

Clinical assessment of relapse with antiosteoporotic drugs after orthodontic Teeth Movement (Experimental Study)

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Abstract: Relapse after orthodontic tooth movement is an undesirable outcome after orthodontic treatment.

Aims: The purpose of this study is to investigate the influence of administration of bisphosphonate i.e. (antiresorptive drug), during orthodontic tooth movement in experimental rabbits.

Materials & Methods: a total of (60) local rabbits separated into three groups of 5 rabbits for each group (control, clodronate & clodronate + vitamin D3). The lower incisors of the rabbits were moved distally by a fixed orthodontic appliance for 15 days and the drugs given IM. for 1, 2, 3 & 4 weeks then, the appliances were removed and the amount of relapse were measured.

Results & Discussion: Clinically we note during the experiment great & quick loss of space occur in the 1st 3 days after removing the appliance. In the two drugs groups the mean value larger than control group. This gives us idea about relapse occur more in control group than the two drugs groups, and the difference is significant. Clodronate may be consider as substitute of retainers after removing the appliance.

Key words: orthodontic tooth movement, clodronate, vitamin D3, bone formation.

علاج الأسنان التقويمي. هدف البحث : إن الغرض من هذه الدراسة هو Aims. الخلاصة: الانتكاس بعد حركة الأسنان هو نتيجة غير مرغوب فيها بعد ، بعد تقويم الأسنان في الأرانب التجريبية. المواد والطرق: مجموعته مكونة من (60) من الأرانب المحلية تم (antiresorptive drug) دراسة تأثير () تم عمل جهاز تقويمي ثابت للقواطع . (clodronate + vitaminD3 , clodronate فصلها إلى ثلاث مجموعات 5 أرانب لكل مجموعة (السيطرة، و لمدة 1،2،3 و 4 أسابيع ثم تم إزالة الجهاز التقويمي و تم قياس مقدار السفلية للأرانب لمدة 15 يوما و الأدوية تعطى عن طريق الحقن بالعضلة الانتكاس. النتائج و المناقشة : سريريا نلاحظ أثناء التجربة خسارة كبيرة و سريعة من الفراغ المحدث بجهاز التقويم يحصل في 3 أيام الاولى بعد إزالة الأجهزة في مجموعات العلاج، القيمة المتوسطة لهم أكبر من المجموعة الضابطة . هذا يعطينا فكرة ان الانتكاس يحدث أكثر في المجموعة الضابطة . كبدل عن المثبتات بعد إزالة جهاز التقويم Clodronate من مجموعتي العلاج ، وهناك فرق معنوي عند مقارنتهما يمكن اعتبار

Introduction

One of the keys for successful orthodontic treatment is to avoid undesirable anchored tooth movement. Loss of anchorage may be prevented by using bisphosphonates. Several laboratory studies have demonstrated that orthodontic tooth movement can be controlled by topical injection of bisphosphonates. In 1994, Igarashi et al. reported that bisphosphonate could prevent orthodontic tooth movement or enhance relapse in rats when it was administered systemically or by topical injection. Furthermore, they showed that topical injection of bisphosphonate exerted its effect at the local site of injection^{1,2}

For a tooth to move, osteoclasts must be formed so that they can remove bone from the area adjacent to the compressed part of the PDL. Osteoblasts also are needed to form new bone on the tension side and remodel resorbed areas on the pressure side. Prostaglandin E has the interesting property of stimulating both osteoclastic and osteoblastic activity, making it particularly suitable as a mediator of tooth movement .

During mastication tooth moves in its socket within a few seconds but few hours at most , the resulting change in the chemical environment produces a different pattern of cellular activity . Animal experiments have shown that increased

levels of cyclic adenosine monophosphate (AMP) , the "second messenger" for many important cellular functions including differentiation, appear after about 4 hours of sustained pressure^{3,4}.

Retention is defined as the phase of orthodontic treatment that attempts to keep teeth in their corrected position following orthodontic braces, and is thus a very integral part of the treatment⁵. Without a means of retention, orthodontic treatment results are potentially unstable and may revert back to their pre-treated form, this occurs due to three major reasons:

- (1) the gingival and periodontal tissues affected by orthodontic tooth movement require time for reorganization after the appliances are removed.
- (2) soft tissue pressures surrounding oral cavity exert pressures tending toward relapse; and
- (3) changes produced by growth may alter the therapeutic alignment of teeth⁶.

