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Original Article

Clinical efficacy and safety of Tinidazole combined with minocycline in treating peri-implantitis

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Abstract: Objective: To evaluate the effects of tinidazole (TNZ) combined with minocycline (MINO) on therapeutic effectiveness, bone resorption, and inflammation in peri-implantitis (PI). Methods: This retrospective study included 96 PI patients admitted between January 2023 and February 2024. Patients were divided into a control group (n = 46) treated with MINO and a research group (n = 50) treated with TNZ plus MINO. Therapeutic effectiveness, post-treatment plaque biofilm activity at different depths, periodontal indexes [modified plaque index (mPLI), modified sulcus bleeding index (mSBI), probing depth (PD), and peri-implant marginal bone loss (MBL)], inflammatory markers [interleukin (IL)-1β, IL-8, and matrix metalloproteinase-8 (MMP-8)], pain scores [Visual Analogue Scale (VAS)], quality of life [Short Form 36 Item Health Survey (SF-36)], and adverse reactions were compared. Univariate and multivariate analyses were performed to identify factors influencing therapeutic effectiveness. Results: The research group demonstrated significantly higher therapeutic effectiveness and lower mPLI, mSBI, PD, MBL, and plaque biofilm activity at different depths compared to the control group (all $P < 0.05$). Additionally, greater reductions in VAS scores and increases in SF-36 scores were observed in the research group post-treatment (both $P < 0.05$). No severe adverse reactions occurred in either group, and the incidence of adverse events showed no significant inter-group difference ($P > 0.05$). Univariate analysis revealed that disease duration, history of periodontitis, smoking, and treatment modality were significantly associated with therapeutic effectiveness (all $P < 0.05$). Multivariate analysis identified smoking as an independent factor influencing treatment outcome. Conclusions: TNZ combined with MINO is a highly effective and safe treatment for PI. This combination reduces plaque, alleviates periodontitis, and improves patients' quality of life.

Keywords: Tinidazole, minocycline, peri-implantitis, dental plaque

Introduction

As advancements in materials and oral implant techniques continue, dental implants have revolutionized oral rehabilitation and have become a routine treatment for restoration and rehabilitation [1]. However, the risk of complications following implantation cannot be overlooked [2]. Various factors contribute to peri-implant complications, including a history of periodontitis, smoking, poor oral hygiene, and systemic conditions such as osteoporosis and diabetes.

Peri-implantitis (PI) is a progressive, irreversible condition affecting the hard and soft tissues surrounding implants. It is characterized by progressive bone loss, resorption, reduced osseointegration, pocket formation, and suppuration [3]. With the growing popularity of dental implants, PI has emerged as a global health challenge, affecting an estimated 63.4% of implant patients and 30.7% of functional implants [4]. The primary objectives of PI treatment are to control infection, reduce inflammation, and preserve and restore surrounding soft and hard tissues [5].

Currently, non-surgical PI treatments include mechanical and pharmacological therapies. Due to the complex anatomy of peri-implant sites and the variability in implant morphology, mechanical therapies like subgingival scaling

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alone are often insufficient to eliminate pathogens. As a result, adjunctive or systemic antibiotic therapies are frequently employed to enhance treatment outcomes [6, 7]. However, the optimal antibiotic regimen for PI remains undefined, necessitating further exploration of superior therapeutic strategies to improve patient outcomes. This is critical for preventing post-implant complications and advancing oral rehabilitation.

Tinidazole (TNZ) and Minocycline (MINO) are commonly used antibiotics, but their combined application in PI treatment is rarely documented. Existing research has primarily focused on their use in treating conditions like chronic periodontitis and periodontal-endodontic lesions. This study evaluates the efficacy and safety of TNZ combined with MINO in treating PI, aiming to expand the clinical applications of this combination and address the gap in its use for PI management.

Materials and methods

Patient selection

This retrospective study included 96 patients diagnosed with PI at the North China University of Science and Technology Affiliated Hospital between January 2023 and February 2024.

