

## Original Article

# Minocycline hydrochloride ointment combined with Vitapex paste is effective for middle-aged and elderly patients with combined periodontal-endodontic lesions

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**Abstract:** Objective: This study was designed to determine the efficacy of minocycline hydrochloride ointment (MHO) combined with Vitapex paste on middle-aged and elderly patients with combined periodontal-endodontic lesions (CPELs) and its effect on the inflammatory factors. Methods: The data of 88 elderly patients with CPELs treated in the First Affiliated Hospital of Gannan Medical University from March 2020 to March 2022 were analyzed retrospectively. Among them, the patients treated with MHO and iodoform zinc oxide clove oil paste were assigned into the control group (n = 42) and the rest of the patients treated by MHO and Vitapex paste were assigned to the study group (n = 46). The inflammatory factors, periodontal indexes and efficacy were determined and compared between the two groups. The MOS 36-Item Short-Form Health Survey (SF-36) was adopted to evaluate the quality of life (QoL) of patients before and after treatment. Additionally, the adverse reactions of the two groups during treatment were analyzed and compared. The prognosis of the two groups of patients was analysed, and factors impacting their prognosis was analysed through the Logistic regression analysis. Results: Before treatment, the levels of interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) were not significantly different between the two groups (all  $P > 0.05$ ), while after treatment, these levels in both groups decreased significantly, with notably lower levels in the study group than those in the control group (all  $P < 0.05$ ). Before treatment, the gingival index (GI), plaque index (PLI), probing depth (PD) and bleeding index (BD) of the two groups were similar (all  $P > 0.05$ ); however, after treatment, the levels of GI, PD, PLI and BI of both groups decreased significantly (all  $P < 0.05$ ), with more notable decreases in the study group than those in the control group (all  $P < 0.05$ ). The study group showed a significantly higher overall response rate than the control group ( $P < 0.05$ ). Before treatment, the SF-36 scores of the two groups were not significantly different ( $P > 0.05$ ), while after treatment, both groups had significantly increased SF-36 scores, and the score in study group was significantly higher than the control group ( $P < 0.05$ ). In addition, the incidence of adverse reactions was not notably different between the two groups ( $P > 0.05$ ). According to univariate analysis, age, dental lesion grade, course of disease, and persistent dull pain were the risk factors affecting the prognosis of patients. According to multivariate analysis, dental lesion grade was the independent risk factor affecting the prognosis. Conclusion: MHO combined with Vitapex paste is effective for middle-aged and elderly patients with CPELs, which can effectively inhibit the patients' inflammatory reaction and improve their periodontal condition and QoL, with a low adverse reaction rate, so it is worthy of clinical promotion.

**Keywords:** Minocycline hydrochloride ointment, Vitapex paste, combined periodontal-endodontic lesions, efficacy, inflammatory factors

## Introduction

As a common oral disease, combined periodontal-endodontic lesions (CPELs) are mainly triggered by bacterial infection that damage the

periodontal tissue and dental pulp tissues [1]. Due to tooth wear, gingival atrophy, dentin exposure and physiological alveolar bone resorption, middle-aged and elderly people present a higher incidence of CPELs than young people [2].

With the characteristics of both periodontal disease and dental pulp disease, CPELs have complicated symptoms, resulting in difficulty for clinicians in diagnosis and therapy [3]. In recent years, the research on CPELs at home and abroad has been deepened, and some progress has been achieved in terms of its pathogenesis, diagnosis and therapy.

