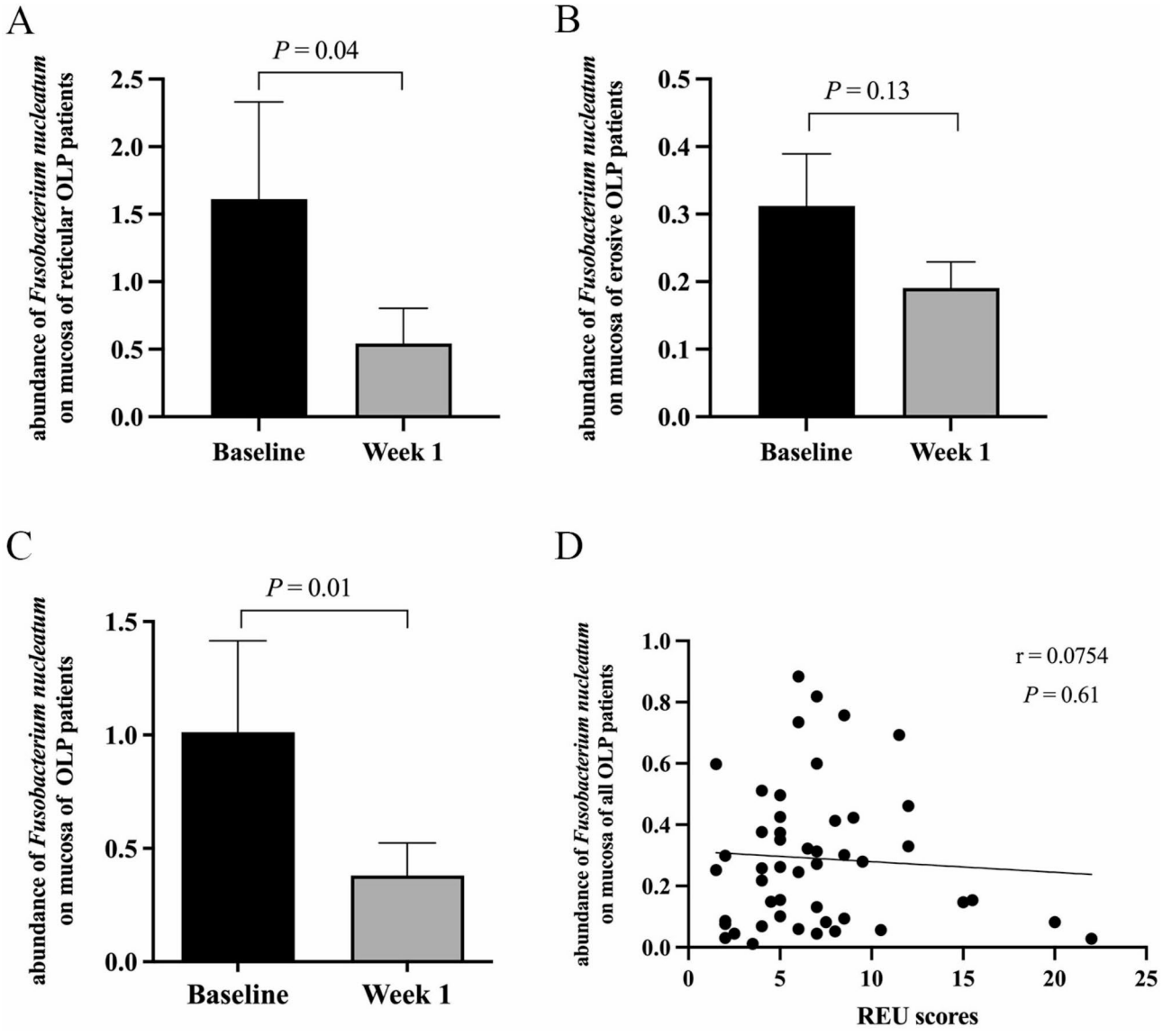

Fig. 5 Relative abundance of *Fusobacterium nucleatum* (*F.n*) on the damaged mucosa surface and its correlation with REU scores in OLP patients before and after treatment with tinidazole mouth rinse. (**A**) Abundance of *F.n* on mucosa of reticular OLP patients. (**B**) Abundance of *F.n* on mucosa of erosive OLP patients. (**C**) Abundance of *F.n* on mucosa of reticular OLP patients. (**D**) Correlation between the relative abundance of *F.n* on mucosa and REU scores in OLP patients

disease should include addressing the microbial imbalance and restoring the normal microbiome [24]. Nevertheless, clinical trials targeting host bacteria in OLP have yet to receive significant attention.

