

The effect of bisphosphonate risedronate emulgel on the inhibition of tooth movement relaps

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ABSTRACT

Background: Orthodontic treatment is performed to correct the malocclusion, and after treatment is complete. The position of the teeth must be maintained because the teeth can move back to their original position, commonly known as relapse. Various attempts have been made, such as using retainers, and various studies have used pharmacological agents such as bisphosphonate risedronate to inhibit relapse, but these studies still used the injection method, which is inconvenient to apply and has a systemic effect. For this reason, changing the bisphosphonate preparation to an emulgel will facilitate its application and have a local effect, but it is necessary to test and determine its effectiveness in inhibiting the relapse.

Method: An experimental laboratory study was conducted on 18 guinea pigs, which were divided into three groups: I (control), II (emulgel without risedronate), and III (emulgel with risedronate). The teeth were moved with open coil springs on both lower incisors for seven days, stabilized for seven days, and emulgel applied in groups II and III. The coil spring was removed, and the distance between the two incisors was measured on the third and seventh days.

Result: Using One-Way ANOVA and Post Hoc LSD, the data analysis results showed significant differences between the control and the risedronate emulgel groups on the third and seventh days. The largest relapse occurred in the control group, while the smallest was in the emulgel group with risedronate.

Conclusion: These results indicate that risedronate bisphosphonate in the form of emulgel influences inhibiting the movement of tooth relapse.

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INTRODUCTION

Orthodontics is one of the fields of dentistry, which studies facial growth, tooth development and occlusion, and the diagnosis, intercept, and treatment of occlusive anomalies. Using orthodontic appliances, treatment is beneficial for improving dental health and quality of life related to oral health, aesthetics, and function.¹ Public awareness regarding orthodontic treatment is getting better as is the result of research by Aditya et al, which stated that parents in a school already have good knowledge about preventive orthodontics and have good behavior in preventing dental malocclusion in children.² Orthodontic treatment needs to be done as early as possible to prevent the treatment from getting worse using various types of orthodontic devices, so that good function and aesthetics are obtained. The results of treatment by Muslim Yusuf et al stated that treatment of mandibular retrognathic Class II skeletal malocclusion by using removable functional devices at a growing age can increase the total length of the mandible so as to obtain an orthognathic facial skeletal profile. This case report concludes that correction of Class II retrognathic mandibular malocclusion at developmental age can provide good results.³ As well as the results of Merinina et al.'s study concluded that the use of a twin block device for the treatment of class II division 1 dentoskeletal malocclusion with mandibular retrognathism increased mandibular dimensions and anterior facial height. Cervical vertebral maturation stage III (CVMS III) is the most effective time to start treatment with a twin block device.⁴

After treatment with orthodontic appliances is completed, the next stage is the retention phase. The retention phase is the final stage in orthodontic treatment, which serves to maintain the teeth in position. In this case, the tooth tends to return to the

initial malocclusion position, commonly known as relapse.⁵ In a previous study with a sample of 771 patients who returned for control after six months of post-orthodontic treatment using retainers, 72 (10.13%) patients experienced a relapse. In addition, at 12 months after the use of retainers, 41 (5.77%) patients had a relapse. Meanwhile, at 24 months after the use of retainers, 19 (2.67%) patients experienced a relapse.⁶ The results of other studies have shown that tooth stability and relapse movement are unpredictable. The probability of relapse is 33-90% after ten years of orthodontic treatment.⁷ At the beginning, relapses still occur with rapid movement distance after passing through the retention phase.⁸ Based on Franzen et al.'s (2011) research, on the third day after the orthodontic appliance is removed, cells in the periodontal ligament (PDL) begin to form. This process continues until the seventh day, when osteoblasts begin to form around the alveolar bone, indicating new bone deposition.⁷