CPELs require both endodontic treatment and periodontal treatment for alleviation and therapy of the diseased tooth [3, 4]. Minocycline hydrochloride ointment (MHO) has been extensively adopted in patients with CPELs over the past few years. It is a type of periodontal sustained-release local drug, with the main component of minocycline hydrochloride, which has the advantages of broad antibacterial spectrum and few drug-resistant bacteria [5]. It can alleviate various symptoms such as periodontitis and pulpitis caused by *Porphyromonas gingivalis*, *Prevotella intermedia*, *Prevotella melaninogenica*, *Eikenella corrodens*, *Fusobacterium nucleatum* and *Actinobacillus* [6, 7]. However, MHO may bring relatively serious side effects, including gastrointestinal symptoms, gastrointestinal diseases and dizziness [8]. Vitapex paste is a novel type of root canal filler, mainly composed of polysiloxane oil, iodoform and calcium hydroxide. With continuous antibacterial properties, Vitapex can strongly inhibit the reproduction of residual bacteria in root tip and sinus, and prevent reinfection and recurrence of clinical symptoms [9]. With the feature of strong tissue penetration, it can be absorbed by tissues and induce new bone tissue. Moreover, Vitapex has little reaction to foreign bodies in tissues and will not stimulate the inflammatory reaction of surrounding tissues while accelerating the healing of periapical lesions [10]. Shao et al. [11] have revealed that MHO combined with mineral trioxide aggregate has better efficacy than it alone for CPELs. There are few reports about MHO combined with Vitapex paste in the treatment of middle-aged and elderly patients with CPELs. Accordingly, in order to provide reference for the further therapy of CPELs, this study used both MHO and Vitapex paste to treat middle-aged and elderly patients with CPELs, evaluated its efficacy and effects on the inflammatory levels of patients, and also analysed the risk factors affecting the prognosis of patients, which is the innovation of this study.

## Materials and methods

### *Patient data*

The data of 88 elderly patients with CPELs treated in the First Affiliated Hospital of Gannan Medical University from March 2020 to March 2022 were analyzed retrospectively. Among them, the patients treated with MHO and iodoform zinc oxide clove oil paste were enrolled into the control group (n = 42) and the rest of the patients treated by MHO and Vitapex paste were assigned to the study group (n = 46). This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University.

### *Exclusion and inclusion criteria*

Inclusive criteria: (1) Patients who were diagnosed with CPELs based on typical manifestations of apical periodontitis and pulpitis including gingival redness and swelling, pus, bleeding, occlusal pain, deep periodontal pocket of 3-10 mm, and attachment loss > 2 mm [12]; (2) Patients who received treatment on CPELs for the first time; (3) Patients with detailed clinical data.

Exclusion criteria: (1) Patients with more than 50% defective or cracked teeth; (2) Patients who had received antibiotics or non-steroidal anti-inflammatory drugs recently; (3) Patients who were allergic to the drugs adopted in this study; (4) Patients who were unable to cooperate with treatment due to serious disturbance of consciousness or mental illness; (5) Women during pregnancy or lactation.

### *Therapeutic regimen*

Treatment with MHO: (1) Periodontal treatment: X-ray films were taken to determine the degree and extent of periodontal damage and the specific situation around the apical root, and supragingival scaling and subgingival scaling were performed. Periodontal bags were repeatedly and alternately rinsed with 3% hydrogen peroxide solution and normal saline, and cotton balls were used to suck up the exudate in periodontal bags. An appropriate amount of MHO (Sunstar INC Japan, 0.5 g/piece) was slowly injected into the periodontal pocket until it slightly overflowed. The patient was required to avoid eating and gargling for 1 hour. The MHO was used

once a week for 8 weeks. (2) Root canal therapy: Root canal therapy was performed at the same time of periodontal therapy: Root canal preparation was performed by dental pulp opening, dental pulp extraction and application of a K-type file. Then the root canal was rinsed by ultrasonic wave and sealed for 7 days, until the symptoms disappeared. The root canal was filled when it was dry without peculiar smell or exudation. In both groups, the teeth were filled from the root canal to the 1/3 root tip.

Among them, the control group was given routine iodoform zinc oxide clove oil paste (Wuhan Docan Pharmaceutical Co., Ltd.) to fill the whole root canal, and the study group was given injection-type Vitapex paste (Japanese NeoDental Chemical Production). During injection of the paste, the needle was slowly withdrawn so that the paste could completely fill the whole root canal.