Retention can be achieved by placing appliances known as retainers. There are different types of retainers, broadly divided into either removable or fixed⁶.

There are no standard criteria set for the length of time needed to wear a retainer. A longer retention period may be needed depending on the complexity of movement achieved⁷.

there are many factors that may affect the potential for relapse.

Most importantly are: latent growth, degree of dental compensation, a stable balanced oral environment, patient compliance, cessation of habits, and the health of teeth⁸.

Aims of the study

The purpose of this study is to investigate the influence of administration of bisphosphonate i.e. (antiresorptive drug), during orthodontic tooth movement in experimental rabbits.

Materials and Methods

This research project was performed involving a total of (60) local rabbits of age at least 6 months, and weighing 1,25 - 1,75 Kg were used for this experiment. The animals were housed for at least 1 week before the experiment started, under normal conditions and provided the standard diet and they had free access to tap water.

Study Design

A randomly design was used for this experiment to reduce inter individual variation. Animals were separated into three groups of 5 rabbits for each group randomly assigned

1. The control group.
2. Clodronate group.
3. Clodronate + Vitamin D3 group.

1-The Appliance

The Appliance consisted of: figure(1)

1. two stainless steel bands(Dentarum, Dentaform)for incisors teeth, each band were bend to confirm the size of rabbits teeth .
2. A rectangular stainless steel wire of 16*22 inch and 20mm in length used as arch wire for teeth movements.
3. Nickel Titanium open coil spring (.010 x .030mm, Rocky Mountain Orthodontics. Denver, CO) consisted of 5 circles and about 5mm in length, the spring was determined in order to deliver the amount of force needed to sprats the teeth by activation of the spring.
4. Ligature wire 0.01 inch for ligation the arch wire to the brackets band .

2-Design of spring

Each band were bend from the distal side ,to avoid space interference ,then the band fixed with ligature to the arch wire,the two bands finally ligated together with ligature to close the space created from the coil spring . All the springs were fabricated by the investigator. With both arms touching, the spring were capable of exerting a reciprocal lateral force . figure(2)

3-Technique of Positioning of spring

The animals were anesthetized with an intramuscular injection of ketamine 10mg/Kg (ketamine hydrochloride, 50 mg/ml, holden, India), and xylazine 2mg /Kg (xylazine as HCL 20mg/ml, alfasan , Woerden- Holland).

Isolation of the work field with the use of cotton role ,then stripping of both incisors in the midline with sand strip prior to appliance placement and tooth movement , then cementation with Zinc Carboxylate cement .no space between the bands.

4-Measurement of Force & Tooth Movement

The force exerted by the spring was determined prior to insertion, with a tension gauge.The measurements of force that to be applied to the teeth about 50 gm applied to the two lower incisors . a reciprocal force applied by the spring to open space between the teeth of about 3-5mm . All the measurements performed were obtained using a digital caliper, with precision of 0.01 mm.,between the mesial point of incisal edge of the lower incisors.the measurements done after 10 to 15 day of appliance fixation, and for period after removal of the appliance .

Drugs to be used :

1. Clodronate which belongs to the family of bisphosphonates (BPs), bone-seeking agents that are potent inhibitors of osteoclasts. disodium clodronate under trade name(CLODRONATO ABC) 100mg/3.3ml .disodium Clodronate confirm the elimination of macrophages cells that considered to be the precursor of osteoclast cells⁹ . The higher dose was five times higher for safety.
2. Vitamin D3(DEVIT-3, 300.000 I.U. Turkey) anti-osteoporotic drug which inhibit osteoclast activity .also given intramuscular injection in dose of 5000 IU daily .

Administration of Drugs

The animals in groups 2 and 3 were administered 20 mg/kg disodium clodronate intramuscular injection twice a week with 23"disposable syringe .While in group 3an addition vitamin D3 given 4 days weekly with insulin syringe of 1ml.the administration route was selected because of the quick absorption less side effect in injection, in addition a low absorption of clodronate after oral administration is low .

