

## **Comparison of alendronate sodium gel and simvastatin gel administration in the treatment of mandibular molar furcation involvement.**

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### **Abstract**

**Objective:** To compare and analyse the effect of alendronate sodium gel and simvastatin gel topical administration in the treatment of mandibular molar furcation involvements.

**Methods:** A total of 80 patients with mandibular molar furcation involvement treated in our hospital were selected as cases from March 2015 to January 2017. They were randomly divided into groups A and B, 40 cases in each group. Both groups were treated with ultrasound, in which group A was treated with topical administration of alendronate sodium gel and group B was treated with topical administration of simvastatin gel. Gingival Index (GI), Sulcus Bleeding Index (SBI), Bleeding on Probing (BOP), Probing Depth (PD), Probing Pyorrhea (POP), clinical curative effect and level changes of TNF- $\alpha$ , IL-1 $\beta$  and LPS in gingival crevicular fluid were measured in both groups before the treatment and 4 weeks after it.

**Results:** There was no significant difference in the levels of PD, SBI, GI, BOP and POP between the two groups before treatment. The levels of PD, SBI, GI, BOP and POP in group B were significantly higher than those of group A after 4 w of treatment. The levels of TNF- $\alpha$ , IL-1 $\beta$  and LPS in gingival crevicular fluid of two groups showed no significant difference before treatment. The levels of TNF- $\alpha$ , IL-1 $\beta$  and LPS of group B were significantly lower than those of group A after treatment. The total effective rate of group B was 95%, which was significantly higher than that of group A after 4 w of treatment (82.5%). The difference was statistically significant.

**Conclusion:** Compared with alendronate sodium gel, clinical effect of topical administration of simvastatin gel in the treatment of mandibular molar furcation involvements is more significant. It can not only improve the gingival index, sulcus bleeding index and other clinical indicators, but also reduce TNF- $\alpha$ , IL-1 $\beta$  and LPS levels in gingival crevicular fluid, deserves further application and promotion.

**Keywords:** Alendronate sodium, Simvastatin, Topical administration, Mandibular molar, Furcation involvement.

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### **Introduction**

Furcation involvement refers to the involvement of periodontitis spread to the root furcation of multiple teeth. It can occur in any type of periodontitis and has the highest prevalence of mandibular molars, which is the common and frequently occurring disease in the old people [1]. Dental plaque, occlusal trauma and anatomical factors of teeth are the main causes of the disease [2]. With the development of periodontitis, the root bifurcation of multiple teeth will be involved, forming a kind of special clinical periodontitis associated with lesions [3]. Root furcation area can be exposed to the mouth directly and can also be covered by periodontal pocket. Patients are often accompanied by periodontal inflammation and suppurative pus, and bleed easily when they are diagnosed. They may also have acute periodontal abscess associated with spontaneous toothache, tooth sensitive and

other symptoms. Clinical treatments of root bifurcation lesions include supraliminal scaling, subgingival scaling (root planning), maxillary calculus, flap surgery, root canal therapy and so on [4]. Although root canal therapy has been very well established, patients still have different degrees of occlusal pain. There is repeated local gingival swelling, and even with fistula formation of pus and other symptoms. After repeated washing and anti-inflammation, it is still difficult to completely solve the furcation involvement. Inflammation will lead to continuous absorption of alveolar bone until the teeth loose and fall, which brings great difficulties to the clinical treatment [5]. Therefore, it is necessary to explore the effective treatment of mandibular molar furcation involvements.

Related studies have shown [6] that alendronate sodium could prevent and cured osteoporosis, and has some application effect on oral and periodontal tissue intervention in alveolar

bone absorption. Studies have shown that [7] simvastatin can promote the proliferation and differentiation of dental pulp stem cells, enhance the regeneration of dental pulp and reduce the development of dental pulp inflammation, which in turn is conducive to the restoration of dental pulp stable environment as soon as possible and promote the regeneration of dentin repair. However, there are no reports about the curative effect of topical administration of alendronate sodium gel and simvastatin gel in the treatment of mandibular molar furcation involvements [8]. 80 patients with mandibular molar furcation involvement admitted in our hospital were treated with topical administration of alendronate sodium gel and simvastatin gel from March 2015 to January 2017, to clarify the value of these two drugs in the mandibular molar furcation involvement.