The teeth in both groups were sealed with gutta percha tips. At the 8th week, the paste inside the root canal was removed and permanent root canal filling was performed. The affected teeth of both groups were fixed for 2 to 3 weeks to ensure oral cleanliness and tooth tapping exercise, and the patients were re-examined regularly.

### Outcome measures

Primary outcome measures: (1) Interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ): Fasting venous blood (5 mL) was extracted from each patient before and after treatment, followed by centrifugation to acquire the supernatant, and then the inflammatory indexes in serum were determined. An automatic biochemical analyzer (AU5800) purchased from Beckman Coulter Company of the United States was adopted to determine IL-6, TNF- $\alpha$  and IL-1 $\beta$  by enzyme-linked immunosorbent assay with kits from MyBio-Source Company (Lot numbers: MBS2019894, MBS824943 and MBS335481) under strict instructions of the kits. (2) The gingival index (GI), plaque index (PLI), probing depth (PD) and bleeding index (BI) of the two groups were recorded before and after treatment. (3) The efficacy in the two groups was evaluated according to the following criteria: Markedly effective: disappearance of clinical symptoms, no conscious pain, disappearance of sinus at the root tip, recovery of the masticatory func-

tion to normal, negative results of BI, and decrease of PD by  $> 3$  mm; Effective: notable alleviation of clinical symptoms and self-conscious symptoms, existence of sinus in the apical area, no secretion, greatly improved masticatory function, negative result of BI, and a decrease of PD by 2-3 mm; Ineffective: the above criteria were not met or the condition was aggravated. The overall response rate = (number of markedly effectively treated cases + that of effectively treated cases)/total number of cases  $\times 100\%$ . (4) Factors impacting the prognosis of the patients: the prognosis of the two groups was analysed, and factors impacting their prognosis was analysed using the Logistic regression analysis.

Secondary outcome measures: The MOS 36-Item Short-Form Health Survey (SF-36) was adopted to evaluate the patients' quality of life (QoL) in the two groups [13]. A higher score indicates better QoL. The adverse reactions during treatment were compared between the two groups.

### Statistical analyses

This study adopted SPSS version 22 statistical software for statistical analyses of acquired data and used GraphPad Prism 8 for visualization of the figures. Counting data were described by rate, and their inter-group comparison was conducted using the chi-square test. The measurement data were described by mean  $\pm$  SD, and their inter-group comparison and intra-group comparison was conducted using the independent-samples t test and paired t test, respectively. The risk factors impacting the prognosis were analyzed by logistics regression.  $P < 0.05$  indicated a notable difference.

## Results

### Baseline data of patients

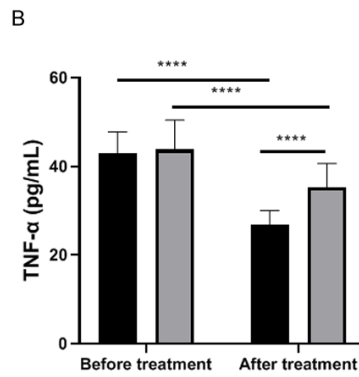
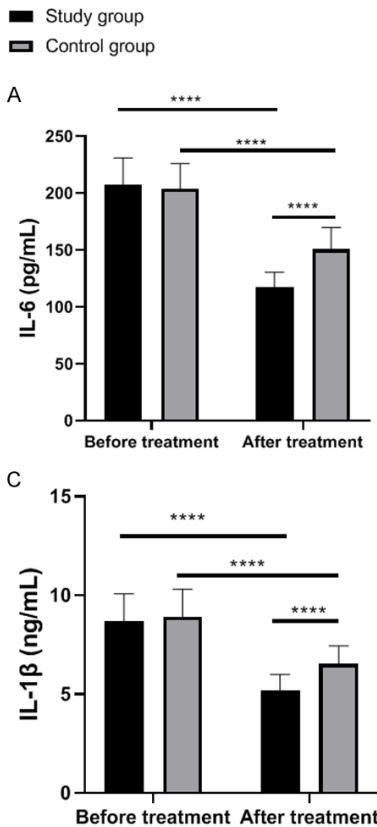
The two groups were not greatly different in terms of age, sex, body mass index (BMI), dental lesion grade, course of disease and place of residence (all  $P > 0.05$ ), so the two groups were comparable (**Table 1**).