Clinical assessment of relapse

After completion the steps of appliance fixation in rabbits mouth, the appliance allow to be active . tooth movement completed within 15 days, the appliance remain 1 week (as fixed retainer) for initial retention then determination of the groups according to periods which are 1,2,3 &4 weeks. At the end of each period ,the appliance removed from the rabbits teeth and the space measured with the digital caliper. The measurements done every 2 days for the following 2 weeks.

For statistical analysis the space between the teeth measured directly at the time of removing the appliance(sp0),the measurement repeated every 2 days till 2 weeks of appliance removal(as the relapse of the teeth stopped at this time). Documented space at end of 1st week (sp1w) and the end of 2nd week (sp2w).

sp0-sp1w= amount of relapse at the end of 1st week .

sp0-sp2w= amount of relapse at the end of 2nd week.

Then the percentage of each measurement was calculated for all the groups .

Percent of relapse = (amount of relapse at the end of 1st week, or 2nd week / sp0)*100 .

Results

A descriptive statistics that includes minimum, maximum, mean & standard deviation shown in tables (1,2 &3)for all groups that describe the amount of space between the lower incisors at time of removing the appliance ,1 week and 2 weeks after removal of the appliance .

In table (1) we note that the mean of all the groups (control, clodronate & clodronate +vitamin D3) were around three mm. this because the standard appliance design ,length of open coil sprig with 5 circles of all the sprigs .while in table (2) we can note that the two drugs groups have mean value larger than control group. This gives us idea about relapse occur more in control group than the two drugs groups .the same can be seen for table(3) as for table(2) .

In table (4) which is the comparison amount of relapse in 1st & 2nd week among the groups ,a significant differences for the majority of the paired groups using paired t-test analysis .

Table(5) description the percent of relapse after 1 week, in all the group we see a gradual decrease of mean values from 1st till the 4th week .

In table (6) which is for description the percent of relapse after 2 weeks ,100% of relapse seen in 1st week of control group ,and a lowest mean value seen in clodronate group of 2 week drug administration .

Table (7) the most important one because it represent the comparison of percent of relapse ,that gives a real picture about drugs and period effect on relapse, a significant differences seen between control – clodronate and between control – clodronate+vitamin D3 group .while a non significant differences seen between clodronate – clodronate+vitamin D3 group.

Graph (1&2) represent the distribution percent of relapse for the three groups with the four period of drug administration after 1& 2 weeks .

Discussion & Conclusion

The fixed orthodontic appliance used in this study was designed to produce a distal bodily movement of the incisors by applying the same amount of force for all animals. The animals tolerated the appliance well and resumed their normal activity in a few days. during the first 3 days of the study, the gingiva of animals were of normal color and texture except for slight gingival inflammation in few animals. No bleeding tendency or gingival enlargement was noted. During the period till to 15th days.

no study was able to determine a single and most successful method of retention, nor was there an explanation on how to ideally prevent the problem of relapse following orthodontic treatment. Finding a “perfect retainer” for patients is difficult because orthodontic retention is an individualized problem¹¹.

There are few number of studies have been documented on animal models with administration of Bps related to tooth movement. Keles etal¹², Seifi etal¹³, Kim etal¹⁴, Igarashi et al¹ and Adachi¹⁵ have done various animal experimental studies and reported that Bps cause a reduction in orthodontic tooth movement.

The results of present study were similar to those studies. However, all previous experimental studies were carried out on rats,or mice . In this study rabbits were used because of ease of handling and fabrication of intraoral appliance is comfortable compared to mice administration of bisphosphonate in rabbits led to decrease in orthodontic tooth movement. This seen clearly in the mean values of clodronate and clodronate+vitamin groups table(3), Larger than that of control group ,so less relapse in the treatment groups .this finding agreed with Keles etal¹² research ,they found 77% reduction of tooth movement in a mouse model with the use of bisphosphonate(pamidronate,) drug administered subcutaneously .also studies by Seifi etal¹³ and Kim etal¹⁴ stated that the systemic administration of pamidronate in rats was resulted in reduction of relapse ,the same result reported by Adachi¹⁵ but he use Risedronate . Igarashi et al¹ studied the effect of locally administered bisphosphonate (alendronate) and concluded that there was a significant reduction of buccal movement of molars in drug induced rats.

