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Radiographical&Clinical Study by Applying Laser&Vegf on Bone Remodeling in Experimental Tooth Movement

KEYWORDS

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ABSTRACT *Aim of the Study The main aim of this study:*

To evaluate the effect of the Low Level Laser Therapy (LLLT) on the rate of post experimental tooth movement clinically, biologically and radiographically, and on the bone remodeling histologically and immunohistochemically. Radiographicevaluation of the effect of local application of LLLT and VEGF (alone and in combination) on orthodontic movement.The present study shows the LLLT Laser and VEGF exerts a fundamental role in remodeling periodontal ligament and is also involved in bone resorption and formation.

Introduction

Low Level Laser Therapy (LLLT) is a simple and inexpensive method that can be used easily in the dental practice for different purposes .The stimulatory effect of low-level laser therapy is well known and includes enhancement in tissue growth and tissue regeneration, resolvement of inflammation (1.Chiari,2015) , pain reduction(2.Stein et al.,2015) ,enhancement of wound healing(3.Martins et al.,2015). Some studies investigated the efficacy of low power lasers in reducing burning mouth pain (4.Arbabi-Kalati et al.,2015) ,promoting bone regeneration in the midpalatal suture during expansion and stimulating tooth movement(5.Marquezan et al.,2013).

The vast majority of therapeutic lasers are semiconductor lasers today(6.Dalaie et al.,2015). There are three diode types:

1. Indium, Gallium-Aluminum-Phosphide (InGaAlP) laser

2. Gallium-Aluminum Arsenide (GaAlAs) semiconductor laser

3. Gallium-Arsenide (GaAs) semiconductor laser

In recent research projects, the effect of laser therapy was tested regarding the stimulatory effect on bone remodeling with the potential to influence the tooth movement rate as related to photo-biological responses of oral tissue after application of laser(7.Seifi &Vahid-Dastjerdi 2015).

There are three effects that commonly occur as a result of tissue exposure to laser photons (8.Torri &Weber ,2013). They are:

Primary effects of photoreception are a result of the interaction of photons and cell mitochondria which capture, direct, and transduce photon energy to chemical energy used to regulate cellular activity.

Secondary effects occur in the same cell in which photons produced the primary effects and are induced by these primary effects. Secondary effects include cell proliferation, protein synthesis, degranulation, growth factor secretion, myofibroblast contraction and neurotransmitter modification—depending on the cell type and its sensitivity.

Tertiary effects are the indirect responses of distant cells to changes in other cells that have interacted directly with photons. They are the least predictable because they are dependent on both variable environmental factors and intercellular interactions.They are, however, the most clinically significant. Tertiary effects include all the systemic effects of phototherapy. Primary, secondary, and tertiary events summate to produce phototherapeutic activity.

Orthodontic tooth movement occurs in the presence of a mechanical stimuli sequenced by remodeling of the alveolar bone and periodontal ligament (PDL). Bone remodeling is a process of both bone resorption on the pressure site and bone formation on the tension site(9.Baloul, 2015). Orthodontic tooth movement can be controlled by the size of the applied force and the biological responses from the PDL .The force applied on the teeth will cause changes in the microenvironment around the PDL due to alterations of blood flow(10.McCormack et al.,2014), leading to the secretion of different inflammatory mediators such as cytokines, growth factors, neurotransmitters, colony-stimulating factors, and arachidonic acid metabolites (11.Kumar et al.,2015). As a result of these secretions, remodeling of the bone occurs .The most important growth factor is Vascular endothelial growth factor (VEGF) ,this protein is a member of the PDGF/VEGF growth factor family and encodes a protein that is often found as a disulfide linked homodimer. This protein is a glycosylated mitogen that specifically acts on endothelial cells and has various effects, including mediating increased vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth, promoting cell migration, and inhibiting apoptosis.VEGF is involved in tissue neo-formation that is strictly correlated with the presence of blood vessels(12.Wu. et al.,2009).

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During orthodontic tooth movement, compressive forces induce angiogenesis of periodontal ligament together with the role of mediator of the VEGF. The localization of VEGF was analyzed in many in vivo researches and illustrated an increment in it's expression in periodontal tissue during experimental tooth movement(13.Salomão et al.,2014). Therefore, VEGF exerts a fundamental role in remodeling periodontal ligament and is also involved in bone resorption and formation.