Alterations in the structure of the microbiota on mucosal surfaces damaged by OLP have been shown [17, 25]. In our previous clinical cohort study, we utilized 16S rRNA sequencing and real-time PCR to detect and analyze the flora structure on the mucosal surface of OLP patients compared with healthy controls. The results revealed a significant increase in the abundance of *Fusobacterium nucleatum* on the mucosal surface of OLP lesions compared to those of healthy individuals [10]. Based on these findings, we speculate that *Fusobacterium nucleatum* may play a role in the pathogenesis of OLP. *Fusobacterium nucleatum* is a gram-negative anaerobic bacterium commonly found in the human oral cavity, acting as both a commensal and opportunistic pathogen. Its pro-inflammatory effects have been validated in chronic inflammatory diseases such as periodontal disease and inflammatory bowel disease where reducing *Fusobacterium nucleatum* load has proven effective in prevention and treatment [26]. Therefore, the aim of this study was to investigate the short-term efficacy of tinidazole mouth rinse and to analyze the correlation between its clinical

efficacy and the reduction of *Fusobacterium nucleatum* abundance on mucosal surfaces of OLP patients.

This pilot clinical study demonstrated that in patients with erosion OLP, there was no significant difference in the improvement of REU scores between the tinidazole group and the triamcinolone acetonide dental paste group, although the latter showed superior analgesic effects. These findings suggest that tinidazole mouth rinse offers promising clinical efficacy, warranting further investigation in large-scale randomized controlled trials. Consistent with previous clinical trial results, our study reaffirms that topical corticosteroids remain the preferred treatment for erosive OLP. At the same time, only one OLP patient withdrew from the trial because of nausea. In reticular OLP patients, tinidazole treatment did not significantly reduce REU scores compared to pretreatment levels, although VAS values were significantly lower. We speculate that this discrepancy may be attributed to placebo effects and small sample size. Although our previous study indicated an increased abundance of *Fusobacterium nucleatum* on the mucosal surface in OLP patients compared with healthy controls, no statistically significant correlation was found between the abundance of *Fusobacterium nucleatum* and REU scores in reticular, erosive, or all OLP patients in this trial. This suggests that the therapeutic response may not be solely explained by a *Fusobacterium nucleatum* colonization. It is also possible that the observed decrease in *Fusobacterium nucleatum* abundance reflects the restoration of mucosal epithelial barrier function and subsequent symptom improvement in OLP patients. Factors such as sample size, sampling method, identification technique, and the periodontal condition of the patients may influence the results [27]. Therefore, further large-scale clinical studies are necessary to obtain more accurate findings.

Tinidazole exhibits activity against a broad spectrum of obligate anaerobic bacteria and is a nitroimidazole antianaerobic drug with high efficacy and favorable tolerance. Compared with metronidazole, tinidazole is more readily absorbed and sustains higher plasma concentrations for a prolonged period [14]. Numerous studies have confirmed that tinidazole significantly inhibits the activity of anaerobic pathogens in periodontal tissues, making it a commonly used drugs for treating periodontitis in clinical practice [28]. Oral metronidazole has been reported to be effective in LP patients. (11, 29–30) However, side effects limit long term usage of oral metronidazole; these include encephalopathy, peripheral neuropathy, diarrhea and abdominal pain [31]. Consistent with the above reports, our clinical trial demonstrated that tinidazole mouth rinse effectively reduced REU scores in OLP patients. The mouth rinse, which is not absorbed by the human digestive tract and has infrequent side effects, shows great potential for clinical application [32]. In summary, tinidazole mouth rinse may serve as an alternative therapy for OLP, especially erosive OLP.

We are aware of the limitations of this pilot study, including the restricted sample size, monocentric study, lack of a control group, limitations of the bacterial study and the short follow-up period. In addition, our preliminary correlative study did not elucidate the precise mechanism by which tinidazole reduces REU scores in erosive OLP patients but not in reticular OLP patients. A substantially larger-scale clinical and laboratory study is needed to obtain more accurate and comprehensive findings.

Acknowledgements
Not applicable.

Author contributions
Ruru Shao: contributed to volunteer recruitment, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. Zhenyuan Wang: contributed to volunteer recruitment, data analysis and performed all statistical analyses. Chenglong Yang: contributed to volunteer recruitment and data analysis. Lei Pan: contributed to data acquisition and revised the manuscript. Xu Chen: contributed to conception and experiment design, data interpretation and critically revised the manuscript. Guanhuan Du: contributed to conception and experiment design, volunteer recruitment, data analysis and interpretation, drafted and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

Funding
This work was supported by the National Natural Science Foundation of China (82101008,82020108010 and 62273231) and an Intrahospital Research Grant (2022yxyjxys). Xu Chen was supported by the Shanghai Pujiang Program (23PJD047) and on-job postdoctoral program.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Human ethics and consent to participate declarations
The study was approved by the Institutional Review Board of Shanghai Ninth People's Hospital (SH9H-2020-T76-2). Informed consent obtained from all the subjects.

Conflict of interest
The authors declare no conflicts of interest.

Clinical trial number
Not applicable.

Consent to publish
Not applicable.

Received: 14 May 2024 / Accepted: 6 September 2024
Published online: 27 September 2024

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