General significant decreased of tooth movement in treating groups at end of 1st & 2nd with control one when compared together , was observed in table (4) using paired t-test analysis. but a non significant differences within the treating groups because the two drugs have the same mode of action on the bone as they belonged to bisphosphonate group .

In tables(5,6) description of percent of relapse in that sp1 or sp2/sp0 *100,(sp=space. 0,1,2 at time of appliance removal,1st & 2nd week respectively), those represent the real behavior of the experiment along four weeks among the groups . we see the decrement decrease of mean value from 1st to 4th week for all the groups with some variability ,this due to the great variation among the rabbits .

Generally the two drug groups have mean values less than that of control group; in that the mean value of 1 & 2 weeks of the treating groups were about the half of control one . this due to anti resorptive effect/anti osteoclastic effect of bisphosphonate . Clinically we note during the experiment great & quick loss of space occur in the 1st 3 days after removing the appliance .this specially seen in the difference from 1-2 week within each group in the two tables (5,6).

Loss of space continue from removing the appliance but stopped at the end of 2nd week .The less mean values of percent of relapse; the less amount of relapse , so the better drug action. This seen in the 2 week of clodronate group, followed by 3rd, 4th week of same group & in 2 week of clodronate+vitamin group which represent the best period for maximum retention .

Table (7)for comparisons the percents of relapse of the three groups ,a significant differences seen between control with each of clodronate & clodronate+vitamin groups, a non significant differences between clodronate & clodronate+vitamin groups .

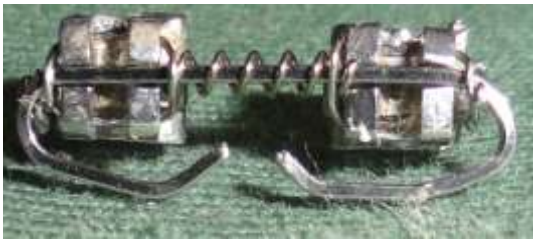
In conclusion , Loss of space continue from removing the appliance but stopped at the end of 2nd week , the results of the study indicate that the use of bisphosphonate (clodronate) is benefit for improving retention of teeth after removing the appliance. That it may consider a substitute of retainers.

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Table(1) Descriptive Statistics of the groups for clinical relapse at time of app. Removal

groups	Weeks	Minimum	Maximum	Mean	Std. Deviation
Control	1	2.83	3.52	3.25	0.28
	2	2.73	3.17	2.95	0.22
	3	3.24	3.77	3.51	0.26
	4	3.58	3.84	3.68	0.13
Clodronate	1	3.00	3.33	3.21	0.13
	2	2.96	3.65	3.30	0.26
	3	3.20	3.56	3.32	0.14
	4	2.87	3.43	3.18	0.23
Clodronate +vitamin	1	3.00	3.43	3.13	0.17
	2	3.75	3.97	3.88	0.09
	3	3.52	3.71	3.61	0.08
	4	3.65	3.83	3.73	0.09



figure(1) parts of the appliance



figure(2) the appliance in passive form

Table(2) Descriptive Statistics of the groups for clinical relapse 1 week of app. Removal

groups	Weeks	Minimum	Maximum	Mean	Std. Deviation
Control	1	0.50	0.90	0.66	.15
	2	1.35	1.50	1.43	.07
	3	1.58	1.72	1.67	.05
	4	2.37	2.46	2.40	.04
Clodronate	1	1.40	2.45	1.91	.43
	2	2.40	2.98	2.62	.24
	3	2.43	2.87	2.66	.17
	4	2.12	2.60	2.40	.18
Clodronate +vitamin	1	1.64	1.96	1.75	.13
	2	2.70	3.12	2.98	.16
	3	2.00	2.87	2.43	.31
	4	2.50	3.00	2.75	.19

Table(3) Descriptive Statistics of the groups for clinical relapse 2 weeks of app. Removal