Material and Method
Orthodontic Appliance Design and LLL therapy

The orthodontic appliance consists of orthodontic bands, arch wires, and NiTi open-coil spring. The bands were customized for each rabbit. Briefly, the animals were anesthetized with general anesthesia, induced by an intramuscular injection of a ketamine (50 mg/ml) at a dose of 50mg/kg body weight and muscle relaxant Orbarcaine 2% at a dose of 5mg/kg body weight. The two drugs were mixed at the ratio of 2:1 (Ketamine: Orbarcaine), impression for mandibular central incisors (MCIs) of each rabbit was taken first with silicone material ,study stone models of the MCIs and the surrounding region were made ,which used for preparing of individual resin trays for each rabbit; that then used to take precise final impressions with alginate material and the master stone models .Orthodontic bands were prepared to fit the teeth sizes ,using band strips(Dentaurum-Germany) and then welded under pressure by using of Welder device. Then a round buccal tube with wings welded to thehand made bands in a horizontal direction and used as labial tube. The bands were cemented to its co-related MCIs after the removing of the orthodontic elastic separator, so that the superior border of the cemented bands was 3mm away from the incisal edge to allow for wear of the teeth and the lower border about 2mm away from the cervical area to avoid a trauma of the surrounding tissue.Orthodontictooth movement was generated by the insertion of a stainless steel arch wire with diameter of 0.016" and 15 mm in length through the labial tubes and the NiTi open-coil spring(ORTHO. TECHNOLOGY USA) with 3-4 mm in length (about 4-6 coils) was inserted along the arch wire from the non-bend end and subjected to constrict pressure with tucker in order to be inserted between the labial tubes, so that it will apply a pushing force on both MCIs (in distal direction) with a total orthodontic force of (100 gm.)divided into two teeth so that each incisor receive a light continuous force of (50gm) according to Proffit et al. (6).This force was measured by pressure-gauge (CORBLX , Dent arum –Germany). Two coils at both ends of the arch wire were made in one plan ,and it serves as stopper for the arch wire and as non-traumatic end. Experimental tooth movement was conducted for 21 days. The experimental group

(A) Was received the LLL therapyat 810 nm, with an output of 250 mW

, and exposure of 20 s for each 7 days.While the experimental group

(B) was received the0.1μm of VEGF in pressure side and about 0.2 mm subgingivally, for each 7 day.

Experimental group (C) treated with a combination of LLL therapyand 0.1μm VEGF and for each 7 days.

Radiographical Study
An intra-oral radiograph will be taken for the three groups before and after application of LLLT and VECF separately and in combination. Itan conventional Mono path size 2 ultra-speed type radiographic dental film.

Results
1Results Of theClinical Measurements

The data of the all experimental periods include the experimental tooth movement measurements(cumulative Measurements)and percentage , both of them were analyzed using both Descriptive and Inferential statistics as follows:

1.1Measurements of distance (mm) between MCIs
A bodily tooth movement was observed in all groups. The means of the weekly measurements of the distance between the mandibular central incisors (MCIs) of each group and their comparisons among groups and within group are shown in **Table (1)**, and **(Figure 1)**.It was found that, there was gradual increase in the amount of tooth movement from the 1st week till the 3rd week as follow:

After 1 week: the mean ± SD values of separation were increased and the highest one was (0.79±0.01), in combination group, then (0.66±0.01 mm) in laser, then (0.34±0.02 mm) inVEGF, and the least one was (0.32±0.01 mm) in control.

After 2 week: the mean ± SD values of separation were increased and the highest one was (1.22 ±0.01), in combination group, then (1.08±0.04 mm) in laser, then (0.78 ±0.01 mm) inVEGF, and the least one was (0.51 ±0.01 mm) in control.

After 3 week: the mean ± SD values of separation were increased and the highest one was (1.95 ±0.11), in combination group, then (1.78 ±0.03 mm) in laser, then (1.23±0.01 mm) inVEGF, and the least one was (0.92±0.01 mm) in control.

Figure(.2) illustrates Stem-Leaf Plots for clinical measurements of distance (mm) between MCIs among studied groups at the 3rd week.