One way to maintain tooth stability and prevent relapse is to use retainers. There are two types of conventional retainers: removable retainers highly dependent on patient compliance and fixed retainers. Fixed retainers are permanently attached so that the treatment success does not depend on the patient's compliance in wearing the retainers but causes accumulation of plaque and calculus; thus, oral hygiene must be maintained properly.⁹ In addition, retention methods in the orthodontic field have evolved with the additional use of biological agents and procedures, such as low-level laser therapy (LLLT) during the retention period. Several biologic agents have been investigated, including strontium, relaxin, and bisphosphonates.¹⁰

Specifically, bisphosphonates are drugs used for diseases that affect bone metabolism due to imbalanced bone remodelings, such as

osteoporosis or cancer. Bisphosphonates are divided into bisphosphonates without nitrogen and bisphosphonates with nitrogen. Some examples of nitrogen-containing bisphosphonates are zoledronate, alendronate, and risedronate.¹¹ In this case, risedronate is a bisphosphonate whose chemical structure has two branches (sidechain). The R₂ branch binds to pyridyl-methylene and the R₁ branch to a hydroxyl group. The compounds contained are hydrophilic with poor oral absorption but have a high affinity for bone hydroxyapatite. This type of bisphosphonate appears to be successful in accelerating the occurrence of osteoclast apoptosis in mice and initiating osteoclast apoptosis in vitro.¹² In prior research, injection of 10 g/kg risedronate into previously ovariectomized Sprague-Dawley mice decreased the mice of tooth movement and reduced the number of osteoclasts on days 3, 7, and 14 compared to a group of mice not given risedronate. Risedronate also has the potential to have side effects such as lower osteonecrosis than other bisphosphonates.¹³ Besides, intraperitoneal injection is widely used in research but has drawbacks, including passing through a high first-pass metabolism, requiring sterility, and causing damage to the abdominal organs if the procedure is inappropriate.¹⁴

In this case, emulgel combines two formations, emulsion and gel, as a topical drug preparation to accelerate local drug absorption.¹⁵ The advantages of emulgel preparations are good stability, ease of formulation and application, and patient comfort.¹³ Hence, it is necessary to know the effect of risedronate bisphosphonate in the form of emulgel on the inhibition of tooth relapse movement to prevent relapse with an easy and convenient application.

RESEARCH METHOD

Emulgel preparations were made in the Pharmaceutical Technology Laboratory, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta. The release test was carried out, and the results showed that the risedronate bisphosphonate emulgel produced controlled release compared to the pure solution.¹⁷ In addition, the sample used in this study was 18 guinea pigs whose two lower incisors were moved distally. Then, the samples were divided into two groups: nine to see the movement of relapse on the 3rd day and nine on the 7th day. Of the nine guinea pigs, they were further divided into three: group I (control), group II (emulgel application without risedronate), and group III (emulgel application with risedronate) with three each.

In this study, the guinea pigs were kept in cages for five days at a room temperature of 25°C to adapt to the same environment at the Research Laboratory, Universitas Islam Indonesia. The guinea pigs were anesthetized first with a solution of ketamine and xylazine (0.2 mg) by intramuscular injection in the thigh. The guinea pig's teeth were cleaned, a rubber separator was installed to form a small distance, and then etched. After forming the distance, the rubber separator was removed, the molar band was attached with a flowable composite adhesive, and a light cure was performed. The two lower incisors were moved distally utilizing an open coil spring for seven days until a distance was formed, and seven days were added for stabilization (Figure 1).