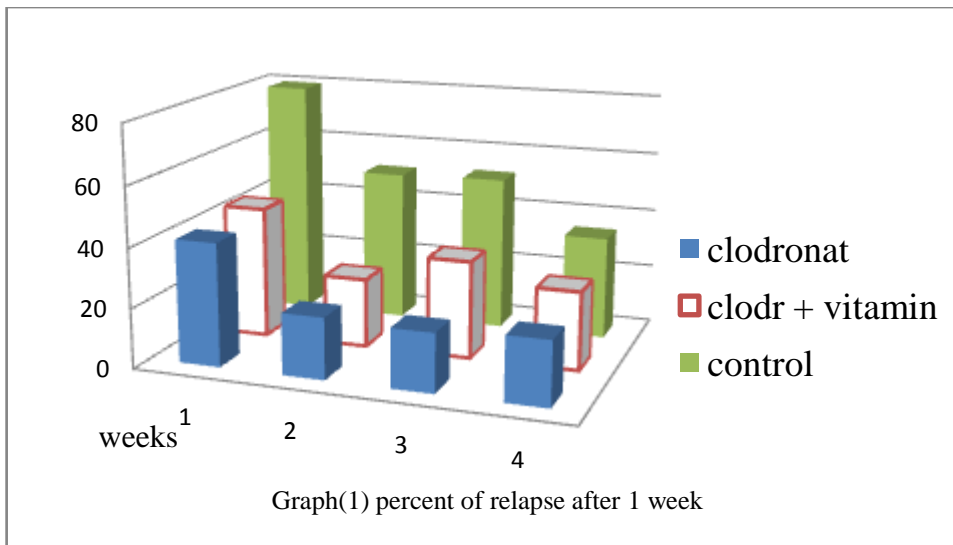
groups	Weeks	Minimum	Maximum	Mean	Std. Deviation
Control	1	0.00	0.00	0.00	.00
	2	0.64	0.73	0.68	.04
	3	1.12	1.40	1.28	.12
	4	1.35	1.42	1.38	.03
Clodronate	1	1.04	1.50	1.36	.18
	2	2.10	2.67	2.31	.26
	3	1.89	2.47	2.06	.23
	4	1.00	1.80	1.36	.32
Clodronate +vitamin	1	1.20	1.76	1.43	.21
	2	2.40	2.87	2.60	.23
	3	1.80	2.40	2.05	.22
	4	1.87	2.50	2.23	.28

Table(4) Comparisons of groups of clinical relapse

Paired groups	t	Sig.
Con1w1 - clod1w1	-7.58	.002
Con1w2 - clod1w2	-16.10	.000
Con2w1 - clod2re1	-12.59	.000
Con2w2 - clod2re2	-14.06	.000
Con3w1 - clod3w1	-13.24	.000
Con3w2 - clod3w2	-5.94	.004
Con4w1 - clod4re1	0.10	.925
Con4w2 - clod4re2	0.13	.899
Con1w1 - vit1w1	-11.52	.000
Con1w2 - vit1w2	-14.91	.000
Con2w1 - vit2w1	-16.47	.000
Con2w2 - vit2w2	-18.06	.000
Con3w1 - vit3w1	-4.74	.009
Con3w2 - vit3w2	-6.30	.003
Con4w1 - vit4w1	-4.23	.013
Con4w2 - vit4w2	-6.49	.003
Clod1w1 - vit1w1	0.72	.511
Clod1w2 - vit1w2	-0.52	.625
Clod2re1 - vit2w1	-3.05	.038
Clod2re2 - vit2w2	-1.95	.123
Clod3w1 - vit3w1	1.52	.203
Clod3w2 - vit3w2	0.06	.949
Clod4re1 - vit4w1	-3.58	.023
Clod4re2 - vit4w2	-3.277	.031