By using Receiver Operating Characteristic Curve(ROC Curve) analysis was listed in table (2)& figure(3) that show area under the curve (ROC) for clinical measurements of distance (mm) between MCIs in contrast of control group at different periods,for 1 week the area (0.056)with sensitivity (100) and specificity (88.9),while for the 2 & 3 week they illustrate area (0.00) with sensitivity (100) and specificity (100).

Table (3) & figure(4) record (0.191)area under the curve (ROC) for distance (mm) between MCIs in contrast of control group with other groups.

Area under the curve (ROC) for clinical measurements of distance (mm) between MCIs in contrasts of all pair wise groups was reported in table(4)& figure(5).Wide area (0.66) was recoded for laser group pair wise VEGF group ,with a high 95% Confidence Interval(LB 0.486-UB 0.847).

1.2 percentages of movement (P.M.)
Descriptive statistics for percentages of movement (P.M.) for each contrast's periods at different groups and Comparisons significant was recorded in table (5).High percentage recorded in **1w. & 3w.** and specifically to group VEGF **(261.76).**

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The results that shows in table (6) illustrates that most pairs comparisons of contrasts of periods of (P.M.) factor are accounted highly significant at P<0.01, except between (1w. & 2w. X 2w. &3w.) at P>0.05.

Figures (6,7) show a Photograph for Biopsies that show the difference in the distance that remained between MCIsafter 3 weeks duration of the experiment.

1.3 Radiographic evaluation
At the end of the experiment period (at the end of 3rd week) all the study groups were subjected to x-ray to evaluate the distance that remained between MCIs as show in figure(8).

It was notice that**,** the radiographical measurement results of the distance that remained between MCIs at the end of experiment was coincide with the results of the clinical measurement at the same period, with statistically no significant difference (P > 0.05) between the two measurements of each group, as show in table(7) and figure(9).

1.4 The Width of the Mandibular Suture (Mand.S)
The highest mean values of the Mand.S width at three points that measured through radiographs at the end of the experiment was in combination group, mean± SD was(0.492±0.04mm), and in laser(0.455±0.01mm), while-VEGF records a low value (0.242 ±0.02mm) and control is the least one (0.215±0.01mm) ,as show in figure(10).

Table (3.8)&figure (3.11) illustrate the Area(0.056) under the curve (ROC) for amount of width mandibular suture (mm) in contrast of control group with sensitivity (100) and specificity (94.4).

1.5 The Width of the Periodontal Ligament (PDL):
The mean± SD values of the width of PDL (means of three points) were shown as follow

Figure (3.12)illustrates Stem-Leaf Plots for Width of PDL of Right and Left mesial side among studied groups. The highest values was recorded by combination group ,M±SD for the mesial right side was(0.285±0.01mm) and for left side(0.263±0.02mm).

Figure (3.13) shows Stem-Leaf Plots for Width of PDL of Right and Left distal side among studied groups. The highest values was recorded by combination and laser groups ,M±SD for the mesial right side was(0.222±0.02mm) that equal for both groups ,while for the left side ,laser group records a high value (0.232±0.01mm),followed by combination (0.227±0.01mm).

Table (9)and figure(14) show Area under the curve (ROC) for Width of PDL of Right and Left Mesial Side and Distal Side in contrast of control group at different intervals.

For right mesial side the area was (0.11 6)with sensitivity (100) and specificity (61.1),and for the left mesial side the area was (0.199) with sensitivity (100) and specificity (50).

For rightdistal side the area was (0.287)with sensitivity (100) and specificity (44.4),and for the left distal side the area was (0.199) with sensitivity (100) and specificity (55.6).

