Am J Transl Res 2024;16(5):2122-2131
www.ajtr.org /ISSN:1943-8141/AJTR0152590

Original Article

Minocycline hydrochloride plus metronidazole versus metronidazole alone for peri-implantitis: a comparative study

Yonghong Zhang, Tianyan Gao, Xiaoyu Fan

Dental Department, 980 Hospital, Joint Logistics Support Force of The People's Liberation Army, Shijiazhuang 050082, Hebei, P. R. China

Received August 2, 2023; Accepted December 13, 2023; Epub May 15, 2024; Published May 30, 2024

Abstract: Objective: To evaluate the efficacy of minocycline hydrochloride combined with metronidazole versus metronidazole alone in treating peri-implantitis and their impact on specific inflammatory markers. Methods: A retrospective review was undertaken of 107 patients with peri-implantitis from January 2018 to January 2021. Patients were treated either with metronidazole alone (Con group, n = 57) or with additional minocycline hydrochloride (Exp group, n = 50). Inflammatory markers, including interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and matrix metalloproteinase-8 (MMP-8) were determined before and after treatment. Clinical outcomes were determined using the plaque index (PLI), gingival sulcus bleeding index (SBI), and periodontal probing depth (PD). Furthermore, receiver operator characteristic (ROC) curves analyzed the clinical relevance of the markers. Logistic regression was conducted to analyze the risk factors affecting efficacy in patients. Results: The Exp group exhibited more favorable clinical outcomes and showed lower levels of IL-6, IL-1β, TNF-α, and MMP-8 than the Con group. IL-1β, TNF-α, and MMP-8 levels were significantly correlated with treatment success ($P < 0.05$), but IL-6 was not ($P > 0.05$). The ROC curves for IL-1β and TNF-α significantly outperformed those for IL-6 and MMP-8 ($P < 0.05$). Logistic regression analysis showed that only IL-1β and TNF-α were independent risk factors affecting efficacy in patients. Conclusion: Combining minocycline hydrochloride with metronidazole yields better outcomes for peri-implantitis compared to metronidazole alone. Of the factors analyzed, only IL-1β and TNF-α emerged as dependable independent efficacy indicators.

Keywords: Inflammatory factors, minocycline hydrochloride, metronidazole, peri-implantitis, efficacy

Introduction

Implant restoration is a common and crucial method to restore missing teeth in the clinic, including for patients with periodontitis [1]. With the continuous optimization of implant methods, the safety, reliability, and wearing comfort of implant restoration have been greatly improved [2]. Despite the high success rate of dental implants, complications such as peri-implantitis are still frequently seen [3]. Peri-implant diseases that affect the tissue around the implant can lead to inflammation [4]. The average prevalence of peri-implant mucositis based on the implant and on the subject are 29.48% and 46.83%, respectively [5].

Reportedly, inflammation is central to the progression and pathology of peri-implantitis. Certain inflammatory markers have gained attention as potential indicators of disease progression and therapeutic outcome. Specifically, interleukins (ILs), such as IL-6 and IL-1β, and tumor necrosis factor α (TNF-α) are key pro-inflammatory cytokines in the pathology of inflammatory conditions, including peri-implantitis [6]. IL-6, a multifunctional cytokine with crucial function in immune response modulation, has been found to increase in the peri-implant crevicular fluid (PICF) of peri-implantitis sites [7]. Its levels are correlated with the severity of inflammation and bone resorption. IL-1β, another significant pro-inflammatory cytokine, has been shown to be instrumental in the initiation of a host response against microbial challenges, especially in the oral environment. Elevated IL-1β concentrations in PICF are consistently associated with clinical signs of peri-

https://doi.org/10.62347/PYGW1604

implant inflammation and tissue breakdown [8]. TNF-α is a central mediator of the inflammatory response and is related to osteoclastogenesis, a critical process of bone loss in peri-implantitis. Recent research has shown that increased TNF-α in PICF can be a potent indicator of active peri-implant tissue destruction [9]. Matrix metalloproteinases (MMPs), particularly MMP-8, have also been highlighted in the context of peri-implant diseases. MMP-8, often termed collagenase-2, is involved in the degradation of extracellular matrix in pathologic processes. Elevated levels of MMP-8 have been reported in peri-implantitis sites, suggesting its involvement in the degradation of peri-implant tissues [10].

Currently, there is no standard treatment plan for peri-implantitis in clinical practice. Peri-implantitis is mainly intervened by active prevention and anti-infection therapy [11]. Metronidazole is a commonly used periodontal antibacterial drug. By inhibiting the synthesis of sensitive bacteria deoxyribonucleic acid, it can kill a variety of bacteria, and substantially alleviate symptoms such as gingival bleeding and periodontal pocket pyorrhea, so it has become a first choice for clinical therapy of periodontal diseases [12, 13]. However, treatment with only one drug delivers relatively lower clinical efficacy, so it is frequently prescribed with other drugs [14]. The antibacterial spectrum of minocycline hydrochloride is close to that of tetracycline, and its mechanism of action is to inhibit the synthesis of proteins by binding to the A position of bacterial ribosome 30S subunit, thereby preventing extension of the peptide chain, which is effective against tetracycline/penicillin-resistant Staphylococcus aureus, Streptococcus, Escherichia coli, and other drug-resistant bacteria [15, 16]. Minocycline hydrochloride and metronidazole are extensively used for treatment of peri-implantitis.