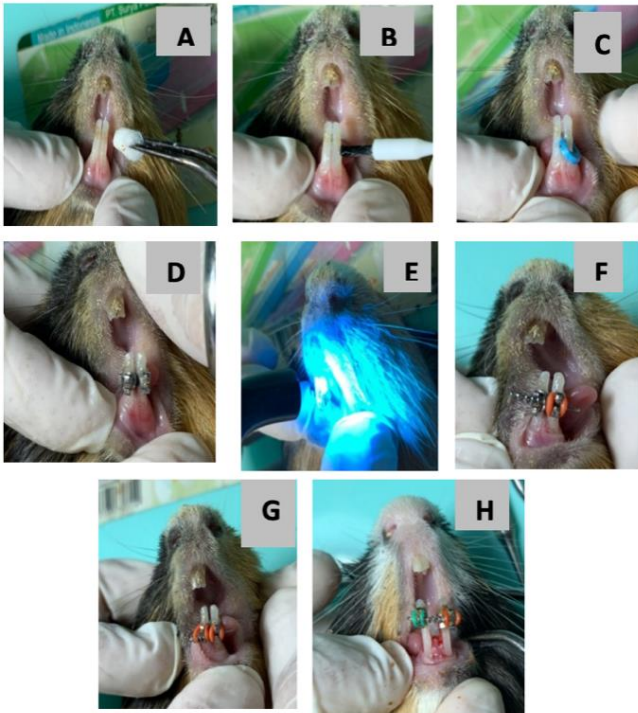


Figure 1. A: Isolating and cleaning the guinea pig's teeth; B: Performing tooth etching; C: Installing the separator; D: Installing brackets; E: Cementation and light cure using flowable composite; F: Installing the open coil spring; G: Installing open coil spring; H: Orthodontic movement of the incisors.

During the 7-day stabilization period, emulgel was applied to group II (emulgel without risedronate) and group III (emulgel risedronate). Emulgel was applied at 0, 4, and 8 hours to the labial and lingual mucosa of the incisors topically using a cotton bud (Figure 2). A cotton bud was applied to the mucosa at a dose of 25 mg in a circular motion and spread evenly for 2 minutes. After seven days of stabilization, the open coil spring was removed, and the distance between the two lower incisors was measured (initial distance). Emulgel application was still carried out until distance measurements were made on the 3rd and 7th days (final distance).



Figure 2. A. Emulgel application on the labial and lingual mucosa, B. Spread evenly for 2 minutes.

The movement distance measurement was carried out utilizing a calibrated digital sliding caliper three times, and the mean was calculated (Figure 3). After knowing the initial and final distances, it was subtracted, and the distance (movement) of relapse was obtained. Data were analyzed using One-Way ANOVA and Post Hoc LSD.



Figure 3. Distance measurement utilizing digital sliding calipers

RESULTS

The initial and final distance measurement results in the 3rd and 7th-day groups can be seen in Tables 1 and 2 and Figures 4 and 5. It is seen that, both in the 3rd and 7th-day groups, the largest relapse distance occurred in group I, namely the group without emulgel application, while the smallest relapse distance was in group III, namely the group with risedronate emulgel application.

Table 1. Measurement of inter-incisor distance on the 3rd day

Group	Guinea pig	H0 (mm)	H3 (mm)	H0- H3 (mm)	Mean H0- H3 (mm)
Group I (Control)	A31	2.25	1.40	0.84	1.138
	A32	2.68	1.69	0.99	
	A33	3.11	1.53	1.58	
Group II (Emulgel without risedronate)	B31	2.36	1.71	0.65	0.751
	B32	2.57	1.8	0.77	
	B33	1.47	0.64	0.82	
Group III (Emulgel risedronate)	C31	1.83	1.21	0.62	0.394
	C32	1.76	1.36	0.4	
	C33	1.67	1.50	0.16	