Inclusion criteria: Aged 18-60 years. Underwent implant restoration for ≥ 6 months. Peripheral mucosal congestion without implant loosening, accompanied by local edema, modified sulcus bleeding index (mSBI) ≥ 1, and keratinized gingival width ≥ 2 mm. Presence of plaque and tartar on the implant surface and abutment, with a probing depth (PD) ≥ 4 mm. Evidence of progressive bone absorption at the implant neck on X-rays using the parallel cone technique. No occlusal overload. Availability of relevant clinical data for study indicators.

Exclusion criteria: Pregnant or lactating women. Allergic to the drugs used in this study. Recent (within 3 months) use of antibiotics, hormones, or immune preparations. Psychiatric disorders. Refusal to participate. This study was reviewed and approved by the Ethics Committee of the North China University of Science and Technology Affiliated Hospital. All participants and their families were informed about the study and voluntarily signed consent forms. Data were retrieved through the hospital's medical record system. A study flowchart is shown in **Figure 1**.

Treatment

This study employed a retrospective cohort design. Patient data meeting the inclusion and exclusion criteria were screened through the hospital's medical record management system. Patients were grouped based on their treatment regimen: Control group (n = 46): Treated with MINO hydrochloride ointment. Research group (n = 50): Treated with MINO hydrochloride ointment combined with TNZ sustained-release film.

Treatment plans were formulated based on patient conditions, and the advantages and limitations of each plan were explained. Patients selected their treatment regimen after receiving detailed information.

In the control group, before treatment, periodontal plaque on the implant was thoroughly removed. After rinsing with normal saline, MINO hydrochloride ointment (New-Era Co., Ltd., Japan; Approval Number: H20100244; Specification: 0.5 g) was applied to the periodontal pocket around the implant. Patients were advised not to rinse or eat for 30 minutes post-application. The ointment was applied once a week for 4 weeks.

In addition to the above treatment, the research group was given TNZ sustained-release film was applied to the bottom of the periodontal pocket once daily for 4 weeks.

Preparation of TNZ Sustained-Release Film: The film was prepared using the following materials: TNZ (Zhejiang Supor Pharmaceuticals Co., Ltd.; Approval Number: H10940132; purity ≥ 99.9%), tetracaine (0.5 g), saccharin (0.1 g), glycerol (4 g), PVA17-88 (10 g), and distilled water (100 ml). After thorough mixing, a film of 1000 cm^2 was prepared, cut into 0.5 cm × 1.0 cm segments, each containing 1 mg of TNZ, and stored for use.

Data extraction

Patient information and data regarding clinical efficacy evaluation, gingival index testing,