However, there is a lack of biological indicators for evaluating the efficacy of peri-implantitis. Given the evidence pointing towards the significance of these markers in peri-implantitis, the present study aims to further elucidate their roles in the context of specific therapeutic interventions, offering a more nuanced understanding of disease progression and treatment outcome.

Methods and data

Clinical data

Data of 107 patients with peri-implantitis treated in 980 Hospital, Joint Logistics Support Force of the People's Liberation Army from January 2018 to January 2021 were retrospectively analyzed. Among them, 57 patients treated with metronidazole were assigned to a control group (Con group), and the other 50 receiving additional minocycline hydrochloride were assigned to an experimental group (Exp group). This study was approved by the Medical Ethics Committee of 980 Hospital, Joint Logistics Support Force of the People's Liberation Army. Inclusion criteria: Patients who exhibited a gingival sulcus bleeding index (SBI) > 1, periodontal probing depth (PD) > 4 mm, and plaque index (PLI) > 1; patients who had their dental implant for over 6 months; patients with complete medical records; patients who received the specified drug treatment and inflammatory factor examinations after operation. Exclusion criteria: Patients without detailed clinical case data; patients with tumors, cardiovascular or cerebrovascular diseases, or other systemic conditions; patients who had consumed antibiotics or immunosuppressants within the two weeks prior to their consultation; patients who did not complete the treatment. A flow chart is provided in **Figure 1** to diagram the study.

Therapeutic regimen

Therapeutic regimen of the Con group: Each patient was given conventional therapy supplemented by metronidazole (Shandong Fangming Pharmaceutical Group Co., Ltd., China, State Food and Drug Administration (SFDA) approval number: H20057598, 20 g/0.15 g). Specifically, the upper gum was cleaned and scraped to remove tartar. Both the crown surface corresponding to the implant teeth and the implant abutment were cleaned with a curette. The surrounding implants were replaced and cleaned alternately using hydrogen peroxide and 0.9% sodium chloride solution, and adjuvant therapy with metronidazole was carried out by injecting metronidazole gel into the area around the prosthesis once a week, for 4 weeks.

Therapeutic regimen of the Exp group: On the basis of the Con group, additional minocycline

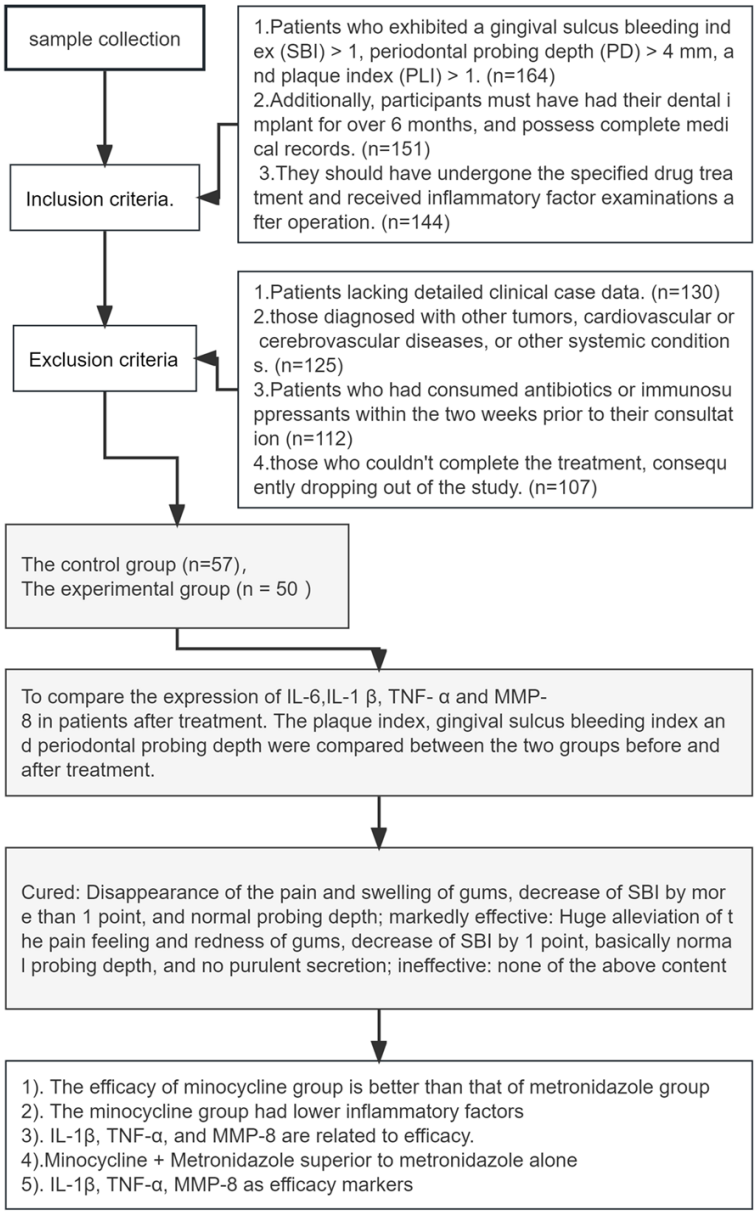

Figure 1. Study flow chart. Notes: PLI: plaque index; SBI: gingival sulcus bleeding index; PD: periodontal probing depth; IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; MMP-8: Matrix metalloproteinase-8.

therapy was given to the Exp group. Specifically, minocycline hydrochloride ointment (Japan, Sunstar INC, approval number: H20150106) was injected into the area around the implant, once a week, for 4 weeks.