Clinical Measurements of distance (mm) between MCIs

Table 1: Descriptive statistics of Clinical Measurements of distance (mm) between MCIs among studied groups at different intervals with comparisons significant

Marker	Groups	Mean	SD	SE	ANOVA test F-test	P-(*) Value
Week 1	Control	0.32	0.01	0.01	1290	0.000 HS
	Lazar	0.66	0.01	0.00		
	VEGF	0.34	0.02	0.01		
	Combination	0.79	0.01	0.01		
Week 2	Control	0.51	0.01	0.00	1111	0.000 HS
	Lazar	1.08	0.04	0.02		
	VEGF	0.78	0.01	0.01		
	Combination	1.22	0.01	0.00		
Week 3	Control	0.92	0.01	0.00	462	0.000 HS
	Lazar	1.78	0.03	0.01		
	VEGF	1.23	0.01	0.00		
	Combination	1.95	0.11	0.04		

(*) HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P>0.05

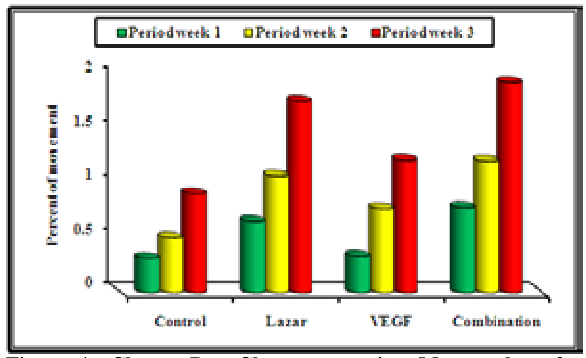

Figure 1: Cluster Bar Chart concerning Mean values for Clinical Measurements of distance (mm) between MCIs among studied groups at different intervals

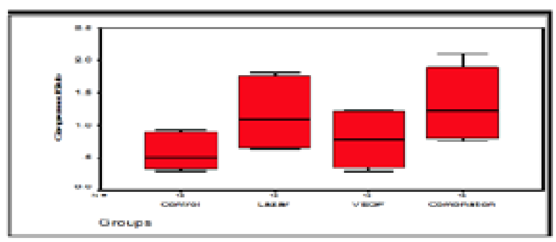

Figure 2: Stem-Leaf Plots for Clinical Measurements of distance (mm) between MCIs among studied groups at 3rd week.

Table 2: Area under the curve (ROC) for Clinical Measurements of distance (mm) between MCIs in contrast of control group at different periods

Area Under the Curve							
Test Result :working side- intervals							
Periods	Area	Std. Error	Asymptotic Sig.	95% C.I. L.B.	95% C.I. L.B.	Sen.	Spec.
1 week	0.056	0.047	0.001	-0.037	0.148	100	88.9
2 week	0.000	0.000	0.000	0.000	0.000	100	100
3 week	0.000	0.000	0.000	0.000	0.000	100	100

Cutoff Point (0.33) at 1 week; Cutoff Point (0.52) at 2 week; Cutoff Point (0.93) at 3 week

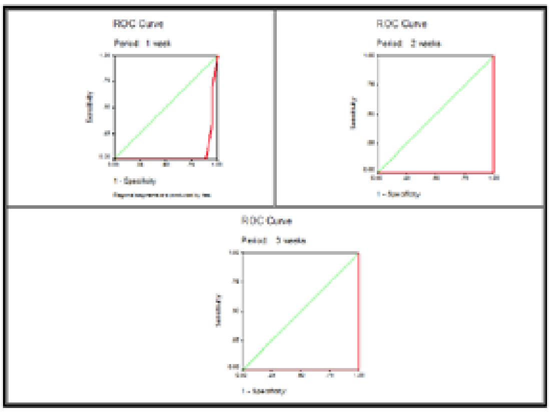

Figure 3: Receiver Operating Characteristic (ROC) curve for Clinical Measurements of distance (mm) between MCIs in contrast of control group at different intervals

Table 3: Area under the curve (ROC) for Clinical Measurements of distance (mm) between MCIs in contrast of control group at different sources of variation

Area Under the Curve					
Test Result: working side-groups					
Control with others groups	Area	Std. Error	Asymptotic Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
	0.191	0.055	0.000	0.084	0.299

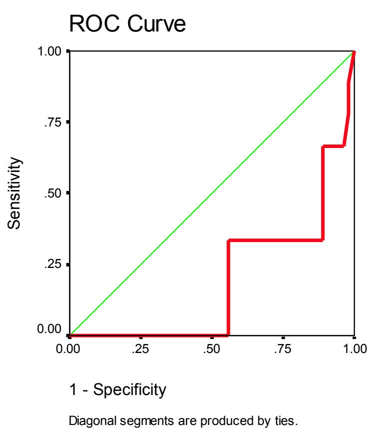

Figure 4: Receiver Operating Characteristic (ROC) curve Clinical Measurements of distance (mm) between MCIs in contrast of control group at different sources of variation