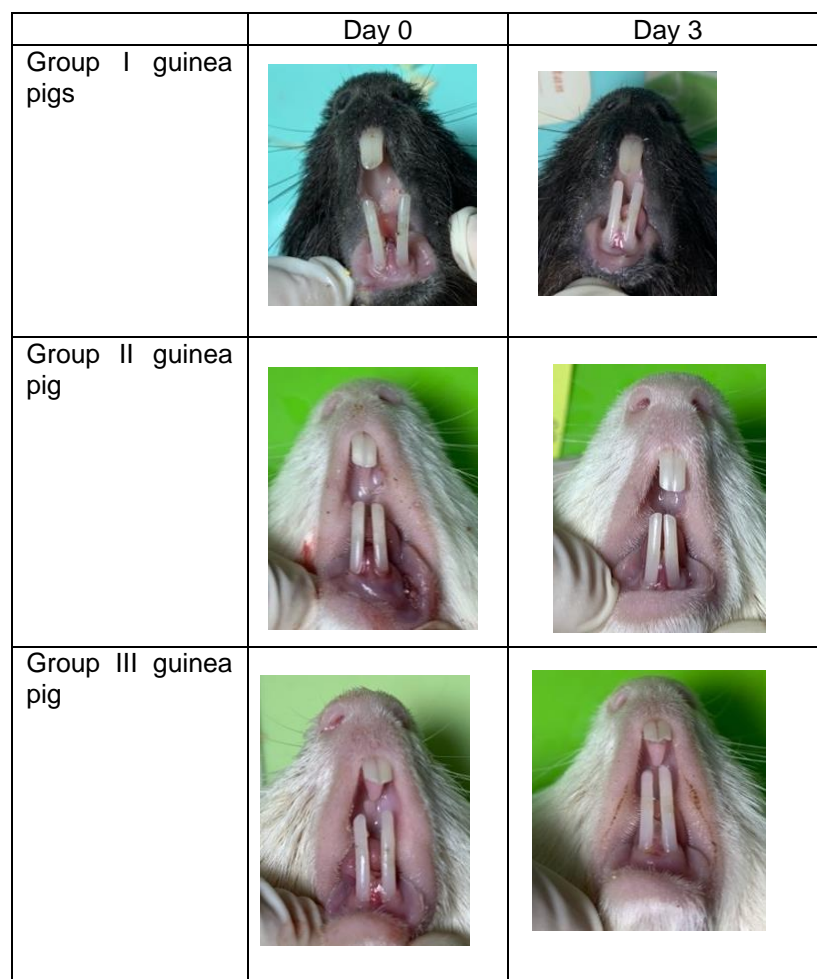
**Figure 4.** Movement of tooth relapse on day 3

Table 2. Measurement of inter-incisor distance on the 7th day

Group	Guinea pig	H0 (mm)	H3 (mm)	H0-H3 (mm)	Mean H0- H3 (mm)
Group I (Control)	A71	2.54	1.246	1.293	1.254
	A72	2.336	1.06	1.276	
	A73	2.67	1.48	1.19	
Group II (Emulgel without risedronate)	B71	2.32	1.43	0.89	1.021
	B72	2.216	1.346	0.87	
	B73	2.21	0.906	1.303	
Group III (Emulgel risedronate)	C71	1.446	0.966	0.48	0.732
	C72	2.313	1.44	0.873	
	C73	1.613	0.77	0.843	