## Materials and Methods

### Normal information

From March 2015 to January 2017, a total of 80 patients, including 50 males and 30 females, with mandibular molar furcation involvement treated in our hospital were enrolled in the study. All patients age from 22 to 53 y with an average of  $37.3 \pm 1.8$  y old. All patients were randomly divided into study group and control group, 40 cases in each group. The general characteristics of the patients between the two groups did not differ significantly. The Hospital Ethics Committee approved this study and patients signed informed consent forms.

**Inclusion criteria:** Patients diagnosed as root bifurcation lesions with mandibular molars according to chief complaint and clinical examination. Patients without alendronate, simvastatin and other drug allergy history. All patients signed the informed consent.

**Exclusion criteria:** Patients with abnormal dental pulp vitality or received dental pulp treatment. Pregnant women and lactating women. Patients with systemic diseases. Patients whose tooth tissue caries/defect/split in root furcation area. Patients who are unable to cooperate with the experimenter.

### Therapeutic method

All cases were treated with ultrasonic scaling first (supraliminal scaling and subgingival scaling), washed with 3% hydrogen peroxide and 0.9% saline alternately, separated from the wet. Patients of group A were treated with topical administration of alendronate sodium gel. Alendronate sodium gel was filled into the periodontal pocket of patient in the right first molar, and iodine glycerol was filled into the periodontal pocket of patient in the left first molar. Topical administration was given once a week and used 4 times a course. Patients of group B were treated with topical administration of simvastatin gel. Simvastatin gel was filled into the periodontal pocket of patient in the right first molar, and iodine glycerol was filled into the periodontal pocket of patient in the left first molar. Topical administration was given once a week and used 4 times a course. Patients in two groups were not allowed to gargle or eat immediately after topical administration. The whole

treatment process was completed by the same doctor and was not allowed to take alendronate, simvastatin or other drugs. Meanwhile, the diet needs to be light, without smoking and drinking.

### Observation index

Gingival Index (GI), Sulcus Bleeding Index (SBI), Bleeding on Probing (BOP), Probing Depth (PD), Probing Pyorrhea (POP), were recorded and compared in two groups before the treatment and 4 w after it.

**Evaluation method:** 1. Periodontal probe was used to exam along the long axis of the tooth in the cheek (lip), tongue distal, central and proximal surfaces, recorded the depth of diagnosis at 6 sites. 2. SBI: 0=The gingival margin and gingival papilla were healthy, and no bleeding after gingival sulcus was detected lightly; 1=The gingival margin and gingival papilla were healthy, and bleeding after gingival sulcus was lightly detected; 2=Gums have a color change due to inflammation, no swelling or edema, bleeding after gingival sulcus was detected; 3=Gums have a color change and mild edema due to inflammation, bleeding after gingival sulcus was detected; 4=Gums not only have a color change and obvious swelling, bleeding after gingival sulcus was detected; 5=Gums have a color change and obvious swelling, sometimes with ulcers, bleeding or spontaneous bleeding after gingival sulcus was detected. 3. GI: The periodontal probe was placed at the opening of the gingival margin and slid gently along the gingival margin. The grades were classified as grade 4 according to the degree of gingival lesions. 0=normal gingiva, 1=gingival edema, no bleeding after probing, 2=bleeding after probing, 3=spontaneous bleeding tendency or ulceration. 4. BOP: The tip of the blunt periodontal probe was placed under the gingival margin 1 mm or less. It was denoted as BOP positive or negative after sliding along the gingival margin for a short period of time to see if there was any bleeding, which was an objective index to indicate whether the gum had inflammation or not. 5. POP: It was denoted as BOP positive or negative according to the presence of pus overflow in the periodontal pocket. The pus was formed after the necrosis of leukocytes, with greater toxicity, indicating purulent inflammation of the inner wall of the bag.