Table 4: Area under the curve (ROC) for Clinical Measurements of distance (mm) between MCIs in contrasts of all pair wise groups at different sources of variation

Area Under the Curve					
Test Result: working Side – study groups					
Contrasts	Area	Std. Error	Asymptotic Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
Control X **Lazar**	0.111	0.054	0.000	0.006	0.217
Control X **VEGF**	0.352	0.094	0.129	0.169	0.535
Control X **Comb.**	0.111	0.054	0.000	0.006	0.217
Lazar X **VEGF**	0.667	0.092	0.088	0.486	0.847
Lazar X **Comb.**	0.336	0.092	0.094	0.156	0.517
VEGF X **Comb.**	0.230	0.077	0.006	0.078	0.382

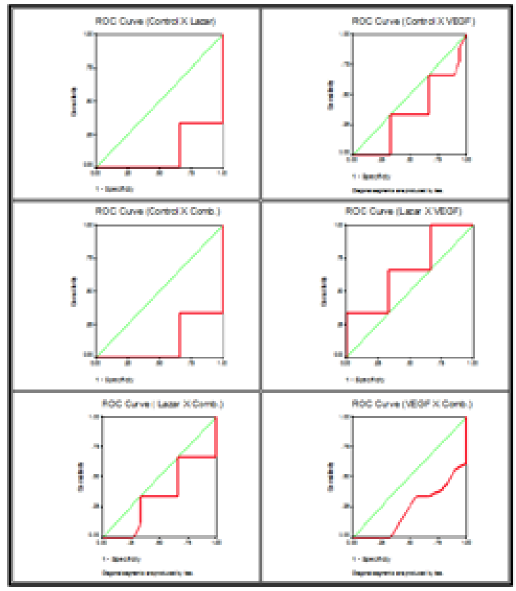

Figure 5: Receiver Operating Characteristic (ROC) curve for Clinical Measurements of distance (mm) between MCIs in contrasts of all pair wise groups at different sources of variation

Table (5): Descriptive statistics for percentages of movement (P.M.) for each contrast's periods at different groups and Comparisons significant

S.O.V.				ANOVA		ANOVA	
Periods	Groups	Mean of P.M.	Std. Dev.	Periods	P(*)-value	Groups	P(*)-value
1w. & 2w.	Control	59.38	35.33	F=23.90	0.001 HS	F=2.715	0.138 NS
	Lazar	63.64					
	VEGF	129.41					
	Combination	54.43					
2w. & 3w.	Control	80.39	10.2484				
	Lazar	64.81					
	VEGF	57.69					
	Combination	59.84					
1w. & 3w.	Control	187.5	49.74				
	Lazar	169.7					
	VEGF	261.76					
	Combination	146.84					
R Squared = 0.903 (Adjusted R Squared = 0.822							

(*) HS: Sig. at P<0.05; NS: Non Sig. at P>0.05

Table (6): Multiple comparisons by (LSD) among all pairs of contrast's periods for (P.M.)parameter

Parameter	Statistical tests	periods	periods	Mean Diff.	Sig.	C.S. (*)
Contrasts	LSD	1w. & 2w.	2w. & 3w.	11.03	0.604	NS
			1w. & 3w.	-114.74	0.001	HS
		2w. & 3w.	1w. & 3w.	-125.77	0.001	HS