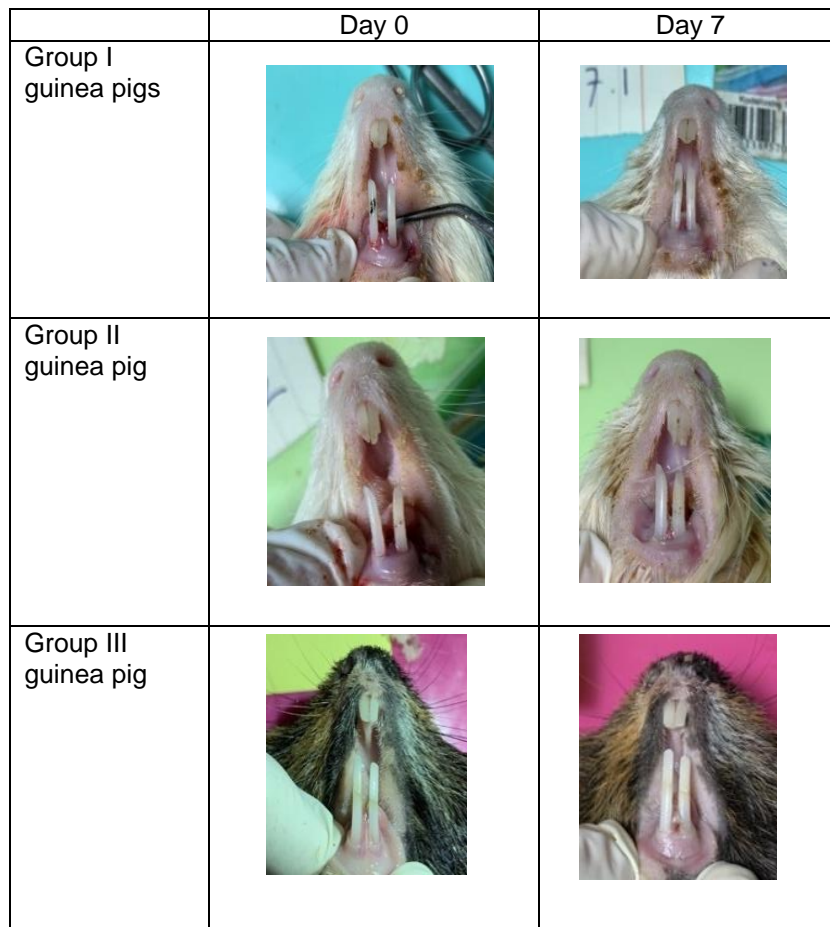


Figure 5. Movement of tooth relapse on day 7

The normality test obtained significant results for all groups above 0.05, so it can be said that the data were normally distributed. The homogeneity test showed 0.119 and 0.063, indicating that the data were homogeneous or had the same variance. Furthermore, a one-way ANOVA test was performed, and the significant data on day 3 and

day 7 was 0.038 and 0.043, signifying significant differences between groups I, II, and III (Table 3). Next, the LSD Post Hoc test was conducted (Table 4).

Table 3. One-way ANOVA test results

		Sum of Squares	df	Mean Square	F	Sig.
3 rd day	Between groups	0.832	2	0.416	5.926	0.038
	Within groups	0.421	6	0.070		
	Total	1.253	8			
7 th day	Between groups	0.411	2	0.205	5.567	0.043
	Within groups	0.221	6	0.037		
	Total	0.632	8			

Table 4. LSD post hoc test results

	Mean Difference	Sig.	Descriptin
3 rd day			
I	II 0.38778	0.123	H0 is accepted
II	III 0.74444*	0.014	H0 is rejected
III	III 0.35667	0.150	H0 is accepted
7 th day			
I	II 0.23333	0.187	H0 is accepted
II	III 0.52222*	0.016	H0 is rejected
III	III 0.28889	0.115	H0 is accepted

The LSD Post Hoc Test showed which group had the most significant difference. Significant group differences were indicated by assign (*) in the mean difference column. The data are said to have a significant difference if $p < 0.05$. The significance of groups I and III on the 3rd and 7th days was 0.014 and 0.016, meaning there was a significant difference between groups I and III.

DISCUSSION

The results uncovered a significant difference between the group without emulgel application (group I) and the group with risedronate emulgel (group III) on day 3 and day 7. The largest mean relapse distance occurred in group I, whereas the smallest relapse distance was in group III. It indicates that the modified risedronate in the emulgel dosage form was still effective in reducing the movement of relapsed teeth. The presence of risedronate bisphosphonate content in the emulgel solution applied to group III also functioned to inhibit

the bone resorption process carried out by osteoclasts. The results of this study align with previous research conducted by Anggraini (2016), who reported that the administration of bisphosphonate zoledronate in the form of a gel emulsion could penetrate the mice's alveolar bone and increase osteoclast apoptosis, which was observed by counting osteoclast apoptotic cells.¹⁸