### Enzyme linked immunosorbent assay (ELISA)

ELISA was used to measure and compare the changes of TNF- $\alpha$ , IL-1  $\beta$  and LPS levels in gingival crevicular fluid in two groups before and after treatment. ELISA kits for TNF- $\alpha$ , IL-1  $\beta$  and LPS were purchased from Shanghai Xin Le Biotechnology Co., Ltd., operated according to the operating instructions of the kit strictly.

### Efficacy evaluation criteria

**Significant effect:** Inflammation is controlled, no subjective symptoms, the teeth without discomfort, no swelling of the gum suppuration, no loosening, chewing function is normal, the root bifurcation probe within 2 mm, the periodontal pocket

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cannot be tightened exploration People, X-ray film shows the shadow disappeared at the bifurcation. Valid: no subjective symptoms, no discomfort in the teeth, chewing function recovery, root bifurcation probing within 4 mm, the periodontal pocket contraction cannot be explored, X-ray showed the shadow of the lesion area disappeared or reduced. Invalid: no significant improvement in subjective symptoms, phenomenon of deep pockets and overflow pus. Good and effective cases were recorded as markedly effective cases. Effectiveness rate (%)=(good teeth+effective teeth)/total teeth in the group × 100%.

**Statistical analysis**

The SPSS 21.0 software was used for analysis. Enumeration data in two groups were analysed using paired-samples t-test

**Table 1.** Comparison of indexes of PD, SBI, GI, BOP and POP in two groups.

Group	N	PD		SBI		GI		BOP positive rate		POP positive rate	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	40	6.82 ± 1.26	3.91 ± 0.85	6.76 ± 0.61	3.27 ± 0.36	4.55 ± 0.28	2.46 ± 0.48	68.31 ± 2.25	33.47 ± 3.64	37.22 ± 3.41	9.83 ± 0.29
Group B	40	6.83 ± 1.34	3.02 ± 1.27	6.79 ± 0.73	2.04 ± 0.58	4.57 ± 0.19	1.03 ± 0.72	68.62 ± 2.39	20.12 ± 2.45	37.34 ± 4.06	4.72 ± 0.35
t		0.34	6.79	0.4	6.5	0.51	6.79	0.2	7	0.16	8.12
P		0.275	0.022	0.291	0.017	0.311	0.019	0.167	0.029	0.152	0.017

**Comparison of TNF- alpha, IL-1 beta and LPS levels in gingival crevicular fluid of two groups**

The levels of TNF-α, IL-1β and LPS in gingival crevicular fluid of two groups showed no significant difference before

**Table 2.** Comparison of TNF-alpha, IL-1 beta and LPS levels in gingival crevicular fluid of two groups.

Group	N	TNF-α (ng/L)		IL-1β (ng/L)		LPS (u/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	40	43.32 ± 3.47	23.64 ± 2.95	116.73 ± 5.46	45.67 ± 2.33	467.84 ± 45.62	245.69 ± 23.38
Group B	40	43.56 ± 4.05	16.02 ± 3.03	117.04 ± 6.69	31.85 ± 3.45	469.04 ± 41.37	136.71 ± 20.06
t		0.12	7.09	0.14	8.53	0.20	7.86
P		0.196	0.030	0.187	0.016	0.151	0.027

**Comparison of clinical efficacy in two groups**

The total effective rate of group B was 95%, which was significantly higher than that of group A after 4 w of treatment (82.5%) (Table 3).

**Table 3.** Comparison of clinical efficacy in two groups.

Group	N	Significant effect	Valid	Invalid	Effective rate (%)
Group A	40	21	12	7	82.5
Group B	40	30	8	2	95

before and after treatment. Differences between measurement data in two groups were analysed by the Chi-square test. P<0.05 suggests the difference is statistically significant.

