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Original Article

Efficacy of minocycline hydrochloride ointment in combination with tinidazole to treat chronic periodontitis

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Abstract: Objective: The goal of this study was to evaluate the clinical efficacy and safety of minocycline hydrochloride ointment in combination with tinidazole for the treatment of chronic periodontitis. Methods: A total of 140 patients with chronic periodontitis were analyzed prospectively and randomly divided into a control group (N=70) and an observation group. The control group were administered minocycline hydrochloride ointment (the control group); the injection was administered once a week for 4 weeks. The observation group was treated with 250 mg/d tinidazole for 4 weeks along with provision of the ointment as done for the control group. After the course of treatment, clinical efficacy, plaque index (PLI), periodontal pocket depth (PPD), gingival index (GI), and the incidence of adverse reactions were compared between the two groups. Results: After treatment, the PLI, PPD, and GI of the two groups were significantly different from those before the treatment ($P<0.05$). There was a significant difference in the decreased indices of the two groups ($P<0.05$) where patients in the control group exhibited symptoms such as nausea, skin pruritus, and dizziness, which were not statistically significant as compared to those observed in the observation group participants ($P>0.05$). The differences in effectiveness percentages for the two groups were statistically significant ($P<0.05$). Conclusion: The use of minocycline hydrochloride ointment in combination with tinidazole is effective in the treatment of chronic periodontitis, and the administration of this drug combination does not increase the incidence of adverse reactions.

Keywords: Minocycline hydrochloride, tinidazole, combined application, chronic periodontitis, safety assessment

Introduction

Chronic periodontitis (CP) is an infectious disease that manifests as an inflammatory reaction due to the obstruction of periodontal support tissues by microbes in dental plaques [1]. The incidence of periodontitis all around the world is high. Statistics [2] indicate its incidence in adults to be up to 30% with more than 10% of the patients suffering from severe periodontal injury. Surveys in Asia and other regions have shown that [3] this periodontal disease accounts for a large proportion of adults with dental problems and is the main cause of tooth loss in them as well. Clinically, periodontal disease is characterized by redness and swelling of gums. A small amount of bleeding, alveolar bone resorption, and tooth loosening has been reported from probe examinations [4]. These dental problems exert negative effects on the daily life and diet of patients. At present, the main treatment method for CP is removal of plaque by mechanical means, but mechanical cleaning has its limitations in reaching the infection present in deep locations within the mouth. Therefore, patients with such infections are usually treated with drugs, which achieve good efficacy, and thus, have been widely applied in clinics [5]. Supragingival and subgingival administration are the two methods of drug application, whereby antiseptic drugs are applied by mouth washing or by flushing via periodontal pocket controlled release system, respectively, to relieve patients of the condition [6]. Studies [7] have demonstrated that an ideal treatment of chronic periodontitis can be achieved by local application of doxycycline polymer, tetracycline fiber, minocycline gel, and tinidazole gel.

Tinidazole (TNZ) is a nitroimidazole derivative with a better curative effect, a short course of treatment, and better tolerance than metronidazole [8]. Its key function is to inhibit the synthesis of DNA in microbial cells, degrade microbial DNA, destroy the cell structure, and block transcription and replication, and ultimately, cause cell death [9]. Studies [10] have shown that the plasma concentration of TNZ, when administered orally, is very close to the drug concentration in gingival crevicular fluid (GCF) and has a significant antibacterial effect on periodontal bacteria. Minocycline hydrochloride (MH) is a broad-spectrum antibiotic in Class I, with a mechanism of action to block the synthesis of bacterial proteins. In clinics, MH ointment is applied to treat periodontitis [11].

In this study, the efficacy of TNZ in combination with MH ointment for the treatment of CP was investigated.

Materials and methods

A total of 140 patients, who were diagnosed with CP and were admitted in Affiliated Hospital of Yangtze University, were prospectively analyzed. According to the random number table method, 70 patients were included in the control group; among these 35 were males and 35 were females in the age range of 22-58 years. The average age was 35.3±12.8 years. 70 cases were included in the observation group; 36 of these were males and 34 were females in the age range of 26-56 years with an average age of 36.8±11.6 years. The study was approved by the Medical Ethics Committee of Affiliated Hospital of Yangtze University. All the patients' families were informed and requested to sign for informed consent.

The inclusion and exclusion criteria

Inclusion criteria: Patients were all older than 18 years and did not suffer from any congenital disease, diabetes, or hypertension, etc. All patients had more than 2 teeth with periodontitis in which the pocket probing device reached deeper than 4 mm. The patients had no history of allergy to the drugs investigated in this study.

Exclusion criteria: Patients with facial tumors, incomplete limbs, HIV infection, pregnant women, incompliance to the treatment and follow-up, and those with incomplete clinical data were excluded.