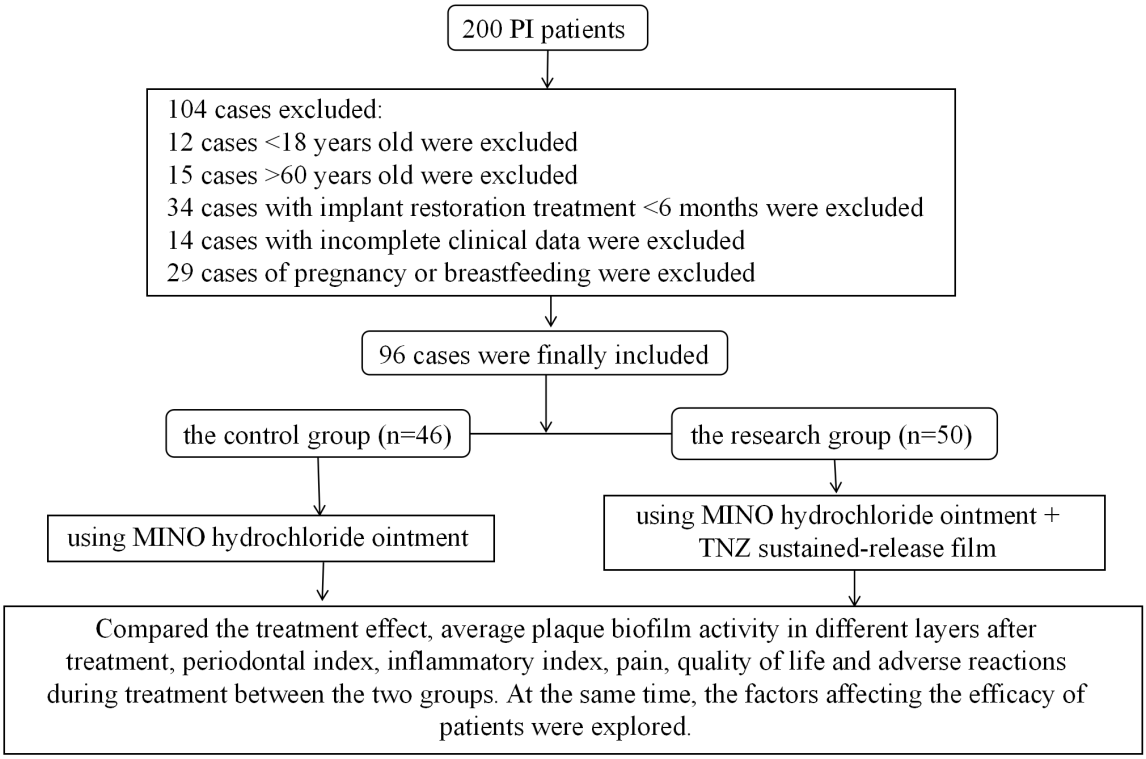

Figure 1. Flowchart of this study. PI, peri-implantitis; MINO, minocycline; TNZ, Tinidazole.

plaque biofilm activity detection, inflammatory cytokines in gingival crevicular fluid (GCF), pain levels, quality of life, and adverse reactions were extracted from the hospital's medical record system. These data were used to validate the clinical advantages of the combined use of MINO and TNZ in treating PI.

Outcome measures

The evaluations were conducted before treatment and 4 weeks after treatment. Clinical efficacy, gingival indices, pain levels, quality of life, and adverse reactions were designated as primary outcome measures, while plaque biofilm activity and inflammatory cytokines served as secondary outcome measures.

Demographic data: Patient demographic characteristics included age, body mass index (BMI), disease duration, number of implants, gender, history of periodontitis, smoking history, and educational level.

Clinical efficacy evaluation: Therapeutic effectiveness was classified based on criteria from previous studies [8]: Cured: Complete resolution of gingival swelling, pain, and redness, with mSBI decreased by > 1 and PD restored to normal. Markedly effective: Significant improvement in gum swelling, pain, and redness, with mSBI decreased by 1 and no pus discharge from the peri-implant pocket. Effective: Improvement in gum swelling, pain, and redness, with PD reduced by 1-2 mm. Ineffective: No improvement or worsening of gum swelling, pain, and redness.

Gingival index testing: Gingival indices, including modified sulcus bleeding index (mSBI), modified plaque index (mPLI), PD, and peri-implant marginal bone loss (MBL), were measured before and after treatment: mSBI: A pressure-controlled plastic probe (-0.2 N) was used to assess bleeding along the gingival margin. Grades were as follows: severe bleeding (3), linear bleeding (2), punctate bleeding (1), and no bleeding (0). mPLI: Using a fine probe, plaque on the implant surface was graded as follows: large amounts of plaque (3), visible plaque (2), plaque visible only with the probe tip (1), and no plaque (0). PD: A pressure-controlled plastic probe (-0.2 N) measured the distance

from the gingival margin to the bottom of the periodontal pocket. MBL: Changes in marginal bone loss at the implant edge were assessed through imaging examinations post-implant superstructure placement.

Plaque biofilm activity detection: Saliva samples were collected from patients before and after treatment and placed on glass slides to allow plaque biofilm formation without interference from labial, buccal, or lingual tissues. The biofilm was observed using a laser confocal scanning microscope, where red fluorescence indicated dead bacteria and green fluorescence indicated live bacteria. The thickest part of the plaque biofilm was identified, and a tomography scan was conducted with a 2 μm pitch, yielding plaque biofilm thickness twice the number of scanned rows. Images were processed using Zeiss LSM Image Browser software (Germany), and green and red fluorescence intensities were quantified. Plaque biofilm activity was calculated as: plaque biofilm activity = green fluorescence/(green fluorescence + red fluorescence) × 100%. The average activity at different depths within the plaque biofilm was evaluated.