**Results**

**Comparison of indexes of PD, SBI, GI, BOP and POP in two groups**

There was no significant difference in the levels of PD, SBI, GI, BOP and POP between the two groups before treatment. The levels of PD, SBI, GI, BOP and POP in the B group were significantly higher than those in the A group after 4 w of treatment (Table 1).

treatment. The levels of TNF-α, IL-1β and LPS of group B were significantly lower than those of group A after treatment (Table 2).

χ <sup>2</sup>	8.05
P	0.019

**Discussion**

Root bifurcation is one of the difficulties of elderly periodontal treatment. Conventional methods will reduce alveolar bone and attachment levels and it is still difficult to remove plaque at the root bifurcation. As the inhibitor of Hydroxy-Methylglutaryl Coenzyme A (HMG-CoA) reductase, simvastatin is widely used to reduce blood cholesterol and low-density lipoprotein in

clinical, prevent atherosclerosis and reduce incident rate of cardiovascular risk [9]. The biological effects of simvastatin on anti-inflammatory and lipid-lowering, protection of the kidneys of diabetic patients, promotion of tumor cell apoptosis, promotion of bone formation and inhibition of bone resorption have been reported [10]. In recent years, it has been found that simvastatin can promote the proliferation and differentiation of dental pulp stem cells and has the anti-inflammatory effect in dental pulp environment [11]. Alendronate sodium is the third generation of bisphosphonates, which has a good effect on inhibiting osteoclast activity and does not inhibit the adverse effects of bone mineralization. It is currently used in the treatment of osteoporosis, which has a good inhibitory effect on osteoclast activity. A therapeutic dose of alendronate has no adverse effects on bone mineralization, and has been used for the treatment of osteoporosis currently. Relevant studies have shown [12] that alendronate can effectively improve the healing of delayed replantation of dry teeth, increase cementum healing, and reduce the inflammatory absorption and alternative resorption of the root. It has also been reported [13] that alendronate sodium inhibits osteoclast activity indirectly by inhibiting the release of inflammatory cytokines (IL-1, TNF- $\alpha$ ) and osteoclast activity indirectly. The main component of Iodine Glycerol is 10 mg/ml of iodine. Accessories are: potassium iodide, glycerin, purified water. It is a red brown viscous liquid with iodine special smell, is suitable for sterilization of the convergence, oral ulcer, treatment of gingivitis, periodontitis and pericoronitis, used for periodontal clean local administration commonly [14,15]. At present, there are no reports about the efficacy of alendronate sodium gel and simvastatin gel in the treatment of mandibular molar furcation lesions. The results of this study show that there was no significant difference in the levels of PD, SBI, GI, BOP and POP between the two groups before treatment. The levels of PD, SBI, GI, BOP and POP in the B group were significantly higher than those in the A group after 4 w of treatment. The total effective rate of group B was 95%, which was significantly higher than that of group A after 4 w of treatment (82.5%). This suggests that clinical effect of topical administration of simvastatin gel in the treatment of mandibular molar furcation involvements is more significant compared with alendronate sodium gel. It can effectively improve the gingival index, sulcus bleeding index and other clinical indicators.

Early inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ ) can directly induce bone resorption by inducing osteoclast differentiation, and the levels of IL-1 beta in gingival crevicular fluid were increased in early experimental gingivitis animal models [15,16]. Because of the presence of Lipopolysaccharide (LPS) on the bacterial envelope, gram negative microorganisms were dominant in the subgingival microenvironment. Moreover, studies have found [17] that LPS can further stimulate the elevation of TNF- $\alpha$  level. Not all individuals are susceptible to periodontal infection resulting in periodontal injury. Periodontitis is not only caused by bacterial infection, but also related to the susceptibility of the host. The levels of TNF- $\alpha$ , IL-1 $\beta$  and LPS in gingival crevicular fluid of two groups

showed no significant difference before treatment. The levels of TNF- $\alpha$ , IL-1 $\beta$  and LPS of group B were significantly lower than those of group A after treatment. This suggests that clinical effect of topical administration of simvastatin gel in the treatment of mandibular molar furcation involvements is more significant compared with alendronate sodium gel. It can effectively reduce TNF- $\alpha$ , IL-1 $\beta$  and LPS levels in gingival crevicular fluid.

