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Radiological (MRI) and Biochemical effects of Low Level LASER therapy in chronic Osteo arthritis in Al-Kharj, Saudi Arabia: A Randomized Control Trial

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ABSTRACT

Osteoarthritis is one of the degenerative diseases and Low level laser therapy (LLLT) has been prescribed as non-operative treatment in physiotherapy. But the available evidences of finding the radiological and biochemical effectiveness of LLLT are very few. So, the purpose of this study is to find the radiological and biochemical effect of Low level laser therapy (LLLT) in the treatment of Osteoarthritis. 34 subjects who fulfilled the inclusion and exclusion criteria were divided into two groups (Active Laser group – ALG & Placebo Laser group - PLG) with randomized sampling method. ALG was treated with active laser head, whereas PLG treated same like ALG but without emission of energy. Both groups were applied with kinesio tape for 4 weeks. The frequency of the treatment was three times per week for 4 weeks in both groups. Subjects were assessed at baseline, 4^{th} and 8^{th} week. Contact area (mm^2) – medial & lateral and cartilage thickness (percentage) - medial & lateral was measured by Magnetic resonance image (MRI) and CTX-II (µmg/mmol) was measured by urine analysis. A statistically significant ($p \leq 0.05$) difference between both groups were noted at the period of 8 week for contact area (lateral) and CTX-II and insignificant ($p \geq 0.05$) difference in contact area (medial) and cartilage thickness (medial & lateral) were noted. In conclusion, the low level laser therapy is helpful in modifying the biochemical components and leads to make changes in the cartilage which subsequently improve the quality of life of OA patients.

Keywords: Low level laser therapy, Magnetic resonance image, Contact area, Cartilage thickness, CTX-II, Osteoarthritis.

INTRODUCTION

Osteoarthritis is one of the degenerating diseases with characteristic features of pain, joint inflammation, impaired muscular stability and functional incapacity. It also damages the articular cartilage and sub chondral bone and leads to joint space narrowing (JSN). The life time risk of developing OA of the knee as per the Centre for Disease Control is estimated to be 46% and its prevalence is increased according to aging population [1,2]. Impaired quality of life and significant physical disability account for its morbidity and increased mortality risks [3].

Bio chemical analysis confirms that inflammation of the synovial membrane plays a key role in the patho physiology of OA [4]. Synovial cells are stimulated by this exaggerated inflammation which releases chemical substances such as cytokines, and chemokines. The cellular activities such as collagen type II C-telopeptide (CTX-II) and functions of articular tissues are affected by this whole chemical substances which may lead to joint degradation and injury which leads to joint space narrowing [5,6].

Reducing symptoms, minimizing disability and limiting the progression of biochemical and structural changes are the main goals in the treatment of OA [7]. According to European League against Rheumatism (EULAR) most of the acute and chronic musculoskeletal conditions can be treated by Low Level Laser Therapy (LLLT) [1].

Various animal studies have proven the positive effect of laser on cartilage formation chemical changes such as production of superoxide dismutase, stress proteins and proliferation of chondrocytes. It also decrease the arthritic degenerating process and increasing the regeneration of articular cartilage and stress proteins and helps us repair of cartilaginous erosion by increasing the number of chondrocyte production and thickness of articular cartilage [8,9]. Evidences suggest that effective treatment procedures are developed in treating OA. Over the past few decades LLLT has been applied with the wave length of (600 – 900 nm) red to infra red to *in vitro* cellular studies and *in vivo* animal studies [10,11]. However the clinical efficacy of LLLT in radiological and biochemical perspective for the treatment of OA in human population is still debatable and needs to be investigated. Hence the radiological (MRI) and biochemical analysis such as CTX-II were used to find the effect in LLLT [12,13,14].

MATERIALS AND METHODS

Participants: Participants were recruited from the University hospital, Prince Sattam Bin Abdul Aziz University, Al-Kharj, Saudi Arabia. To be included in the study, participants have knee osteoarthritis in one knee, pain above 40 cm in VAS scale, osteoarthritis levels 2–4 according to Kellgren–Lawrence grade,[15] aged between 45 and 65 years, both genders, have knee pain and functional disability for at least six months.