Index detection

ELISA was used for quantification of IL-6 (ml058097), IL-1β (ml058059), TNF-α (ml077385), and MMP-8 (ml058676) in patients before and after the treatment with kits from Shanghai Enzyme-linked Biotechnology Co., Ltd. (China). Specifically, serum was extracted from patient blood samples, and 50 μL buffer for sample analysis was added to each well, followed by 2-h incubation with 50 μL serum (or standard) at room temperature. The plate was cleaned 5 times after incubation, followed by addition of biotinylated antibody (100 μl/well), sealing, and 1-h incubation at indoor temperature. Subsequently, the plate was cleaned again, followed by addition of horseradish peroxidase (100 μl/well), sealing, and 20-min incubation at indoor temperature in the dark. Then chromogenic substrate TMB was added (100 μl/well), followed by 20-min incubation at indoor temperature in the dark. Last, stopping solution was added (50 μl/well), and the value was read within 15 min. A microplate reader was adopted to measure the wavelength and determine the maximum absorption wavelength at 450 nm. Three groups of duplicate holes were set, and the assay was performed three times. All indicators were obtained from the patient's electronic medical records.

Evaluation criteria of efficacy

Cured: Disappearance of the pain and swelling around the gums, decrease of SBI by more than 1 point, and normal probing depth; markedly effective: Great alleviation of pain and redness around the gums, decrease of SBI by 1 point, basically normal probing depth, and no purulent secretion; ineffective: None of the above was met [17].

Table 1. Comparison of clinical data

Factor	Control group (n = 57)	Experimental group (n = 50)	*P*-value
Age (years)			0.444
≥ 35	27	20	
< 35	30	30	
Gender			0.194
Male	33	35	
Female	24	15	
BMI (kg/m^2)	22.45±3.40	23.23±3.06	0.217
Course of disease (years)	3.93±2.03	4.37±2.11	0.284
Past medical history			
Hypertension	16	13	0.810
Diabetes mellitus	10	11	0.563
Hyperlipemia	8	6	0.756
Implant restoration time	4.07±0.51	4.06±0.68	0.878

Note: BMI: Body mass index.

Table 2. Comparison of clinical efficacy

Group	Cured	Markedly effective	Ineffective
Control group (n = 57)	18	27	12
Experimental group (n = 50)	27	19	4
Z value		-2.581	
P-value		0.010	

Outcome measures

Primary outcome measures: The two groups were compared in terms of the expression of IL-6, IL-1β, TNF-α, and MMP-8 before and after therapy, and the clinical efficacy on the two groups after therapy was evaluated. PLI, SBI and PD of the two groups were compared before and after therapy. Logistic regression was conducted to analyze the risk factors affecting the efficacy on patients.

Secondary outcome measures: Patients with a cured or markedly effective response were assigned to the effective group, and those with an ineffective response were assigned to the ineffective group. The expression of IL-6, IL-1β, TNF-α, and MMP-8 was compared between these two groups after therapy. The clinical value of the 4 indicators in the efficacy evaluation of patients was analyzed through receiver operator characteristic (ROC) curves. The clinical data were also compared between the two groups.

Statistical analyses

In this study, SPSS20.0 was used for statistical analyses of the collected data, and GraphPad 7 for visualization of the data. A chi-square test was adopted to analyze the general data of patients. In terms of the biologic indicators of patients, the normally distributed data were described as the mean ± SD. Inter-group and intra-group comparisons of the data were conducted using the independent-samples t test and paired t test, respectively. ROC curves were drawn to evaluate the value of inflammatory factors in the evaluation of efficacy on peri-implantitis. Logistic regression was conducted to analyze the risk factors affecting the efficacy on patients. $P < 0.05$ was considered a significant difference.

Results

Comparison of clinical data

According to comparison of clinical data, the two groups did not differ in terms of age, gender, body mass index (BMI), course of disease, past medical history, or implant restoration time (all $P > 0.05$, **Table 1**).

Comparison of clinical efficacy between the two groups

The efficacy in the two groups was statistically analyzed. The Con group had 18 cured cases, 27 markedly effective cases, and 12 ineffective cases, while the Exp group had 27 cured cases, 19 markedly effective cases, and 4 ineffective cases. The rank sum test revealed better clinical efficacy in the Exp group than in the Con group ($P < 0.05$, **Table 2**).