In summary, compared with alendronate sodium gel, clinical effect of topical administration of simvastatin gel in the treatment of mandibular molar furcation involvements is more significant. It not only can effectively improve the gingival index, sulcus bleeding index and other clinical indicators, but also can effectively reduce TNF- $\alpha$ , IL-1 $\beta$  and LPS levels in gingival crevicular fluid, which is worthy of application and promotion.

## References

1. Joseph I, Varma BR, Bhat KM. Clinical significance of furcation anatomy of the maxillary first premolar: a biometric study on extracted teeth. *J Periodontol* 1996; 67: 386-389.
2. Takaya T, Mimura H, Matsuda S. Cytological kinetics of periodontal ligament in an experimental occlusal trauma model. *Int J Med Sci* 2015; 12: 544-551.
3. Campos MLG, Correa MG, Junior FHN. Cigarette smoke inhalation increases the alveolar bone loss caused by primary occlusal trauma in a rat model. *J Periodont Res* 2014; 49: 179-185.
4. Hakkarainen K. Relative influence of scaling and root planning and occlusal adjustment on sulcular fluid flow. *J Periodontol* 2015; 57: 681-684.
5. Petelin M, Perkic K, Seme K. Effect of repeated adjunctive antimicrobial photodynamic therapy on subgingival periodontal pathogens in the treatment of chronic periodontitis. *Laser Med Sci* 2015; 30: 1647-1656.
6. Sambrook PN, Kotowicz M, Nash P. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. *J Am Soc Bone Miner Res* 2003; 18: 919-924.
7. Okamoto Y, Sonoyama W, Ono M. Simvastatin induces the odontogenic differentiation of human dental pulp stem cells in vitro and in vivo. *J Endodont* 2009; 35: 367-372.
8. Sumer M, Keles GC, Cetinkaya BO. Autogenous cortical bone and bioactive glass grafting for treatment of intraosseous periodontal defects. *Eur J Dentistry* 2013; 7: 6-14.
9. Group HP. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg* 2007; 45: 645-654.
10. Chuengsamarn S, Rattanamongkoulgul S, Suwanwalaikorn S. Effects of statins vs. non-statin lipid-lowering therapy on

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- bone formation and bone mineral density biomarkers in patients with hyperlipidemia. *Bone* 2010; 46: 1011-1015.
11. Elsaied HE, Hamdy MD, Elsherbini AI, Mohsen IA. Investigation of proniosomes gel as a promising carrier for transdermal delivery of glimepiride. *Universal Journal of Pharm Res* 2016; 1: 1-18.
  12. Yin L, Chen C, Xie H. Effect of alendronate on the healing of replanted dog teeth after extended dry time. *J Pract Stomatol* 2005; 21: 579-582.
  13. Wang X, Yang Z. The experiment in rat model with alendronate inhibiting abnormal alveolar bone resorption. *J Mod Stomatol* 2001; 36: 193-196.
  14. Geurian K, Branam C. Iodine poisoning secondary to long-term iodinated glycerol therapy. *Arc Int Med* 1994; 154: 1153-1156.
  15. Felix SY, Yunus AA, Dingwoke FJ, Udokwu JC. Abacavir loaded nanoparticles: preparation, physicochemical characterization and in vitro evaluation. *Univ J Pharm Res* 2016; 1: 19-24.
  16. Ozdemir B, Ozcan AG, Karaduman AB. Lactoferrin in gingival crevicular fluid and peripheral blood during experimental gingivitis. *Eur J Dentistry* 2009; 3: 16-23.
  17. Oono H, Nakagawa M, Miyamoto A. Mechanisms underlying the enhanced elevation of IL-1beta and TNF-alpha mRNA levels following endotoxin challenge in rat alveolar macrophages cultured with low-Mg<sup>2+</sup> medium. *Magnes Res Off Organ Int Soc Develop Res Magn* 2002; 15: 153-160.

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