Detection of inflammatory cytokines in GCF: GCF samples were collected before and after treatment using filter paper strips. Tooth surfaces were cleaned prior to sampling to remove large plaques and food debris. Levels of interleukin (IL)-1β, IL-8, and matrix metalloproteinase-8 (MMP-8) in GCF were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Beyotime Biotech).

Pain level and quality of life: Pain severity was assessed before and after treatment using the Visual Analogue Scale (VAS), where a 0-10 scale was used to grade pain intensity (0 = no pain, 10 = worst pain). Patients marked their perceived pain level, with higher scores indicating greater pain.

Quality of life was evaluated using the Short-Form 36 Item Health Survey (SF-36), which assesses eight domains: physical functioning, social functioning, role limitations due to physical and emotional problems, bodily pain, general health, mental health, and vitality. Each domain has a total score of 100 points, with higher scores reflecting better quality of life.

Recording of adverse reactions: Adverse reactions observed during treatment were recorded, including abnormal liver function, nausea, vomiting, abdominal pain, skin itching, and dizziness.

Data processing and statistical analysis

Data were analyzed and visualized using GraphPad Prism 6. Counted data were compared using the chi-square test. Measured data were compared using independent samples t-tests for inter-group differences and paired t-tests for intra-group differences (before and after treatment). Univariate analysis and binary logistic regression were conducted to identify factors influencing treatment efficacy.

All analyses considered $P < 0.05$ as the threshold for statistical significance.

Results

Comparison of general data

The control and research groups showed no significant differences in age, BMI, disease course, number of implants, sex, history of periodontitis, smoking history, or educational level (all $P > 0.05$; **Table 1**).

Comparison of therapeutic effectiveness

The research group exhibited significantly higher therapeutic effectiveness, with a total effective rate of 96.00% compared to 80.43% in the control group ($P < 0.05$; **Table 2**). Univariate analysis identified disease course, periodontitis history, smoking history, and treatment modality as factors significantly associated with therapeutic outcomes (all $P < 0.05$; **Table 3**). Multivariate analysis further revealed that smoking history was an independent factor influencing treatment efficacy ($P = 0.038$; **Table 4**).

Comparison of gingival indexes

Pre-treatment values for mSBI, PD, mPLI, and MBL were similar between the two groups (all $P > 0.05$). Post-treatment, all four gingival indexes significantly improved in both groups (all $P < 0.05$), with the research group showing greater

Table 1. Comparison of general data ([n (%)], x±sd)

Group	Control group (n = 46)	Research group (n = 50)	χ^2/t	P
Age (years)	42.89±10.64	40.70±9.75	1.052	0.295
Body mass index (kg/m^2)	23.58±2.15	23.04±2.06	1.257	0.212
Disease course (month)	6.61±2.86	6.70±2.80	0.156	0.877
Number of implants (n)	2.41±1.20	2.52±1.16	0.457	0.649
Gender			0.909	0.341
Male	26 (56.52)	33 (66.00)		
Female	20 (43.48)	17 (34.00)		
Periodontitis history			0.069	0.793
With	14 (30.43)	14 (28.00)		
Without	32 (69.57)	36 (72.00)		
Smoking history			0.766	0.382
With	18 (39.13)	24 (48.00)		
Without	28 (60.87)	26 (52.00)		
Educational level			0.082	0.775
≤ high school	18 (39.13)	21 (42.00)		
> high school	28 (60.87)	29 (58.00)		

Note: The independent samples t-test and the chi-square test were used for the inter-group comparison of measured data and counted data, respectively.

Table 2. Comparison of therapeutic effectiveness [n (%)]

Group	Cured	Markedly effective	Effective	Ineffective	Total
Control group (n = 46)	12 (26.09)	11 (23.91)	14 (30.43)	9 (19.57)	37 (80.43)
Research group (n = 50)	20 (40.00)	18 (36.00)	10 (20.00)	2 (4.00)	48 (96.00)
χ^2					5.721
P					0.017

Note: The chi-square test was used for comparing counted data between groups.

reductions than the control group (all P < 0.05; **Figure 2**).