Comparison of PLI, SBI, and PD between the two groups

The expression changes in PLI, SBI, and PD were compared between the two groups before and after therapy. Before therapy, the expression of them were similar between the two groups ($P > 0.05$), while after therapy, the

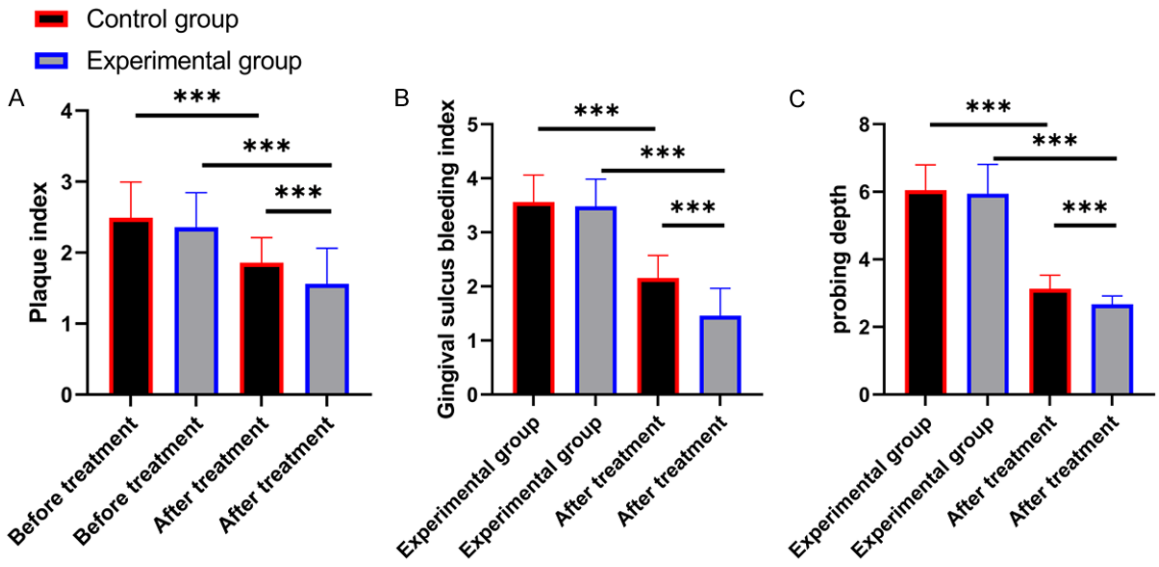

Figure 2. Comparison of PLI, SBI, and PD after therapy. A. Comparison of the changes in PLI between the two groups after therapy. B. Comparison of the changes in SBI between the two groups after therapy. C. Comparison of the changes in PD between two groups after therapy. Notes: ***P < 0.001; PLI: plaque index; SBI: gingival sulcus bleeding index; PD: periodontal probing depth.

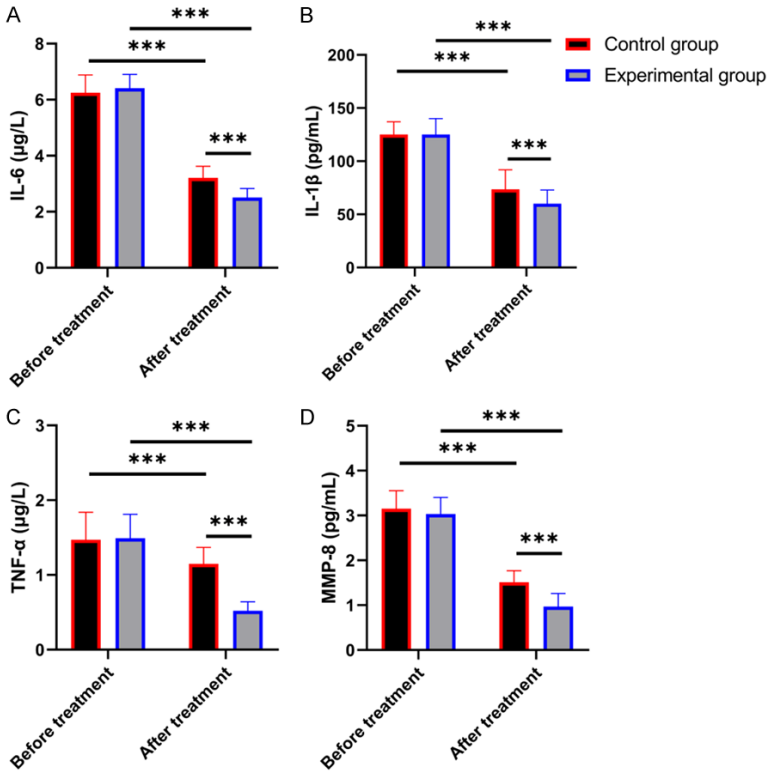

Figure 3. Changes in serum IL-6, IL-1β, TNF-α, and MMP-8 expression before and after treatment. A. Changes in serum IL-6 expression in the two groups before and after treatment. B. Changes in serum IL-1β expression in the two groups before and after treatment. C. Changes in serum TNF-α expression in the two groups before and after treatment. D. Changes in serum MMP-8 expression in the two groups before and after treatment. Notes: ***P < 0.001; IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; MMP-8: Matrix metalloproteinase-8.

expression levels decreased notably in both groups (P < 0.05), with lower expression levels in the Exp group than in the Con group (P < 0.05, **Figure 2**).

Changes in serum inflammatory indexes before and after therapy

The expression changes of IL-6, IL-1β, TNF-α, and MMP-8 were compared between the two groups before and after therapy. Before therapy, the expression of them was similar between the two groups (P > 0.05), while after therapy, the expression levels in both groups decreased (P < 0.05), with lower expression levels in the Exp group than in the Con group (P < 0.05, **Figure 3**).