### Comparison of inflammatory factors between the two groups

The serum inflammatory factors in the two groups were determined. According to the results, before treatment, the two groups were

**Table 1.** Comparison of baseline data between the two groups

Factors	Study group (n = 46)	Control group (n = 42)	X <sup>2</sup> value	P value
Age			0.553	0.457
≥ 55 years old	20	15		
< 55 years old	26	27		
Gender			0.010	0.921
Male	18	16		
Female	28	26		
Body mass index			0.002	0.969
≥ 23 kg/m <sup>2</sup>	21	19		
< 23 kg/m <sup>2</sup>	25	23		
Dental lesion grade			0.398	0.528
≥ Grade II	25	20		
< Grade II	21	22		
Course of disease			0.022	0.147
≥ 3 years	19	18		
< 3 years	27	24		
Place of residence			2.117	0.146
Rural area	29	20		
Urban area	17	22		



**Figure 1.** Comparison of inflammatory factors between the two groups before and after treatment. A: Comparison of IL-6 between the two groups before and after treatment; B: Comparison of TNF-α between the two groups before and after treatment; C: Comparison of IL-1β between the two groups before and after treatment. Notes: IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β. \*\*\*\*P < 0.0001.

not significantly different in the levels of IL-6, TNF-α and IL-1β (all P > 0.05), while after the

treatment, their levels in both groups decreased notably (all P < 0.0001), with more notable decreases in the study group than those in the control group (all P < 0.0001, **Figure 1**).

*Comparison of periodontal conditions between the two groups*

According to comparison of the two groups in the periodontal conditions before and after treatment, the two groups were not greatly different in GI, PLI, PD and BI before treatment (all P > 0.05); while after treatment, GI, PLI, PD and BI of both groups decreased notably (all P < 0.0001), with more notable decreases in the study group than those in the control group (all P < 0.0001, **Figure 2**).

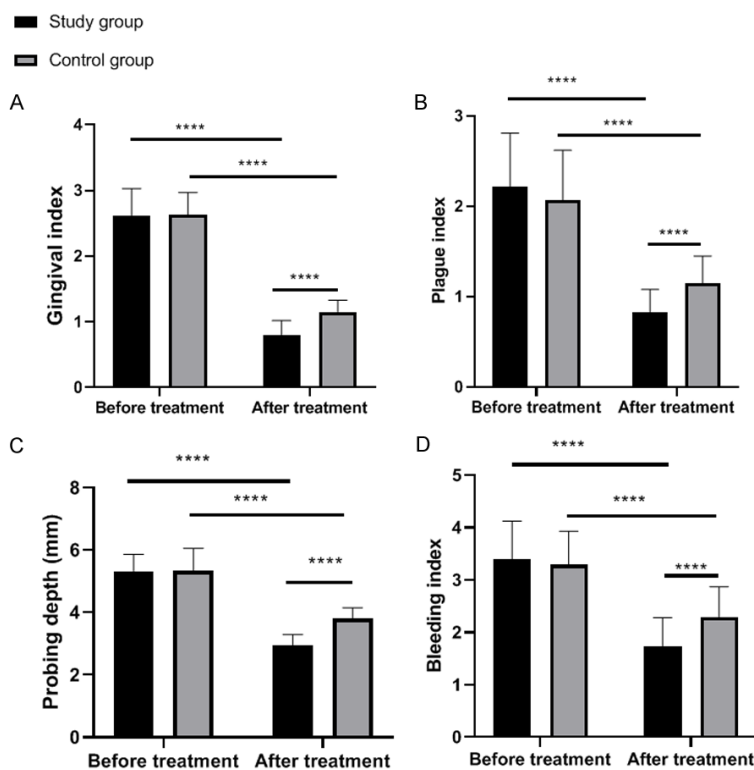
*Comparison of efficacy between the two groups*

Statistical analysis of efficacy in the two groups revealed a notably higher overall response rate in the study group than that in the control group (P = 0.042, **Table 2**).