Participants were excluded if they had cancer, diabetes, osteoarthritis hip, knee joint arthroplasty, joint diseases, deformities, ankylosis, intense synovitis, or were receiving anti analgesics, depressants, inflammatory medications or using medication affecting bone and cartilage and also the usual contraindications for laser therapy. Study was approved by University research human ethics committee according to the Helsinki Declaration II. All subjects provided written informed consent to participate in the study.

Forty eight subjects were selected for the examinations, but only 34 (28 men and 6 women) fulfilled the criteria, 17 of whom were in the active LLLT group and 17 in the placebo LLLT group. Contact area in mm^2 (medial & lateral) and cartilage thickness in percentage (medial & lateral) was measured by Magnetic resonance image (MRI) and CTX-II (µmg/mmol) was measured by urine analysis technique. Parameters were measured at baseline, 4 weeks and 8 weeks of treatment.

The demographic data such as age, height, weight, BMI and OA grade of the patients were noted. A detailed case history and physical status were recorded. Various examinations were conducted prior to treatment in order to rule out other diseases and to attain patient homogeneity.

Randomization: 34 subjects were randomized into one of two groups (Active and Placebo) by an investigator not involved in assessment, diagnosis or treatment. Randomization was performed by using sealed randomly filled envelopes. Subjects and the physiotherapist responsible for the evaluation were unaware of randomization results.

Assessment: All subjects were evaluated by the same blinded physiotherapist at three different measurement intervals: baseline (T1), after four weeks (T2) and after 8 weeks (T3) after LLLT. The physiotherapist was trained to evaluate the same way all patients at all times.

MRI analysis: The image was taken with a 3T scanner (General electric, WI), with 8 channel phased array TR Knee coil. Subjects were placed supine on the top of the loading apparatus, with 20^0 of knee flexion and 10^0 of foot external rotation. The images were acquired with no load applied on the joint and multi slice T2 weighted images were taken. Contact area and cartilage thickness were measured by semi-automated spline based software program [16].

Biochemical analysis: Fasting morning urine samples were collected from all the subjects to analyze the urinary levels of collagen type II C-telopeptide fragments (CTX-II). It was measured by the Urine cartilaps (CTX-II) EIA (Immunodiagnostic systems holdings, NE35 9PD, United Kingdom).This assay uses a monoclonal antibody mAbF46 specific for a six amino- acid epitope (EKGPDP) derived from the collagen type II C-telopeptide. CTX-II was assessed by a standard colorimetric method. For the statistical analysis, the CTX-II values were logarithmically transformed to obtain normality. The urine samples were stored at 220°C until measurement. [17]

Intervention: Subjects in the active laser group received LLLT while the placebo group received placebo therapy three times a week for four weeks following initial assessment. Both the groups' participants have been exercised and applied with kinesio tape (KT) three times a week for 4 weeks which could support the joints and muscles without restricting range of motion with added benefit of lymphatic drainage.

Laser Irradiation: Treatments were administered with an FISIOLASER SCAN - Ga As diode laser with parameters of power 25mW, continuous wave and wavelength 905 nm. The dose delivered was 6 J per point for 8 points for a total dose of 48 J/cm^2. The size of the point in the focus of the laser light was nearly 1 cm^2 and the power density was approximately 25mW. The laser was irradiated on the medial and lateral knee joint line and epicondyle of tibia and femur and posteriorly tendon of the biceps femoris muscle and semitendinosus muscle. In the placebo group, procedures were identical but without emission of energy [18].

Exercises: All patients followed the same exercise training programme for 45 minutes. 10 minutes warming up with ergometer bike followed by 30 minutes of strengthening exercise and 5 minutes of stretching of hamstrings, quadriceps, adductors, and gastrocmenius.

Statistical analysis: Inter group analysis of the data were analysed by independent t test for all the variables. For intra group analysis, evaluation times were compared by repeated-measures ANOVA. Analyses were conducted using the Statistical Package for Social Sciences (SPSS version 17; SPSS Inc., Chicago, IL, USA). An alpha level of 0.05 was set for all data analysis.