Evaluation of inflammation indexes for efficacy in peri-implantitis

According to clinical efficacy, the patients were assigned to an effective group (n = 91) or

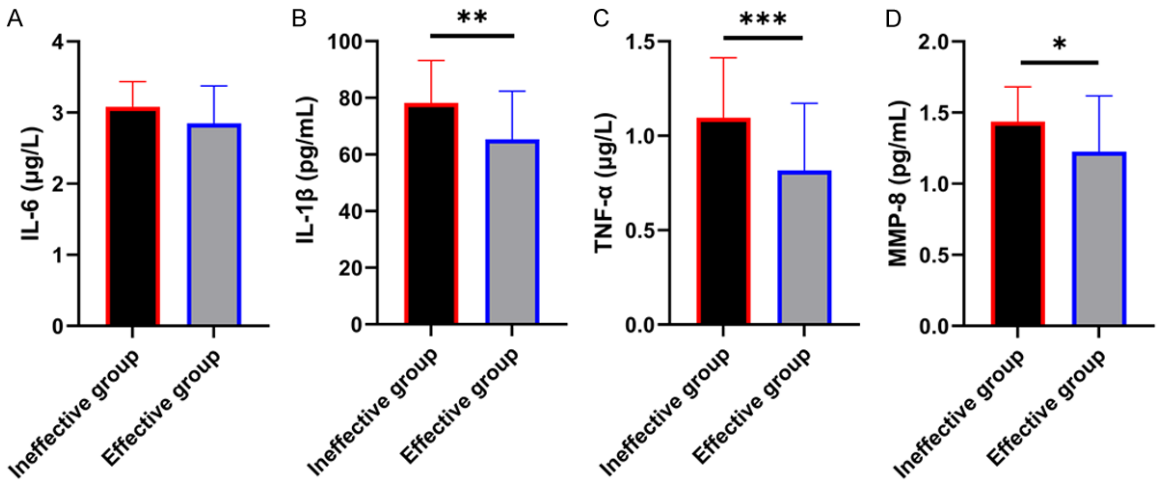

Figure 4. Expression of inflammatory indices in peri-implantitis patients experiencing different efficacy. A. Comparison of serum IL-6 expression between the effective group and the ineffective group after therapy. B. Comparison of serum IL-1β expression between the effective group and the ineffective group after therapy. C. Comparison of serum TNF-α expression between the effective group and the ineffective group after therapy. D. Comparison of serum MMP-8 expression between the effective group and the ineffective group after therapy. Notes: *P < 0.05, **P < 0.01, ***P < 0.001; IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; MMP-8: Matrix metalloproteinase-8.

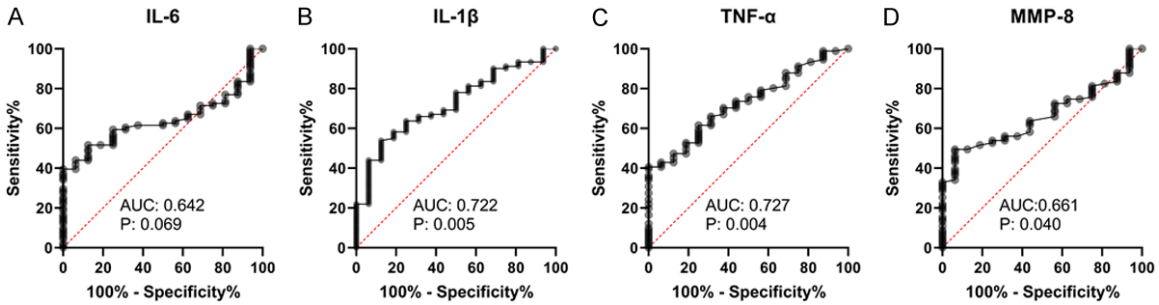

Figure 5. The value of inflammatory indices in evaluating efficacy in peri-implantitis. A. Value of IL-6 expression in evaluating efficacy. B. Value of IL-1β expression in evaluating efficacy. C. Value of TNF-α expression in evaluating efficacy. D. Value of MMP-8 expression in evaluating efficacy. Notes: IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; MMP-8: Matrix metalloproteinase-8.

an ineffective group (n = 16). These two groups were compared in terms of the expression of IL-6, IL-1β, TNF-α and MMP-8 before and after therapy, and notably lower levels of IL-1β, TNF-α, and MMP-8 were found in the effective group than in the ineffective group (all P < 0.05, **Figure 4**), but IL-6 was not different between the two groups (P > 0.05). According to further analysis based on ROC curves, the areas under the curves of IL-6, IL-1β, TNF-α, and MMP-8 for evaluating the clinical efficacy in patients with peri-implantitis were 0.643, 0.722, 0.728 and 0.661, respectively (**Figure 5**), but no statistical difference was found between curve of IL-6 and the standard line (P > 0.05). Therefore, IL-1β, TNF-α, and MMP-8 can be adopted as indices to evaluate the clinical efficacy in peri-implantitis. In addition, Delong test showed that there was no difference in the areas under the curves between IL-1β and TNF-α and between those of IL-6 and MMP-8. However, the areas under the curves of IL-1β and TNF-α were significantly larger than those of IL-6 and MMP-8 (P < 0.05, **Table 3**).