Comparison of average plaque biofilm activity at different depths

Pre-treatment plaque biofilm activity at different depths was comparable between the two groups (P > 0.05). After treatment, both groups demonstrated significant reductions in biofilm activity (P < 0.05), with the research group achieving lower activity levels than the control group (P < 0.05; **Figure 3**).

Comparison of microinflammation indexes in GCF

Baseline levels of GCF IL-1β, IL-8, and MMP-8 were comparable between groups (all P > 0.05). After treatment, these microinflammation indexes decreased significantly in both groups (all P < 0.05), with the research group showing greater reductions compared to the control group (all P < 0.05; **Figure 4**).

Comparison of VAS and SF-36 scores

VAS and SF-36 scores were similar between the two groups before treatment (both P > 0.05). Post-treatment, VAS scores decreased while SF-36 scores increased significantly in both groups (both P < 0.05). The research group exhibited lower VAS scores and higher SF-36 scores compared to the control group after treatment (both P < 0.05; **Figure 5**).

Comparison of adverse reactions

No severe or uncontrollable adverse reactions occurred in either group during treatment.

Table 3. Univariate analysis of factors influencing the ineffectiveness of treatment in peri-implantitis patients ([n (%)], x±sd)

Group	Ineffective group (n = 11)	Effective group (n = 85)	χ^2/t	P
Age (years)			1.724	0.189
< 40	3 (27.27)	41 (48.24)		
≥ 40	8 (72.73)	44 (51.76)		
Body mass index (kg/m^2)			0.380	0.538
< 23	6 (54.55)	39 (45.88)		
≥ 23	5 (45.45)	46 (54.12)		
Disease course (month)			4.575	0.032
< 6	7 (63.64)	34 (40.00)		
≥ 6	4 (36.36)	51 (60.00)		
Number of implants (n)			0.294	0.588
< 3	5 (45.45)	46 (54.12)		
≥ 3	6 (54.55)	39 (45.88)		
Gender			0.666	0.414
Male 59	8 (72.73)	51 (60.00)		
Female 37	3 (27.27)	34 (40.00)		
Periodontitis history			3.873	0.049
With 28	6 (54.55)	22 (25.88)		
Without 68	5 (45.45)	63 (74.12)		
Smoking history			4.239	0.040
With 42	8 (72.73)	34 (40.00)		
Without 54	3 (27.27)	51 (60.00)		
Educational level			0.998	0.318
≤ high school 39	6 (54.55)	33 (38.82)		
> high school 57	5 (45.45)	52 (61.18)		
Treatment modality			5.721	0.017
MINO 46	9 (81.82)	37 (43.53)		
TNZ + MINO 50	2 (18.18)	48 (56.47)		

MINO, minocycline; TNZ, Tinidazole.

Table 4. Multivariate analysis of factors influencing the ineffectiveness of treatment in PI patients ([n (%)], x±sd)

Factor	β	SE	Wald	P	Exp (β)	95% CI
Disease course (month)	-1.221	0.753	2.630	0.105	0.295	0.067-1.290
Periodontitis history	1.281	0.730	3.081	0.079	3.601	0.861-15.053
Smoking history	1.649	0.794	4.320	0.038	5.204	1.099-24.648
Treatment modality	1.471	0.849	3.002	0.083	4.355	0.825-23.001

All adverse reactions resolved spontaneously, with no significant difference in incidence between the two groups (P > 0.05; **Table 5**).