RESULTS

Forty eight subjects enrolled to take part in the study and 34 subjects were included in the study according to selection criteria. They were randomly allocated in two different groups active laser group (n=17) and placebo laser group (n=17).

Of the 34 subjects, all completed the study with follow-up evaluation. A summary of the demographics and baseline values for subjects that completed the study is provided in **Table -1.** The table includes the number of subjects in each treatment group, mean baseline values of age, height, weight, BMI and OA grade which shows the homogeneity (p >0.05) of groups.

A comparison was analyzed for all the parameters for the patients completing the study. Mean, SD, and *t*-test *p*-values for Contact area (medial & lateral), Cartilage thickness (medial & lateral) and CTX-II of active and placebo group's baseline and after 8 week sessions are presented in **Table-2.**

The analysis of the mean contact area in mm^2 (medial) scores of the two groups (active laser group vs placebo laser group) at the base line (122.56 ± 63.51 vs. 121.81 ± 62.59, p >0.05) and 8 weeks after treatment (76.85 ± 62.21 vs. 110.85 ± 61.89, p>0.05) is demonstrated in **Fig-1.** The analysis of the mean contact area in mm^2 (lateral) scores of the two groups (active laser group vs placebo laser group) at the base line (89.64 ± 33.43vs. 87.98 ± 32.71, p >0.05) and 8 weeks after treatment (35.87 ± 32.76 vs. 75.87 ± 32.56, p <0.05) is demonstrated in **Fig-1.**

The analysis of the mean cartilage thickness in percentage (medial) scores of the two groups (active laser group vs placebo laser group) at the base line (-7.86 ± 9.8 vs. -7.56 ± 8.9, p >0.05) and 8 weeks after treatment (-5.21 ± 10.91 vs. -6.96 ± 10.23, p >0.05) is demonstrated in **Fig-2.** The analysis of the mean cartilage thickness in percentage (lateral) scores of the two groups (active laser group vs placebo laser group) at the base line (-1.49 ± 9.22 vs -1.52 ± 7.8, p >0.05) and 8 weeks after treatment (-2.34 ± 10.22 vs. -1.74 ± 9.45, p <0.05) is demonstrated in **Fig-2.**

The analysis of the mean CTX-II values of the two groups (active laser group vs placebo laser group) at the base line (0.23 ± 0.09 vs. 0.24 ± 0.06, p >0.05) and 8 weeks after treatment (0.20 ± 0.01 vs. 0.23 ± 0.02, p <0.05) is demonstrated in **Fig-3.**

A set of (ANOVA) tests for independent samples and repeated measures were used to assess the efficacy of active and placebo LLLT treatment for subjects with completed data at baseline, at 4 weeks and 8 weeks after treatment is presented in **Table-3.**

The repeated measures assessed longitudinally the treatment sessions through 8 weeks shows that active laser group has the significant difference (p = 0.000) in contact area (lateral) and CTX-II insignificant difference in other parameters such as contact area (medial), cartilage thickness (medial & lateral) but insignificant difference in all parameters (p >0.05) in placebo laser group.

DISCUSSION

Osteo arthritis is one of the degenerating disease affecting parts of the joint like sub chondral bone, synovium and joint capsule. It is a simple wear and tear phenomenon but has an active phase and reparative process [19]. The active degeneration phase involves release of several matrix metallo protienases (MMP) leading to further destruction of articular cartilage. The real cause of OA is unknown. This study evaluates the radiological and biochemical effects of low level laser therapy (LLLT) on subjects with knee OA. Compared to placebo groups significant results were obtained in cartilage thickness and biochemical activity.

As per the world association of laser therapy (WALT) dose of 3J on specific points of knee joint primarily relieved pain, in the laser group, [20]. Similar results were obtained by Bjordal et al on knee OA subjects [21]. Meta analysis on effect of LLLT on pain relief by Brosseauet et al states, significantly increased levels of neurotransmitter levels like serotonin may be the reason for endogenous pain modulation [22].