(*) HS: Highly Sig. at P<0.01; NS: Non Sig. at P>0.05

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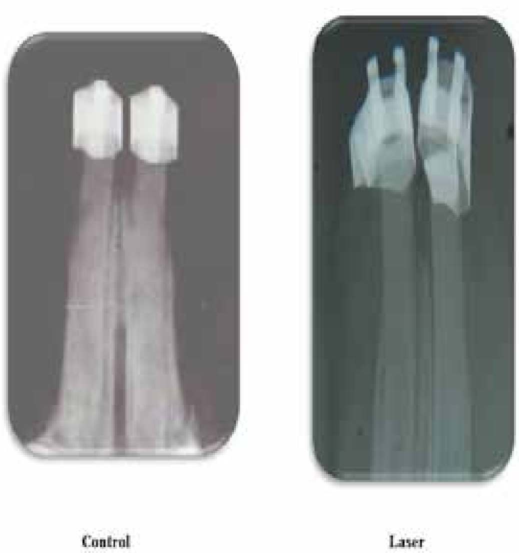
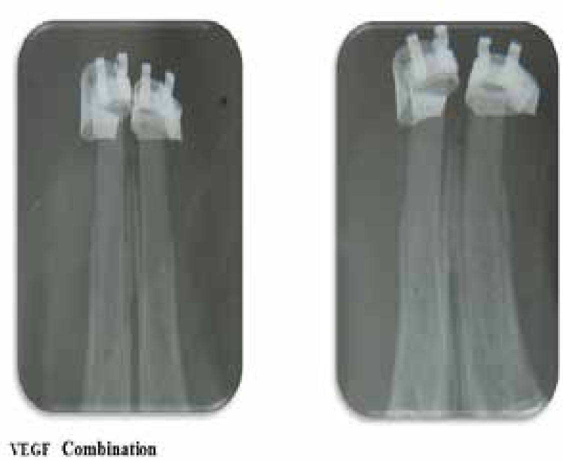
Figure(6)Photo for Biopsies shows the difference in the distance that remained between MCIsafter 3 weeks duration of experiment.

Figure(7) Photo for Biopsies shows the difference in the distance that remained between MCIsafter 3 weeks duration of experiment and after removing of orthodontic appliance.





Figure(8) Radiographical images for the study groups show the difference in the distance that remained between MCIs .

Table (7): Descriptive statistics of Clinical Measurements of distance (mm) between MCIs among studied groups at different intervals with comparisons significant

Marker	Groups	Mean	SD	SE	Student test t-value	Student test P-(*) Value
Control	Radiographic	0.917	0.01	0.00	-0.319	0.756 NS
	Clinical	0.918	0.01	0.00		
Lazar	Radiographic	1.768	0.03	0.01	-0.592	0.567 NS
	Clinical	1.778	0.03	0.01		
VEGF	Radiographic	1.207	0.01	0.00	-4.568	0.551 NS
	Clinical	1.225	0.01	0.00		
Combination	Radiographic	1.933	0.10	0.04	-0.221	0.830 NS
	Clinical	1.947	0.11	0.04		

(*) HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P>0.05

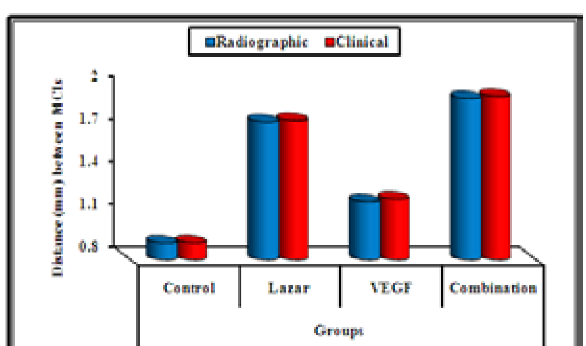


Figure (9): Cluster Bar Chart concerning Mean values for Clinical Measurements of distance (mm) between MCIs among studied groups at the end of third weeks

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Amount of width of mandibular suture (mm)

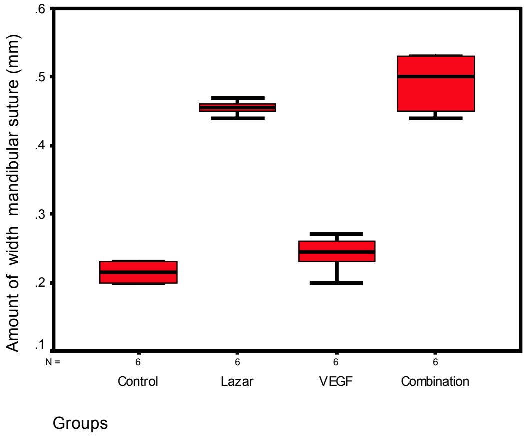

Figure (10): Stem-Leaf Plots for Amount of width mandibular suture (mm) among studied groups