Reagents and instruments

In this study, the dental comprehensive treatment table HB2000B was purchased from Shanghai Siou Medical Equipment Co., Ltd. The MH ointment was purchased from Japan Sunstar Inc. and had a strength of 0.5 g/bottle (batch number: H20100244). Tinidazole was purchased from Hunan Dino Pharmaceutical Co., Ltd and had a strength of 0.5 g/tablet.

Therapeutic method

Patients in the control group were treated with the MH ointment via a periodontal injection for a week. The observation group was orally given 0.25 g/day TNZ for adjunctive therapy along with the treatment given to the control group for 4 consecutive weeks. In this study, the patients were treated for 4 weeks. During this period, the patients were not allowed to take non-steroidal drugs, immune-modulators, anti-inflammatory drugs, and antibiotics for treatment of inflammation.

Outcome measures

Primary outcome measures: Plaque index (PLI), periodontal pocket depth (PPD), and gingival index (GI) were compared between the two groups before and after treatment. Secondary observation: After treatment, the therapeutic effects and occurrence of adverse reactions including nausea, itchy skin, and dizziness in the two groups were evaluated.

Evaluation of treatment efficacy

The two groups of patients were evaluated for criteria defined by excellence, effectiveness, and ineffectiveness. Excellence was defined as a complete disappearance of the clinical symptoms in the patients or disappearance/reduction of the periodontal pocket depth (≤2 mm), a status of rest for alveolar bone absorption, disappearance of the inflammatory response, and the ability of the patient to chew normally. Effectiveness was defined as the condition in which clinical symptoms of the patients improved: the inflammatory response was weakened, the periodontal pocket became shallower (>2 mm), the alveolar bone absorption was stable, and the masticatory ability of the patients improved. Ineffectiveness was defined as the state of no significant improvement after the treatment, although the condition was not further aggravated. Effectiveness rate (%) =

Table 1. Clinical data for patients [n (%)]

Group	Control group (n=70)	Observation group (n=70)	X^2/t	*P* value
Sex			0.029	0.866
Male	35 (50.00)	36 (51.43)		
Famale	35 (50.00)	34 (48.57)		
Age (years)	35.3±12.8	36.8±11.6	0.727	0.469
BMI (kg/m^2)	22.8±1.5	22.6±1.8	0.714	0.476
Course of disease (year)	4.6±2.7	4.7±2.2	0.240	0.810
Average number of affected teeth	2.28±0.41	2.16±0.38	1.796	0.075

Table 2. Comparison of outcome measures before and after treatment

Group	PLI		PPD		GI	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	1.76±0.62	1.26±0.58*	6.05±0.62	3.99±0.60*	2.90±0.53	1.28±0.36*
Observation	1.78±0.58	0.86±0.20$^{*,\#}$	5.94±0.55	2.08±0.36$^{*,\#}$	2.88±0.44	0.59±0.16$^{*,\#}$
t	0.197	5.395	1.110	22.838	0.243	14.654
P value	0.844	<0.001	0.269	<0.001	0.808	<0.001

Note: *indicates that there is a difference between the two groups before treatment as compared to the same group before treatment (P<0.05) While $^\#$indicated comparison with the control group after treatment (P<0.05).

[(excellent cases + effective cases)/total cases] × 100.

Statistical analysis

SPSS 20.0 software was used in the study to statistically analyze the collected data. GraphPad Prism 7 was used to draw the required figures. The counted data are expressed as percentage (%). The recorded data are presented as the mean ± standard deviation (mean ± SD). For intragroup before-and-after comparison, pairwise t test was used. For between group comparisons, independent t test was used. P<0.05 indicated significant difference.

Results

Comparison of clinical data

A comparison of the clinical data from the two groups of patients showed that there was no statistically significant difference between the two groups of patients in their genders, ages, BMIs, the course of disease (periodontitis), or the average number of affected teeth (P>0.05), which indicated that the patients in the two groups were comparable (**Table 1**).

Comparison of observation indices before and after treatment

An examination of the values of PLI, PPD, and GI in the two groups of patients before and after treatment revealed no significant difference in the indices of the two groups before treatment (P>0.05), but there was a significant difference between the indices after treatment (P<0.05). The extent of decrease in the indices in the observation and control groups was significantly different (P<0.05; **Table 2**; **Figure 1**).

Occurrence of adverse reactions in the two groups

By comparing the occurrence of adverse reactions in the two groups of patients during the treatment, it was found out that the symptoms of nausea, itching, and dizziness were not statistically significant as compared to those in the observation group (P>0.05; **Table 3**).