Higher contact area and deformation MRI values in subject with OA are likely related to the reduced compressive stiffness of the cartilage due to the damaged collagen network [23]. In our study, histo morphometry showed that the laser, especially 905 nm, stimulated an increase of collagen III fibers. These collagen fibers were more prevalent in all irradiated groups, contributing to the repair of damaged cartilage. Several studies, clinical and experimental, have shown the effects of laser photo bio stimulation in increased cell proliferation and repair cartilage tissue [24,25].

Animal studies show the modulating positive effectiveness of LLLT in treating inflammatory process and cartilage regeneration in OA [26] but some studies prove otherwise [27]. Morphological studies indicate the relation of biochemical components in the cartilage like ECM, hydrated GAGs and collagen network to susceptibility to injury in OA [28]. Also, degenerative and regenerative properties of cartilage depend upon the type of collagen (collagen type II C-telopeptide) and its proteins. [29].

The specific epitope six amino acid sequence (EKGPDP; CT2), is observed exclusively in collagen type II C-terminal telopeptide. OA subjects show 1.35 fold increases in Cartilap (collagen type II C-telopeptide) as compared to normal [30].

Laser radiation stimulates the blood and bone marrow cells to act directly on the cartilage defect leading to activation of chondrocytes and growth of fibrous cartilage which facilitates repair. It stimulates the specialized phenotype cells through synovial fluid to promote mature chondrocytes and increases the proliferation of heterogenic cells in the cartilage regeneration and takes the control of ECM. Laser application provides natural environment for chondrocytes to restore and repair which totally depends upon the movement velocity of matrix fibrillar components. It allows the diffusion of ECM and structural modification in cartilage and promotes regeneration which was proven in *vivo* experiment on reshaping of porcine ears [31].

The mechanical effect of laser application on water content such as gas bubbles oscillation and laser heating effect on chondrocytes may fasten the repair process [32] by the formation of new collagen and PGs in the cartilage [33]
Finally the results of our study provide the evidence of LLLT dependent reduction of pain and the therapy's ability to inhibit the proliferation of collagen type II C-telopeptide makes it an ideal treatment for subjects with late stages of OA. The study also helps to understand and comprehend the radiological and biochemical changes of LLLT in OA and also make the path way for the future analysis.

Table-1

	Active Laser Group n = 17	**Placebo Laser Group n = 17**	**p - value**
Age(Years)	58 ± 6	60 ± 8	0.3767
Height (cm)	168 ± 6	165 ± 8	0.1877
Weight (kg)	72 ± 12	68 ± 10	0.2593
BMI (Kg/m^2)	26.9 ± 4.8	28.3 ± 3.5	0.2986
OA grade	3.1± 0.71	3.2 ± 0.68	0.6520

Table-2

		Base line Value (T1)			After 8 weeks (T3)		
		Active Laser Group	**Placebo Laser Group**	**p-value**	**Active Laser Group**	**Placebo Laser Group**	**p-value**
Contact Area (mm^2)	Medial	122.56 ± 63.51	121.81 ± 62.59	0.9726	76.85 ± 62.21	110.85 ± 61.89	0.1200
	Lateral	89.64 ± 33.43	87.98 ± 32.71	0.8846	35.87 ± 32.76	75.87 ± 32.56	0.0011
Cartilage Thickness (Percentage)	Medial	-7.86 ± 9.8	-7.56 ± 8.9	0.9261	-5.21 ± 10.91	-6.96 ± 10.23	0.6328
	Lateral	-1.49 ± 9.22	-1.52 ± 7.8	0.9919	-2.34 ± 10.22	-1.74 ± 9.45	0.8601
CTX-II µg/mmol)		0.23 ± 0.09	0.24 ± 0.06	0.6816	0.20 ± 0.01	0.23 ± 0.02	0.0001