*Comparison of SF-36 scores between the two groups*

The SF-36 was adopted to evaluate the QoL of patients in the two groups before and after treatment. According to the results, before treatment, the two groups were not greatly different in SF-36 scores (P > 0.05); while after the treatment, the SF-36 scores of both groups were greatly improved, with a more notable improvement in the study

group than that in the control group (P < 0.0001, **Figure 3**).



**Figure 2.** Comparison of periodontal conditions between the two groups before and after treatment. A: Comparison of gingival index between the two groups before and after treatment; B: Comparison of plaque index between the two groups before and after treatment; C: Comparison of probing depth between the two groups before and after treatment; D: Comparison of bleeding index between the two groups before and after treatment. Note: \*\*\*\*P < 0.0001.

**Table 2.** Efficacy of the two groups [n (%)]

Group	Markedly effective	Effective	Ineffective	Overall response rate (%)
Study group (n = 46)	26 (56.52)	17 (36.96)	3 (6.52)	43 (93.48)
Control group (n = 42)	19 (45.24)	14 (33.33)	9 (21.43)	33 (78.57)
X <sup>2</sup>	1.119	0.126	4.143	4.143
P value	0.290	0.722	0.042	0.042

*Inter-group comparison of adverse reactions*

According to analysis and comparison of the two groups in the incidence of adverse reactions, the study and control groups were not greatly different in the incidence of adverse reactions (P = 0.572, **Table 3**).

*Analysis of related factors affecting prognosis*

The prognosis of the two groups within 3 months after treatment was evaluated. Re-

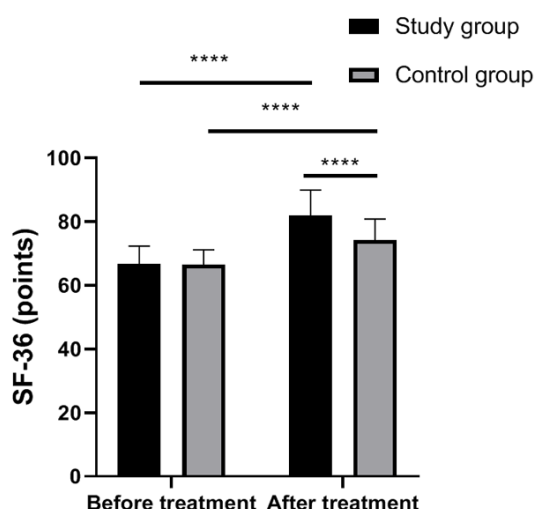
currence within 3 months after treatment was judged as poor prognosis. The patients were re-grouped according to the recurrence after treatment. Patients with recurrence were included into a poor-prognosis group (n = 30) and those without recurrence were included into a good-prognosis group (n = 58). Then the differences in clinical data between the two groups were compared and the data were subjected to univariate analysis. According to the results, age, dental disease grade, course of disease, and persistent dull pain were the risk factors affecting the prognosis of patients (**Table 4**). The indicators with significant differences in the above were assigned (**Table 5**) and subjected to multivariate analysis. According to logistic regression analysis, dental lesion grade was an independent risk factor affecting the prognosis of patients (**Table 6**).

**Discussion**

Combined periodontal-endo-dontic lesion (CPEL) is a common oral disease, with both pulp inflammation and periodontal destruction in the affected teeth [14]. People face an increasing incidence of the disease as they grow, and the disease is generally

more frequently seen in middle-aged and elderly people [15]. Patients with CPELs often suffer symptoms of tooth pain and/or tooth loosening, which can disrupt their daily work and life in severe cases. Because of the double substantial damage of periodontal tissue and pulp tissue, the clinical manifestations of this disease are complicated and its treatment is challenging [16, 17].