Comparison of treatment efficacy in the two groups of patients

A comparison of the treatment efficacy in the two groups of patients demonstrated the therapy to be excellent in the control group in only 19 cases, effective in 37 cases, and ineffective in 14 cases. On the other hand, in the observation group, the treatment was excellent in 37 cases, effective in 29 cases, and ineffective in 4 cases. The effectiveness percentage in the two groups was not significantly different (P< 0.05; **Table 4**).

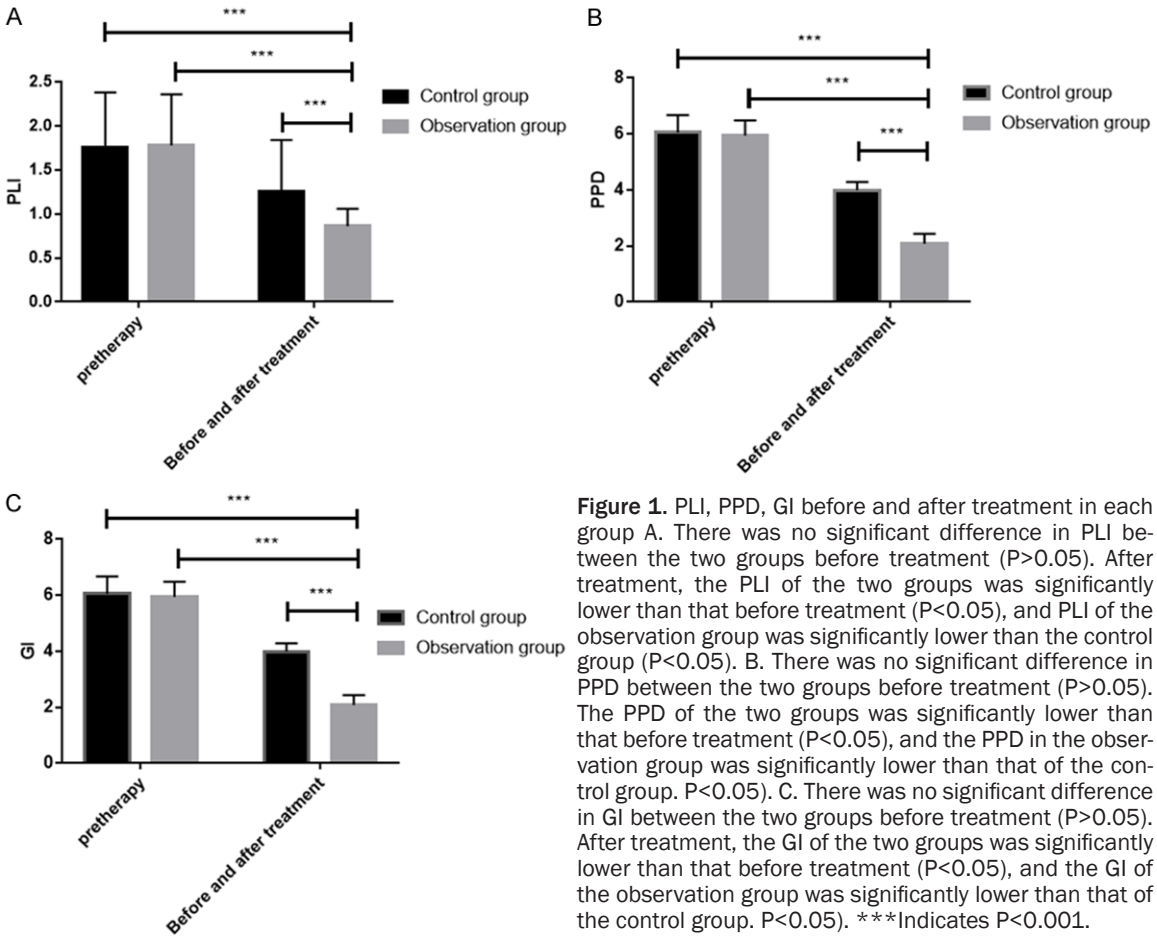

Figure 1. PLI, PPD, GI before and after treatment in each group A. There was no significant difference in PLI between the two groups before treatment (P>0.05). After treatment, the PLI of the two groups was significantly lower than that before treatment (P<0.05), and PLI of the observation group was significantly lower than the control group (P<0.05). B. There was no significant difference in PPD between the two groups before treatment (P>0.05). The PPD of the two groups was significantly lower than that before treatment (P<0.05), and the PPD in the observation group was significantly lower than that of the control group. P<0.05). C. There was no significant difference in GI between the two groups before treatment (P>0.05). After treatment, the GI of the two groups was significantly lower than that before treatment (P<0.05), and the GI of the observation group was significantly lower than that of the control group. P<0.05). ***Indicates P<0.001.