Alveolar bone has one of the cells that play an important role in the occurrence of relapse, namely osteoclasts,¹⁹ thus, inhibition of local osteoclast activity could allow for increased control of individual teeth during orthodontic treatment and prevention of post-orthodontic relapse.²⁰ According to Alberto Consolaro (2014), bisphosphonates (BP) work by inhibiting osteoclast activity through four mechanisms: a) inhibiting cell recruitment to the bone surface, b) inhibiting cell activity, c) reducing cell life span by inducing apoptosis, and d) influencing mineral exchange processes during bone resorption.²¹ Hence, post-orthodontic therapy with BP administration can reduce alveolar bone resorption so that the tooth becomes stable in the alveolar bone and can control relapse.²²

The type of bisphosphonate used in this study was risedronate. Several previous studies have shown that risedronate effectively reduces relapse movements but still uses not easy and less convenient methods, such as the injection method. According to Yadav et al. (2016), bisphosphonate injection can cause substance ineffectiveness due to various conditions, such as changes in pH, enzyme interactions, and gastrointestinal metabolism.²³ Therefore, bisphosphonates are needed, which can be administered topically so that the active drug substance is easily absorbed by the oral mucosa without pain.²⁴ Also, topical preparations with local effects are a way to avoid systemic effects. One of the topical preparations with a local effect is emulgel.¹⁶

The bisphosphonate risedronate in this study was modified as an emulgel with VCO as the oil phase in its preparation. The results revealed that the effectiveness was not much different from previous studies, namely a decrease in the distance of the relapse movement. According to Rasool (2021), the administration of risedronate in the form of an emulgel with a drug delivery system is the process of administering a therapeutic substance using a specific carrier media, with the advantage of being able to release the bioactive drug substance at the right time and location and able to control the toxicity of the drug's active substance.²⁵ The drug preparation in the form of an emulgel can also stick to the mucosa for a long time, has easy-to-administer preparation, has good dispersion, and is more comfortable for patients.²⁴ In addition, emulgels have several advantages as drug delivery media, including blending with hydrophobic drugs, better loading capacity and stability than gel and emulsion preparations, low production and preparation feasibility, controlled release, and no intensive sonication. Meanwhile, the manufacture of emulgel requires several elements, such as oil, water, emulsifier, gelling agent, penetration enhancer, and pH adjusting agent.¹⁵

Moreover, emulgel has a mucoadhesive drug delivery system, which is a drug delivery system that interacts with the mucous layer on the surface of the mucosal epithelium and mucin molecules by establishing intensive contact between the drug and the target area, thereby prolonging the residence time of the drug preparation in the application target area.^{24,26} The mucoadhesive drug delivery system also has a controlled drug release pattern.²⁶ In this study, the emulgel used was virgin coconut oil (VCO) as the oil phase, and a release profile test was carried out. It was found that the risedronate bisphosphonate

emulgel with VCO resulted in a controlled release compared to the pure solution.¹⁷

Nevertheless, the results showed no significant difference between group II (the emulgel treatment group without bisphosphonates) and group III (the emulgel treatment group with bisphosphonates). Still, the mean relapse distance was higher in group II. It might be due to the presence of VCO in the emulgel preparation. In this case, VCO has a possible role in increasing the body's defense against oxidative stress. Oxidative stress causes a reduction in bone formation by inhibiting differentiation and decreasing osteoblast function. Abujaiza et al. (2012) reported that using VCO could balance oxidative stress and agents, thereby increasing osteoblast function and preventing osteoclast activity, thus reducing relapse in teeth.²⁷

CONCLUSION

The bisphosphonate risedronate, converted into an emulgel dosage form, effectively reduced the movement distance of relapsed teeth. Thus, it has the potential to be easy and convenient to apply the preparation. Moreover, it is necessary to know its histological effect, i.e., the effect on osteoclasts and osteoblasts, which play an important role in tooth relapse movement.

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