MHO is a semi-synthetic and efficient tetracycline drug. Minocycline is a broad-spectrum



**Figure 3.** Comparison of SF-36 scores between the two groups before and after treatment. Notes: SF-36: MOS 36-Item Short-Form Health Survey; \*\*\*\*P < 0.0001.

antibiotic, with antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria and other microorganisms [17]. MHO has been extensively applied in the treatment of periodontitis and peri-implantitis [18, 19]. Vitapex paste, with main ingredient of calcium hydroxide, iodoform and polysiloxane oil, is a new type of root filling paste for deciduous teeth [20]. Calcium hydroxide has a favourable killing effect on anaerobic bacteria and can stimulate the formation of calcified tissue [21]. Vitapex paste can promote the formation of root tips. In addition, iodoform can take effect in sterilization and convergence, and strongly promote the absorption of inflammatory lesions [22]. In this study, MHO and Vitapex paste were used together to treat middle-aged and elderly patients with CPELs, and their efficacy and influence on inflammatory factors were evaluated.

In this study, before treatment, the two groups were not significantly different in the levels of IL-6, TNF- $\alpha$  and IL-1 $\beta$ , while after treatment, the levels of them in both groups decreased, with more notable decreases in the study group than those in the control group. The results suggest the two treatment regimens are both effective in alleviating the inflammatory response of middle-aged and elderly patients with CPELs, but MHO combined with Vitapex paste is more effective. Periodontal indexes (GI, PLI,

PD and BI) are objective indexes that reflect the activity of periodontitis and the repair of periodontal tissue injury, and the increase of these indexes indicates a worsening of the disease [23, 24]. In this study, before treatment, the GI, PLI, PD and BI of the two groups were similar, while after treatment, the levels of them of both groups decreased greatly, with more notable decreases in the study group than those in the control group. According to the results, the two treatment regimens were both effective in improving the periodontal indexes, but MHO combined with Vitapex paste performed better. Yuan et al. [25] have revealed that MHO combined with tinidazole can strongly improve the periodontal indexes of patients with chronic periodontitis and also pointed out its high clinical value, which is in agreement with the results in this paper.

This study also compared the overall response rate of the two groups after treatment and used the SF-36 score for evaluation of their QoL before and after treatment. According to the results, the study group showed a notably higher overall response rate than the control group. Before treatment, the SF-36 scores of the two groups were not greatly different, while after treatment, the SF-36 scores of both groups increased notably, and the increase was more notable in the study group. The results imply that MHO combined with Vitapex paste can deliver better efficacy and can improve the QoL of patients more significantly. According to one study by Hu et al. [26], Vitapex paste can promote tissue ossification and calcification, and it has the function of inducing apical tissue development and effectively preventing secondary root resorption. Shao et al. [11] have revealed that MHO is a highly efficient, long-lasting, strong broad-spectrum antimicrobial with sustained-release preparations, and combination with it can effectively treat severe periodontic-endodontic combined lesions, which is similar to the results of this study. Lastly, this study analyzed and compared the adverse reactions of the two groups, and found no notable difference between the study two groups in this aspect, indicating that MHO combined with Vitapex paste was safe and reliable, because it would not cause more adverse reactions. The analysis of prognostic factors showed that age, dental lesion grade, course of disease, and persistent dull pain were risk factors for prognosis,

# Efficacy of minocycline hydrochloride ointment combined with Vitapex paste on CPELs

**Table 3.** Incidence of adverse reactions in the two groups [n (%)]

Group	Oral foreign body sensation	Gingival bleeding	Nausea and vomiting	Dizzy	Adverse reactions
Study group (n = 46)	1 (2.17)	1 (2.17)	0 (0.00)	0 (0.00)	2 (4.35)
Control group (n = 42)	2 (4.76)	1 (2.38)	0 (0.00)	0 (0.00)	3 (7.14)
X <sup>2</sup>	0.447	0.004	/	/	0.320
P value	0.5040	0.948	/	/	0.572