Table (8): Area under the curve (ROC) for Amount of width mandibular suture (mm) in contrast of control group

Area Under the Curve							
Test Result: Amount of width mandibular suture (mm)							
Control with others groups	Area	Std. Error	As-ymp-totic Sig.	95% C.I.		Sen.	Spec.
				L.B.	L.B.		
	0.056	0.049	0.001	-0.040	0.151	100	94.4

<u>Cutoff Point (0.23)</u>

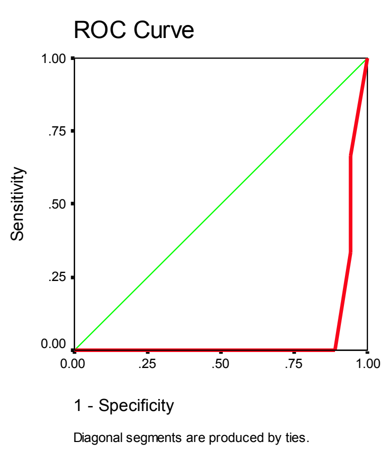

Figure (11): Receiver Operating Characteristic (ROC) curve for Amount of width mandibular suture (mm) in contrast of control group

Width of PDL of Right and Left Mesial & Distal Side

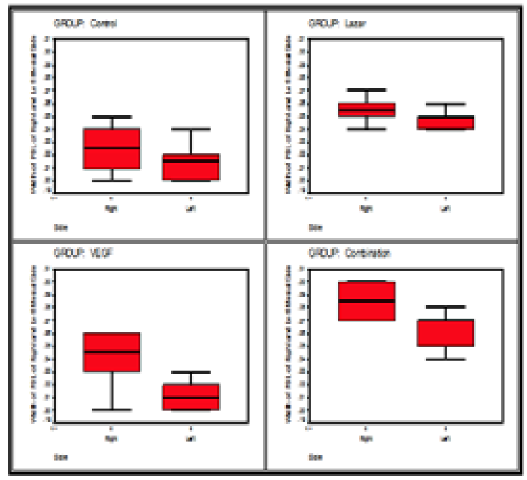

Figure 12: Stem-Leaf Plots for Width of PDL of Right and Left Mesial Side among studied groups

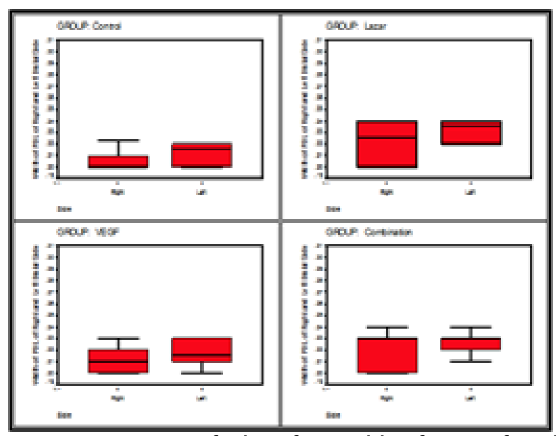

Figure 13: Stem-Leaf Plots for Width of PDL of Right and Left Side and Distal among studied groups

Discussion

It has been proved that the rate of OTM varies from person to another. However, clinical experiments combined with scientific evidence points an average rate of OTM of 1 mm per month **[12,56].**

As an alternative to surgically derived regional accelerations of OTM **[14,57],**several studies have attempted to expedite orthodontic treatment by increasing the velocity of OTM via pharmacological and electromagnetic modulations of the biological processes involved in bonemetabolism.

There have been several publications describing a positive effect on bone metabolism and OTM with the delivery of vitamin D **[89],**prostaglandin E 1 and 2 **[90,91],**osteocalcin**(92),**parathyroid hormone**[93],**long-term or high dose corticosteroids **[93], 1992),**thyroxin**[94],**pulsed electromagnetic fields **[95],**low intensity ultrasound**[96]**and low level laser therapy (LLLT)**[51,71.72,73,75].**Although successful, the major drawback to most of these treatment interventions is the necessity for systemic delivery and the ensuing systemic side effects of pharmacological agents. Alternatively, local delivery of the pharmacological agent requires repeated painful injections while delivery of phototherapy using LLLT necessitates demanding scheduling challenges with the need for repeated and frequent treatment.Greatest appeals of LLLT use to increase tooth movement is its avoidance of many of these risks and disadvantages associated with more invasive techniques. Clinical studies show that there are different Phases in tooth movement. The application of force during orthodontic tooth movement results in bone resorption by osteoclastsand deposition by osteoblasts on the pressure and tension sides of the periodontal ligament.