Discussion

The prevalence of PI has been rising alongside the increasing use of dental implants. If left untreated, PI can result in peri-implant bone resorption and, in severe cases, implant loosening or detachment [9]. Despite various available treatment strategies, PI management remains complex and non-standardized [10]. PI shares pathologic features with periodontitis but is characterized by greater microbial diversity and the absence of a protective periodontal membrane, making it more challenging to

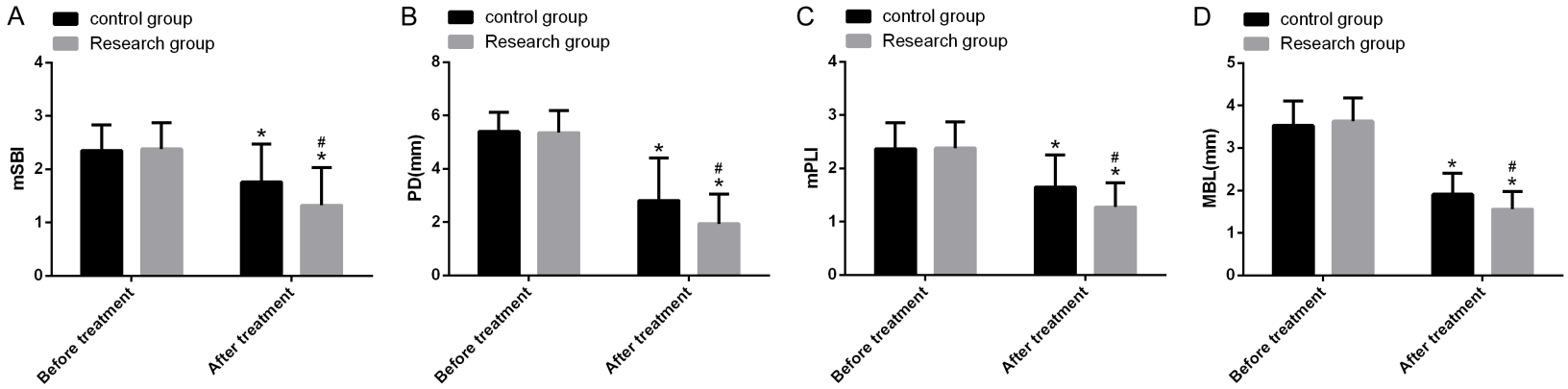

Figure 2. Comparison of gingival indexes. A: Pre- and post-treatment modified sulcus bleeding index (mSBI) in the two groups. B: Pre- and post-treatment probing depth (PD) in the two groups. C: Pre- and post-treatment modified plaque index (mPLI) in the two groups. D: Pre- and post-treatment marginal bone loss (MBL) in the two groups. Note: *P < 0.05 *vs.* before treatment within the group (paired t-test); #P < 0.05 *vs.* control group at the same time point (independent samples t-test).

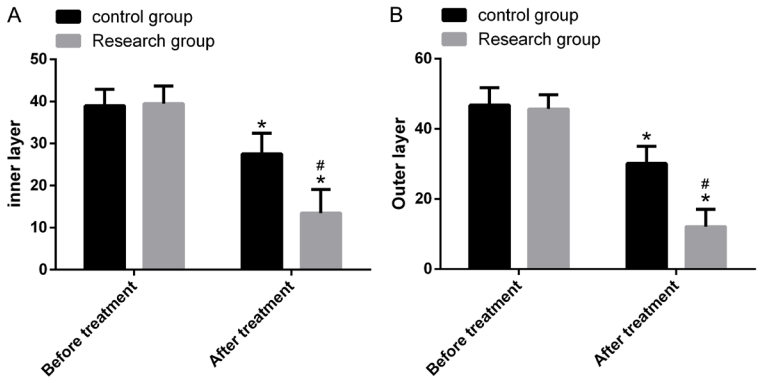

Figure 3. Comparison of average plaque biofilm activity at different depths. A: The average activity of the inner layer of the plaque biofilm in two groups before and after treatment. B: The average activity of the outer layer of the plaque biofilm in two groups before and after treatment. Note: *P < 0.05 *vs.* before treatment within the group (paired t-test); #P < 0.05 *vs.* control group at the same time point (independent samples t-test).

treat [11]. PI is primarily associated with bacterial accumulation and infection, particularly anaerobic and Gram-negative bacteria [12]. Consequently, controlling and eliminating oral pathogens is essential for effective PI treatment and preventing implant failure. Antibiotics, as an adjunct to non-surgical treatment, have shown significant benefits in reducing PD and mSBI [13].