**Table 4.** Univariate analysis

Factors	Good-prognosis group (n = 58)	Poor-prognosis group (n = 30)	X <sup>2</sup>	P value
Age			30.75, 1	< 0.0001
≥ 55 year old	11	24		
< 55 year old	47	6		
Gender			2.479, 1	0.1154
Male	19	15		
Female	39	15		
Body mass index			1.140, 1	0.2857
≥ 23 kg/m <sup>2</sup>	24	16		
< 23 kg/m <sup>2</sup>	34	14		
Dental lesion grade			37.76, 1	< 0.0001
≥ grade II	16	29		
< grade II	42	1		
Course of disease			18.29, 1	< 0.0001
≥ 3 years	15	22		
< 3 years	43	8		
Place of residence			3.781, 1	0.0518
Rural area	28	21		
Urban area	30	9		
Persistent dull pain			36.06, 1	< 0.0001
Yes	10	25		
No	48	5		

**Table 5.** Assignment

Factors	Assignment
Age	≤ 55 years old = 0, > 55 years old = 1
Dental lesion grade	< grade II = 0, ≥ II grade = 1
Course of disease	< 3 years = 0, ≥ 3 years = 1
Persistent dull pain	No = 0, yes = 1
Prognosis	Good prognosis = 0, poor prognosis = 1

while logistic regression analysis showed that dental lesion grade was independent risk factor for prognosis. The possible reasons for the better performance of MHO combined with Vitapex paste are as follows: Vitapex paste is a root canal filling drug composed of iodoform and calcium hydroxide. Iodoform can effective-

ly reduce inflammatory reaction, with good convergence, deodorization and antiseptic effect, has no obvious irritation to periodontal tissue, and can promote inflammatory absorption and induce regeneration and repair [9]. Calcium hydroxide is a slightly alkaline component, which can neutralize the toxic products and pathogenic bacteria in the root canal to a certain extent, and then promote tissue calcification to effectively fight against anaerobic bacteria and promote alveolar bone regeneration [9, 10]. Polysiloxane oil is the auxiliary material of Vitapex paste, which can ensure better drug fluidity and tighter root canal filling [21]. MHO is a broad-spectrum antimicrobial agent, especially against anaerobes, which can further reduce alveolar bone resorption and promote periodontal tissue reattachment by reducing collagenase activity [8]. During local application to periodontitis, MHO can be partially chelated on local hard tissue and slowly released to the surrounding tissue, which can effectively increase the drug availability and

ensure a high drug concentration in the periodontal pocket for a long time, and then play a long-lasting and stable germicidal effect [11].

This study has confirmed the efficacy of MHO combined with Vitapex paste in the treatment of middle-aged and elderly patients with CPELs

**Table 6.** Multivariate analysis

Factors	B	S.E.	Wals	df	Sig.	Exp (B)	95% C.I. of EXP (B).	
							Lower limit	Upper limit
Age	0.264	30625.205	0.000	1	1.000	1.302	0.000	.
Dental lesion grade	5.124	1.508	11.547	1	0.001	168.000	8.745	3227.375
Course of disease	-22.122	15477.986	0.000	1	0.999	0.000	0.000	.
Persistent dull pain	21.260	26426.031	0.000	1	0.999	1710921540.447	0.000	.

and its influence on the inflammatory factors, but it still has some limitations. First of all, the sample size collected in this study is limited, which may result in some bias in the research conclusions. In addition, we have not followed up the prognosis of the patients, so the effect of MHO combined with Vitapex paste on the long-term prognosis of middle-aged and elderly patients with CPELs is still unclear. Therefore, we hope to conduct a more complete and comprehensive analysis on the application of MHO combined with Vitapex paste in the CPELs of middle-aged and elderly people in the future to obtain more effective experimental results.

To sum up, MHO combined with Vitapex paste is effective for middle-aged and elderly patients with CPELs. It can effectively inhibit the patients' inflammatory reaction and improve their periodontal condition and QoL, with a low adverse reaction rate, so it is worthy of clinical promotion.

#### Disclosure of conflict of interest

None.

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## Efficacy of minocycline hydrochloride ointment combined with Vitapex paste on CPELs

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