Recent studies in mice demonstrate that preosteoclasts, and not monocytes, may be recruited to the periodontal ligament during orthodontictooth movement, and these cells may be targeted for acceleration of tooth movement. For the present study the

descriptive statistics for percentages of movement (P.M.) for each contrast's periods at different groups and Comparisons significant was recorded in table (5).High percentage recorded in 1w. & 3w.and specifically to group VEGF (261.76).The energy density is directlyproportional with the exposure time, depending on the equation (Energy Density = Power Density X Exposure Time) Energy Density is a measure indicating the amount of energy received by a given tissue. It is calculated by dividing the energy output, measured in Joules, by the radius, or size, of the tissue receiving the laser application in centimeters² (cm^2). This parameter is reported as J/cm^2. If a patient received 1 J application dose through the stationary placement of a diode fiber tip with the diameter of 1 cm, he/she would receive 1.27 J/cm^2.Power density can be used to distinguish between low and high power lasers. , the absorption coefficient depends on the specific chromphore and wavelength of incident laser beam the meaning of that is photoreactions occur when a photon from light excites an absorbing molecule, result in photoreceptors or photoacceptors.**[135 40]**

This Photon absorption increases the energy state of theelectrons of that molecule. If the increased energy is notreemitted from the molecule as a photon of a longerwavelength or lost as heat, researchers propose themolecule undergo a chemical or morphogenic change which signals or allows for the initiation of a biochemicalevent.**[135]**

While it is not entirely clear which cellularmolecules absorb light and have regulatory control, many studies have implicated components within themitochondria.**[144,146,23]**

Resultingin unique characteristics of laser-tissueinteractions and biological effects that is why it hasbeen reported that multiple irradiation wouldbe more effective for acceleration of cellularproliferation and bone formation with ideal wave length.

Low-level laser therapy (LLLT)

Photobiomodulation or low-level laser therapy (LLLT) is one of the most promising approaches today. Laser has a biostimulatory effect on bone regeneration, which has been shown in the midpalatal suture during rapid palatal expansion [5], and also stimulates bone regeneration after bone fractures and extraction site .It has been found that laser light stimulates the proliferation of osteoclast, osteoblast, and fibroblasts, and thereby affects bone remodeling and accelerates tooth movement. The mechanism involved in the acceleration of tooth movement is by the production of ATP and activation of cytochrome C, as shown in **[6]**that low-energy laser irradiation enhanced the velocity of tooth movement via RANK/RANKL and the macrophage colony-stimulating factor and its receptor expression.

Animal experiments have shown that low-level laser can accelerate tooth movement. Furthermore, clinical trial attempts were made in which different intensities of laser were used and different results were obtained **[5].**Low-level laser therapy can be a very useful technique for acceleration of tooth movement since it increases bone remodeling without side effects to the periodontium. Laser wavelength of 809 nm and output power 25 mW have indicated significant stimulation of bone metabolism, rapid ossification **[7],**and also acceleration of tooth movement to (1.5) fold in rat experiments. Lately in a clinical trial study, the laser wavelength they have used in a continuous wave mode at 800 nm, with an output of 25 mW, and exposure of 10 s was found to accelerate tooth movement at 1.3-fold higher than the control **[8].**In another study done by Kau **[9]**on 90 subjects (73 test subjects and 17 controls), there was (1.12)mm change per week in the test subjects versus (0.49) mm in the control group. Having said this, there are a lot of contradictory results related to the LLLT. Therefore, more experiments are needed to differentiate the optimum energy, wavelength, and the optimum duration for usage.The present study shows2w. & 3w..high significant about

-125.77 0.001 HS $p<0.01$.Whill it -114.7 0.604 NS1w. & 3w. non-significant $p>0.05$

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