Table 3. Occurrence of adverse reactions in patients [n (%)]

Group	Nausea	Itchy skin	Dizziness
Control group (n=70)	4 (6.45)	6 (9.68)	5 (8.06)
Observation group (n=70)	2 (2.86)	2 (2.86)	2 (2.86)
P	0.404	0.145	0.247

Discussion

The incidence of oral diseases in Asian adults is as high as 90%, where CP is among the most common periodontal diseases. Studies [12] have shown that the onset and progression of CP is related to the age of patients. The development in the course of CP is divided into 4 stages. (1) Epithelial cells in the tooth furrow and the nearby capillaries congest and expand and a large number of neutrophils infiltrate the epithelial tissue and the connective tissue below it; (2) The number of inflammatory cells in the connective tissue increases. The collagen is destroyed and the epithelium is proliferated; (3) A large number of immune factors are released in the tooth furrow and form the initial periodontal pocket; (4) The periodontal pockets deepen, and the alveolar bone absorption leads to tooth loss [13, 14]. Due to these subtle stages, CP is not easily diagnosed in its early stage, and thus, delayed treatment may lead to tooth loosening or even loss of masticatory ability in severe cases [15].

The traditional method of treating CP is to perform periodontal scaling and root planing with appropriate instruments to remove plaque from the tooth surface effectively, but plaque present in the periodontal pocket cannot be effectively removed because it has invaded the human body to some extent [16]. As it is the main cause of periodontitis, the plaque must be effectively inhibited and eliminated, which is the key to eradicating periodontitis. Some studies [17] have shown that a significant improvement can be achieved in the treatment of CP via local injection of drugs because it helps to

Table 4. Comparison of treatments in patients [n (%)]

Group	Excellence	Effectiveness	Ineffectiveness	X^2 value	*P* value
Control group (n=70)	19 (27.14)	37 (52.86)	14 (20.00)	12.311	0.002
Observation group (n=70)	37 (52.86)	29 (41.43)	4 (5.71)		

effectively reduce the occurrence of adverse reactions to systematic drug application. Furthermore, direct delivery of the drug to the exact location of infection helps maintain a higher drug concentration.

The MH ointment is a locally-applied agent with sustained release and an active ingredient of minocycline, which works by inhibiting the synthesis of bacterial proteins and deactivating collagenase in periodontal tissue as well as by promoting the proliferation of periodontal ligament fibroblast [18, 19]. There are studies [19, 20] showing that MH ointment has an inhibitory effect on a variety of anaerobes, and that it improves CP caused by Clostridium's nuclear proteins and porphyrin. A new type of antibiotic, TNZ, has strong anti-anaerobic activity, and thus, effectively inhibits the growth of bacteria by blocking DNA transcription in their cells [21]. Studies [21, 22] have shown that the germicidal efficacy of TNZ is much higher than that of metronidazole and it is thus well tolerated by patients. Therefore, TNZ is effective for the treatment of CP and has been widely promoted in clinical practice.

In this study, an improvement in CP was observed by the combined application of two drugs: MH ointment and TNZ. First, PLI, PPD, and GI of the patients in the two groups before and after treatment was analyzed to find out that there was no difference between the two groups before treatment, but a significant difference after treatment. By comparing PLI, PPD, and GI of patients in the two groups after the treatment, each index was significantly higher in the control group than in the observation group. This indicates that the MH ointment had a significant effect on the treatment of CP, which was more obvious, when the ointment was applied in combination with TNZ. In a study by Abbas [23], it was reported that a combination of MH and TNZ significantly improved CP and other periodontal conditions, which is consistent with our conclusions in this study. The occurrence of adverse reactions in patients was also analyzed and there was no difference in the adverse reactions between the two groups, which may be due to the limited number of participants in this study. At the end of the study, the extent of improvement in the two groups of patients was analyzed and revealed that the number of patients with excellent improvement in the observation group that were administered the combination of drugs; improvement in their condition was significantly better as compared to that in the control group. The effectiveness percentage in the observation group was significantly higher than that in the control group. In a study by Yang [23], it has been reported that the combined use of MH and TNZ has a significant effect on CP and that it effectively reduces the recurrence of CP in patients. Although this study suggested that MH in combination with TNZ was effective in the treatment of CP to some extent, there are some limitations. First, the number of subjects was limited. Second, the occurrence of adverse reactions in patients through follow-ups for a long time period was not tracked. In the future, the hope is to increase the number of subjects and increase follow-up time to verify our conclusions and provide better evidence for clinicians.

In summary, the use of MH ointment in combination with TNZ is effective for the treatment of CP. This medication does not increase the chance of adverse reactions, and thus, is suitable for clinical promotion.

Disclosure of conflict of interest

None.

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