Analysis on risk factors of efficacy

Patients were divided into an effective group (n = 91) and an ineffective group (n = 16) according to efficacy. By comparison, it was found that

Table 3. DeLong test

Test pair	Z value	*P* value	AUC difference	Standard error	Asymptotic 95% confidence interval	
					Lower limit	Upper limit
IL6 - IL-1β	-2.334	0.020	-0.079	0.333	-0.146	-0.013
IL6 - TNF-α	-2.339	0.019	-0.085	0.329	-0.156	-0.014
IL6 - MMP-8	-1.216	0.224	-0.018	0.327	-0.048	0.011
IL1β - TNF-α	-0.112	0.910	-0.005	0.338	-0.101	0.090
IL-1β - MMP-8	2.324	0.020	0.061	0.335	0.010	0.113
TNF-α - MMP-8	1.79	0.073	0.067	0.332	-0.006	0.140

Notes: IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; MMP-8: Matrix metalloproteinase-8.

Table 4. Univariate analysis

Factor	Effective group (n = 91)	Ineffective group (n = 16)	*P*-value
Age (years)			0.595
≥ 35	39	8	
< 35	52	8	
Gender			0.639
Male	57	11	
Female	34	5	
BMI (kg/m^2)	23.11±3.83	22.76±3.17	0.460
Course of disease (years)	4.74±2.42	4.04±2.00	0.230
Past medical history			
Hypertension	24	5	0.685
Diabetes mellitus	17	4	0.557
Hyperlipemia	11	3	0.466
Implant restoration time	4.06±0.57	4.07±0.59	0.940

Note: BMI: body mass index.

Table 5. Assignment

Factor	Assignment
Therapeutic regimen	Control group = 1, experimental group = 0
IL-1β	≥ 65.545 = 1, < 65.545 = 0
TNF-α	≥ 0.7 = 1, < 0.7 = 0
MMP-8	≥ 1.4 = 1, < 1.4 = 0
Efficacy	Cured + Markedly effective = 0, Ineffective = 1

Note: TNF-α: Tumor necrosis factor alpha.

IL-1β, TNF-α, and MMP-8 were strongly correlated with the efficacy in patients ($P < 0.05$, **Table 4**). The risk factors were assigned (**Table 5**), and then subjected to logistic regression analysis. As a result, only IL-1β and TNF-α were found to be independent risk factors affecting the efficacy ($P < 0.05$, **Table 6**).

Discussion

After peri-implantitis, there will be inflammatory hyperplasia in the mucosa near the implant, abscess and fistula, which are harmful to patients' oral health. Without treatment, the recipient may eventually lose the implant due to these symptoms [18]. As a direct result of the increasing popularization of dental implants, a growing number of related complications have been found [19]. However, there is currently no standardized therapeutic regimen in clinical practice, so it is of great significance to search for an effective therapeutic regimen for peri-implantitis.

Currently, supragingival scaling and subgingival curettage are usually adopted as basic therapy in clinical scenarios, but subgingival plaque around the implant can trigger peri-implantitis, so metronidazole supplemented with antibiotics can inhibit the formation of bacterial deoxyribonucleic acid as well as the reproduction and growth of bacteria [20]. With a good sterilization effect, metronidazole is the first choice for cli nical therapy of peri-implantitis [21]. However, according to recent research, the use of antibiotics alone will increase the drug resistance in patients and reduce the efficacy [22]. Therefore, combined antibiotic therapy is frequently adopted in clinical practice for higher efficacy. As a semi-synthetic tetracycline antibiotic with broad-spectrum antibacterial activity, minocycline hydrochloride possesses remarkable effects on facultative anaerobes. It can kill the pathogenic bacteria around the implant, and inhibit the bacteria from adhering to the surface of the implant, and serve as a strong anti-inflammato-

Table 6. Risk factor analysis

Factor	β	Standard error	Wald	*P* value	OR value	95% CI	
						Lower limit	Upper limit
Therapeutic regimen	1.159	0.660	3.080	0.079	3.187	0.873	11.629
IL-1β	2.116	0.807	6.875	0.009	8.301	1.706	40.378
TNF-α	1.534	0.721	4.522	0.033	4.638	1.128	19.075
MMP-8	0.423	0.617	0.471	0.493	1.527	0.456	5.115

Notes: IL-1β: interleukin 1 beta; TNF-α: tumor necrosis factor alpha; MMP-8: matrix metalloproteinase 8.

ry drug [23]. The present study compared the effects of minocycline combined with metronidazole and metronidazole alone for peri-implantitis. Similar to the results acquired by Sun et al. [24], the results of the present study showed that minocycline combined with metronidazole delivered higher clinical efficacy and substantially improved the clinical efficacy, PD, PLI, and SBI.