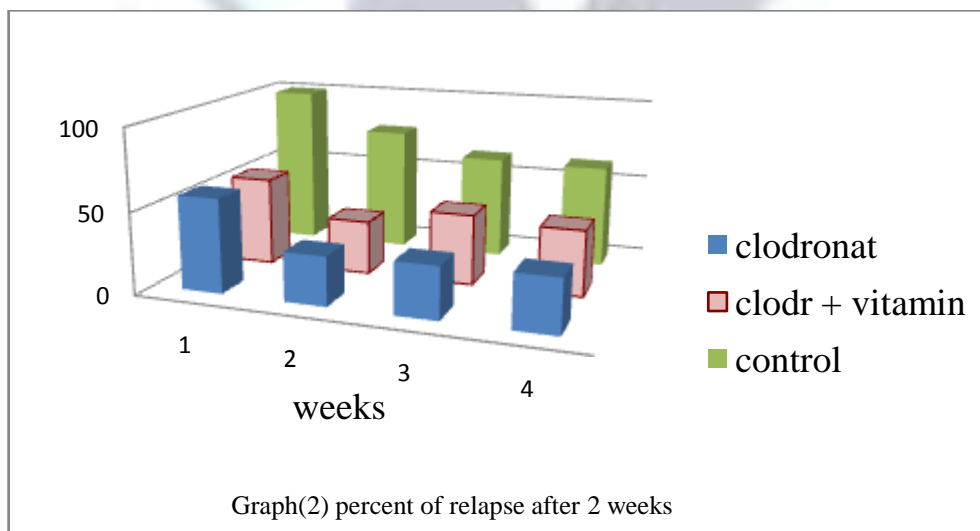
Table (5) Descriptive Statistics of percents of relapse after 1 week

groups	Weeks	Minimum	Maximum	Mean	Std. Deviation
Control	1	74.43	85.80	79.68	4.20
	2	45.05	57.41	51.18	6.17
	3	46.91	55.44	52.01	4.65
	4	32.96	35.94	34.56	1.32
Clodronate	1	36.33	47.50	41.31	4.34
	2	15.54	25.47	20.61	4.04
	3	13.81	27.03	19.71	6.10
	4	20.00	24.13	21.54	1.71
Clodronate +vitamin	1	42.86	45.33	44.14	1.12
	2	19.69	31.99	23.07	5.09
	3	22.64	43.18	32.65	7.82
	4	19.35	34.73	26.19	6.38



Table(6) Descriptive Statistics of percents of relapse after 2 weeks

groups	Weeks	Minimum	Maximum	Mean	Std. Deviation
Control	1	100.00	100.00	100.00	0.00
	2	73.26	79.50	76.80	3.26
	3	62.86	65.43	63.48	1.10
	4	62.01	63.02	62.56	0.44
Clodronate	1	53.13	65.33	57.64	4.73
	2	25.68	34.98	30.04	4.48
	3	25.83	37.50	31.73	5.59
	4	30.03	36.36	32.67	2.60
Clodronate +vitamin	1	43.59	60.00	54.22	7.17
	2	25.91	39.55	32.86	6.00
	3	35.31	48.86	43.16	5.07
	4	32.60	48.77	40.22	7.89



Table(7) Comparisons the percents of relapse

Paired Samples Test	t	Sig.
Per1w1 - per1w1c	15.17	.000
Per1w2 - per1w2cl	20.01	.000
Per2w1 - per2w1cl	20.26	.000
Per2w2 - per2w2cl	34.75	.000
Per3w1 - per3w1cl	8.94	.001
Per3w2 - per3w2cl	12.02	.000
Per4w1 - per4w1cl	12.60	.000
Per4w2 - per4w2cl	24.81	.000
Per1w1 - per1w1vi	18.43	.000
Per1w2 - per1w2vi	14.27	.000
Per2w1 - per2w1vi	6.31	.003
Per2w2 - per2w2vi	13.66	.000
Per3w1 - per3w1vi	4.41	.012
Per3w2 - per3w2vi	9.09	.001
Per4w1 - per4w1vi	2.80	.048
Per4w2 - per4w2vi	6.41	.003
Per1w1c - per1w1vi	-1.62	.179
Per1w2cl - per1w2vi	.99	.378
Per2w1cl - per2w1vi	-.66	.542
Per2w2cl - per2w2vi	-.74	.498
Per3w1cl - per3w1vi	-2.59	.060
Per3w2cl - per3w2vi	-1.13	.320
Per4w1cl - per4w1vi	-.70	.520
Per4w2cl - per4w2vi	2.44	.071