MINO, a broad-spectrum tetracycline antibiotic, inhibits bacterial protein synthesis, thereby preventing growth and reproduction [14, 15]. Its broad antibacterial spectrum and strong tissue penetration make it effective against various bacterial infections, including acne, pneumonia, and urethritis. TNZ, a second-generation nitroimidazole antimicrobial agent, exhibits potent activity against anaerobic bacteria and protozoa by penetrating microbial cell membranes, interacting with DNA, and disrupting its replication and function, leading to bacterial death [16, 17]. TNZ has demonstrated effectiveness against anaerobic bacteria commonly found in PI, such as Clostridium gingivalis and Bacteroides melaninogenicus. Additionally, TNZ can deliver antimicrobials quickly and efficiently into peri-implant defects, achieving higher local concentrations than systemic administration [18].

Previous studies have shown that combining metronidazole and MINO ointment significantly improves treatment success rates in PI compared to mechanical debridement alone [19]. Furthermore, MINO combined with TNZ has proven more effective than MINO alone in treating periodontitis without increasing adverse reactions [20].

Both univariate and multivariate analyses in this study confirmed that smoking history is an independent factor influencing treatment outcome, indicating that PI patients who smoke are at higher risk of treatment failure. The findings demonstrated that the research group (MINO + TNZ) achieved higher treatment efficacy, lower mPLI, mSBI, PD, MBL, and plaque biofilm activity, with a similar incidence of adverse reactions compared to the control group. These results suggest that MINO combined with TNZ effectively alleviates symptoms, reduces dental plaque formation, and is safe and reliable. The following reasons may explain these findings: MINO and TNZ act through different mechanisms and do not interfere with each other, allowing simultaneous and more effective bacterial eradication. The combination increases the antibacterial spectrum and achieves higher local drug concentrations, prolonging antibacterial activity and enhancing bactericidal efficacy.

PI is a microbial infection-induced inflammatory disease primarily caused by bacterial biofilm accumulation on implant surfaces when not effectively removed [21]. Initially, the inflammation remains localized to the soft tissues surrounding the implant, presenting as redness, swelling, and bleeding, or bleeding on probing, a condition known as peri-implant mucositis [22]. If untreated, the inflammation can disrupt peri-implant soft tissues and the supporting function of the osseointegrated implant, progressing to PI and possiblyleading to implant failure or detachment [23]. Furthermore, excessive inflammation can cause pain, worsening the patient's quality of life.

Evidence suggests that inflammatory mediators such as IL-1β, IL-8, and MMP-8 are present

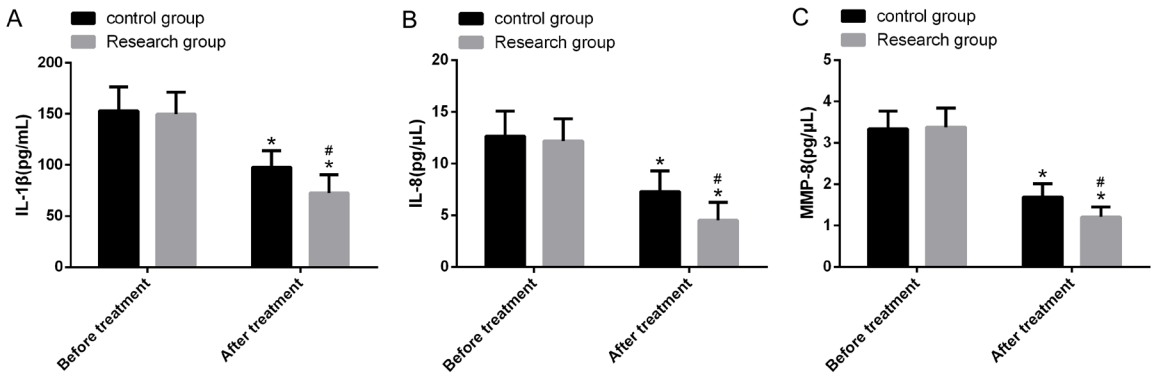

Figure 4. Comparison of microinflammation indexes in gingival crevicular fluid (GCF). A: Pre- and post-treatment interleukin [IL]-1β levels in GCF in two groups. B: Pre- and post-treatment GCF IL-8 levels in two groups. C: Pre- and post-treatment matrix metalloproteinase-8 (MMP-8) levels in GCF in two groups. Note: *P < 0.05 *vs.* before treatment within the group (paired t-test); #P < 0.05 *vs.* control group at the same time point (independent samples t-test).