Peri-implantitis refers to the inflammation-dominated lesions around the implant with osseointegration [25]. The present study analyzed the expression changes in IL-6, IL-1β, TNF-α, and MMP-8 before and after therapy. IL-6 is a pleiotropic cytokine, which participates in not only immune response, but also inflammation, hematopoiesis, bone metabolism, embryonic development, and other basic processes [26]. Prior research has revealed that IL-6 could reflect inflammation by a notably increased expression in the process of human inflammatory reaction [27]. IL-1β is one of the earliest recognized cytokines and an effective pro-inflammatory cytokine, which is crucial for the host's defense response to infection and injury [28]. TNF-α is a frequently seen inflammatory factor produced by the secretion of macrophages and adipocytes in adipose tissue, and its expression increases in the case of inflammation, tumor, or infection in the body [29]. The expression of MMP-8 mainly comes from fibroblasts and macrophages in patients' gingival crevicular fluid, which takes a particularly crucial part in the process of tissue destruction [30]. In the present study, inflammatory indexes in the two groups before and after therapy were determined. After therapy, the Exp group showed notably lower expression of serum IL-6, IL-1β, TNF-α, and MMP-8 than the Con group, indicating that for patients with peri-implantitis, the combined therapy can promote plaque regression and reduce inflammatory reaction. This is primarily due to the fact that with a good affinity to the bone tissue of patients with periodontitis around the implant and strong infiltration ability, minocycline helps to resist the corresponding enzyme activity of collagenase and promote the regeneration of periodontal tissue, thus actively improving the periodontal index and delivering a better local therapy effect. Finally, the value of IL-6, IL-1β, TNF-α and MMP-8 after therapy in the evaluation of efficacy was analyzed. IL-1β, TNF-α, and MMP-8 were found to be useful indices to evaluate peri-implantitis. In addition, through Delong test, it was found that the areas under the curves of IL-1β and TNF-α were larger than those of IL-6 and MMP-8, suggesting a certain value of IL-1β and TNF-α in predicting efficacy.

At the end of the study, it was identified that only IL-1β and TNF-α were independent risk factors affecting the efficacy in patients. IL-1β and TNF-α play a key role in inflammatory reaction and also take a crucial part in chronic inflammation, such as periodontal disease, bone absorption, connective tissue degradation, and immune cell activation. They may affect the severity and treatment response of implant inflammation through these mechanisms. In the development of periodontal disease and implant inflammation, the interaction between host immune response and microorganisms plays a key role. IL-1β and TNF-α can reflect the host's immune response, which may in turn affect the therapeutic effect. However, in the present research, the therapeutic regimen was not an independent risk factor affecting the efficacy in patients, possibly because the therapeutic regimen itself had no significant influence on the efficacy after controlling for other variables (such as the levels of IL-1β and TNF-α).

However, this study still has limitations. Firstly, the sample size collected in this study is small. Secondly, we did not include healthy samples

for comparison. Finally, prior research has found it is more accurate to detect patients' gingival crevicular fluid for diagnosis of gum-related diseases. However, since this study is a retrospective study, it is impossible to collect more clinical samples. Therefore, we hope to carry out a randomized controlled study in the future to improve the study design.

In summary, minocycline hydrochloride combined with metronidazole is superior to metronidazole alone in the treatment of peri-implantitis. Expression of IL-1β and TNF-α can serve as reliable independent predictors for evaluating the clinical efficacy in patients after therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Yonghong Zhang, Dental Department, 980 Hospital, Joint Logistics Support Force of The People's Liberation Army, No. 398 Zhongshan West Road, Shijiazhuang 050082, Hebei, P. R. China. E-mail: zhangyonghong0614@163.com

References

[1] Schwarz F, Derks J, Monje A and Wang HL. Peri-implantitis. J Periodontol 2018; 89 Suppl 1: S267-S290.

[2] Block MS. Single-implant treatment. Oral Maxillofac Surg Clin North Am 2019; 31: 251-258.

[3] Carpentieri J, Greenstein G and Cavallaro J. Hierarchy of restorative space required for different types of dental implant prostheses. J Am Dent Assoc 2019; 150: 695-706.

[4] Fu JH and Wang HL. Breaking the wave of peri-implantitis. Periodontol 2000 2020; 84: 145-160.

[5] de Avila ED, van Oirschot BA and van den Beucken JJJP. Biomaterial-based possibilities for managing peri-implantitis. J Periodontal Res 2020; 55: 165-173.

[6] Lauper K, Iudici M, Mongin D, Bergstra SA, Choquette D, Codreanu C, Cordtz R, De Cock D, Dreyer L, Elkayam O, Hauge EM, Huschek D, Hyrich KL, Iannone F, Inanc N, Kearsley-Fleet L, Kristianslund EK, Kvien TK, Leeb BF, Lukina G, Nordstrom DC, Pavelka K, Pombo-Suarez M, Rotar Z, Santos MJ, Strangfeld A, Verschueren P, Courvoisier DS and Finckh A. Effectiveness of TNF-inhibitors, abatacept, IL6-inhibitors and JAK-inhibitors in 31846 patients with rheumatoid arthritis in 19 registers from the 'JAK-pot' collaboration. Ann Rheum Dis 2022; 81: 1358-1366.

[7] Li M, Li Z, Ma X, Jin S, Cao Y, Wang X, Zhao J, Wang J, Wang X and Xu J. Huangqi Guizhi Wuwu Decoction can prevent and treat oxaliplatin-induced neuropathic pain by TNFalpha/IL-1beta/IL-6/MAPK/NF-kB pathway. Aging (Albany NY) 2022; 14: 5013-5022.

[8] Zhang Y, He F, Chen Z, Su Q, Yan M, Zhang Q, Tan J, Qian L and Han Y. Melatonin modulates IL-1beta-induced extracellular matrix remodeling in human nucleus pulposus cells and attenuates rat intervertebral disc degeneration and inflammation. Aging (Albany NY) 2019; 11: 10499-10512.

[9] Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR and Yang SH. The role of tumor necrosis factor alpha (TNF-alpha) in autoimmune disease and current TNF-alpha inhibitors in therapeutics. Int J Mol Sci 2021; 22: 2719.

[10] Su GJ, Zhang D, Wu JN, Deng YH, Wu CW, Zhang XJ and Huang XJ. Immunoexpression of MMP-8 and MMP-9 in chronic subdural hematoma. Front Neurol 2022; 13: 988854.

[11] Berglundh T, Jepsen S, Stadlinger B and Terheyden H. Peri-implantitis and its prevention. Clin Oral Implants Res 2019; 30: 150-155.

[12] Nadelson S, Reed D, Massey M, Lowder T and Yarberry F. Faculty perceptions of curiosity in the education of nursing and health science students. J Mod Nurs Pract Res 2022; 2: 1.

[13] Hernandez Ceruelos A, Romero-Quezada LC, Ruvalcaba Ledezma JC and Lopez Contreras L. Therapeutic uses of metronidazole and its side effects: an update. Eur Rev Med Pharmacol Sci 2019; 23: 397-401.

[14] Dingsdag SA and Hunter N. Metronidazole: an update on metabolism, structure-cytotoxicity and resistance mechanisms. J Antimicrob Chemother 2018; 73: 265-279.

[15] Zhang T, Qiu Y, Song J, Zhou P, Liao H, Cheng Y and Wu X. Electrosprayed minocycline hydrochloride-loaded microsphere/SAIB hybrid depot for periodontitis treatment. Drug Deliv 2021; 28: 620-633.

[16] Qian W, Qiu J and Liu X. Minocycline hydrochloride-loaded graphene oxide films on implant abutments for peri-implantitis treatment in beagle dogs. J Periodontol 2020; 91: 792-799.

[17] Wang CW, Ashnagar S, Gianfilippo RD, Arnett M, Kinney J and Wang HL. Laser-assisted regenerative surgical therapy for peri-implantitis: a randomized controlled clinical trial. J Periodontol 2021; 92: 378-388.

[18] Mordini L, Sun N, Chang N, De Guzman JP, Generali L and Consolo U. Peri-implantitis re-

generative therapy: a review. Biology (Basel) 2021; 10: 773.
[19] Kotsakis GA and Olmedo DG. Peri-implantitis is not periodontitis: scientific discoveries shed light on microbiome-biomaterial interactions that may determine disease phenotype. Periodontol 2000 2021; 86: 231-240.
[20] Chambrone L, Wang HL and Romanos GE. Antimicrobial photodynamic therapy for the treatment of periodontitis and peri-implantitis: an American Academy of Periodontology best evidence review. J Periodontol 2018; 89: 783-803.
[21] Lin GH, Suarez Lopez Del Amo F and Wang HL. Laser therapy for treatment of peri-implant mucositis and peri-implantitis: an American Academy of Periodontology best evidence review. J Periodontol 2018; 89: 766-782.
[22] Wiedemann TG. A clinical approach to treatment of retrograde peri-implantitis. Compend Contin Educ Dent 2021; 42: 170-175; quiz 176.
[23] Tian B. Clinical observation of minocycline hydrochloride ointment in the treatment of early peri-implantitis. Pak J Pharm Sci 2019; 32: 2535-2538.
[24] Sun W. Clinical efficacy of minocycline and metronidazole in the treatment of peri-implant inflammation. Journal of Clinical Rational Drug Use 2021; 14: 3.
[25] Belibasakis GN and Manoil D. Microbial community-driven etiopathogenesis of peri-implantitis. J Dent Res 2021; 100: 21-28.
[26] Tanaka T, Narazaki M and Kishimoto T. Interleukin (IL-6) immunotherapy. Cold Spring Harb Perspect Biol 2018; 10: a028456.
[27] Tanaka T, Narazaki M and Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014; 6: a016295.
[28] Wang Y, Che M, Xin J, Zheng Z, Li J and Zhang S. The role of IL-1beta and TNF-alpha in intervertebral disc degeneration. Biomed Pharmacother 2020; 131: 110660.
[29] Romanowska-Prochnicka K, Felis-Giemza A, Olesinska M, Wojdasiewicz P, Paradowska-Gorycka A and Szukiewicz D. The role of TNF-alpha and anti-TNF-alpha agents during preconception, pregnancy, and breastfeeding. Int J Mol Sci 2021; 22: 2922.
[30] Hernandez M, Baeza M, Raisanen IT, Contreras J, Tervahartiala T, Chaparro A, Sorsa T and Hernandez-Rios P. Active MMP-8 quantitative test as an adjunctive tool for early diagnosis of periodontitis. Diagnostics (Basel) 2021; 11: 1503.