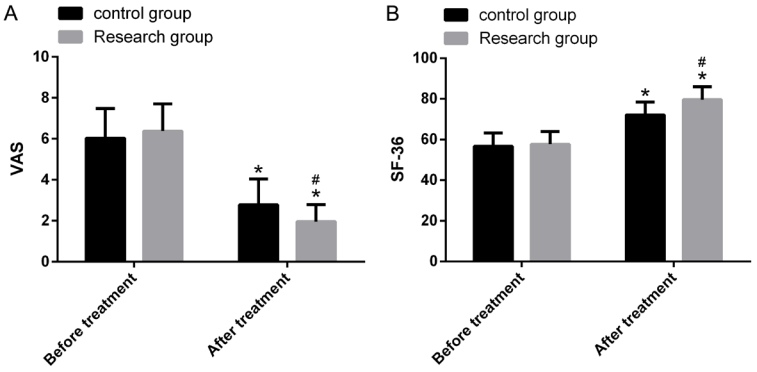

Figure 5. Comparison of Visual Analogue Scale (VAS) and Short-Form 36 Item Health Survey (SF-36) scores. A: Pre- and post-treatment VAS scores. B: Pre- and post-treatment SF-36 scores. Note: *P < 0.05 *vs.* before treatment within the group (paired t-test); #P < 0.05 *vs.* control group at the same time point (independent samples t-test).

in the GCF of patients with periodontitis and PI [24, 25]. Among these, MMP-8 plays a crucial role in degrading periodontal tissues by breaking down the collagen matrix of supporting structures, contributing to periodontal attachment loss and alveolar bone resorption [26]. In the inflammatory milieu of PI, IL-8 recruits macrophages and neutrophils to the site of inflammation, promoting osteoclast activation and subsequent bone loss [27]. IL-1β, a key regulator of inflammation, activates immune cells such as macrophages, neutrophils, and T cells, stimulating the production of additional inflammatory mediators, thereby exacerbating the inflammatory response.

Previous studies have demonstrated that the combination of and TNZ is more effective than MINO alone in reducing serum inflammatory cytokine levels in patients with chronic periodontitis [20]. Consistent with these findings, the current study observed that the research group (MINO + TNZ) exhibited greater reductions in IL-1β, IL-8, and MMP-8 levels, alongside lower VAS scores and higher SF-36 scores, compared to the control group. These results indicate that the combination of MINO and TNZ effectively mitigates inflammation in the periodontal region, reduces periodontal tissue destruction, and further confirms the clinical efficacy of this combination therapy.

These findings support its clinical applicability. However, the study has certain limitations. The optimal dosage of MINO and TNZ for PI treatment remains undetermined. The short duration of the study precluded evaluation of long-term patient outcomes. Microbial changes in PI biofilms were not analyzed. Future research should address these limitations to further refine and validate the treatment approach.

In summary, the combination of MINO and TNZ is effective for treating PI, as evidenced by significant inhibition of plaque biofilm activity, prevention of plaque formation, alleviation of pain, and improved quality of life.

Table 5. Comparison of adverse reactions [n (%)]

Groups	Nausea	Abdominal pain	Dizziness	Itchy skin	Total occurrence
Control group (n = 46)	2 (4.35)	1 (2.17)	1 (2.17)	1 (2.17)	5 (10.87)
Research group (n = 50)	3 (6.00)	2 (4.00)	2 (4.00)	1 (2.00)	8 (16.00)
χ^2					0.539
P					0.463

Note: The chi-square test was used for the comparison of counted data among groups.

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Disclosure of conflict of interest

None.

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