CTX-II- Collagen-II telopeptide,

Table-3

		Active Laser Group (n=17)			p- value	Placebo Laser Group (n=17)			p- value
		T1	**T2**	**T3**		**T1**	**T2**	**T3**	
Contact Area (mm^2)	Medial	122.56 ± 63.51	98.21 ± 61.46	76.85 ± 62.21	0.113	121.81 ± 62.59	115.67 ± 60.87	110.85 ± 61.89	0.875
	Lateral	89.64 ± 33.43	50.34 ± 32.87	35.87 ± 32.76	0.000	87.98 ± 32.71	80.01 ± 33.21	75.87 ± 32.56	0.554
Cartilage Thickness (Percentage)	Medial	-7.86 ± 9.8	-6.86 ± 9.5	-5.21 ± 10.91	0.743	-7.56 ± 8.9	-7.01 ± 9.54	-6.96 ± 10.23	0.980
	Lateral	-1.49 ± 9.22	- 2.01 ± 9.58	-2.36 ± 9.76	0.965	-1.52 ± 7.8	-1.64 ± 8.6	-1.74 ± 9.45	0.997
CTX-II (µg/mmol)		0.23 ± 0.01	0.21 ± 0.01	0.20 ± 0.01	0.000	0.24 ± 0.06	0.23 ± 0.06	0.23 ± 0.02	0.770

CTX-II- Collagen-II telopeptide, (T1-base line, T2-after 4 weeks, T3-after 8 weeks)

Fig-1: Pre (base line) and post (after 8 weeks) values of contact area (mm^2) of Active and Placebo Laser groups

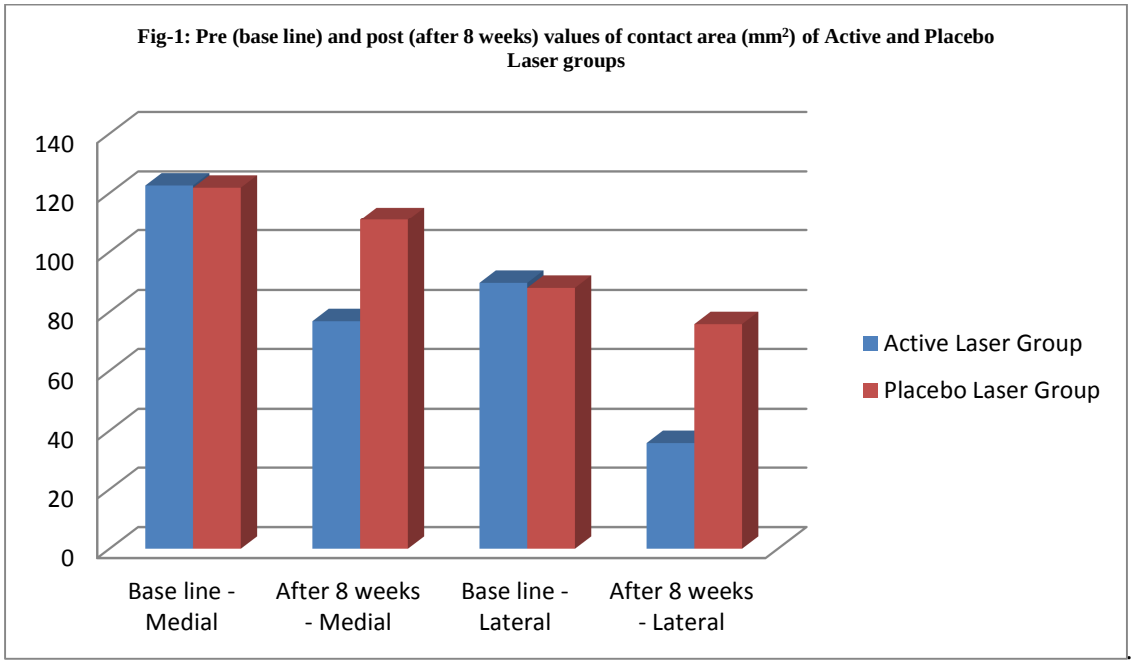


Fig-2: Pre (base line) and post (after 8 weeks) values of cartilage thickness (percentage) of Active and Placebo Laser groups

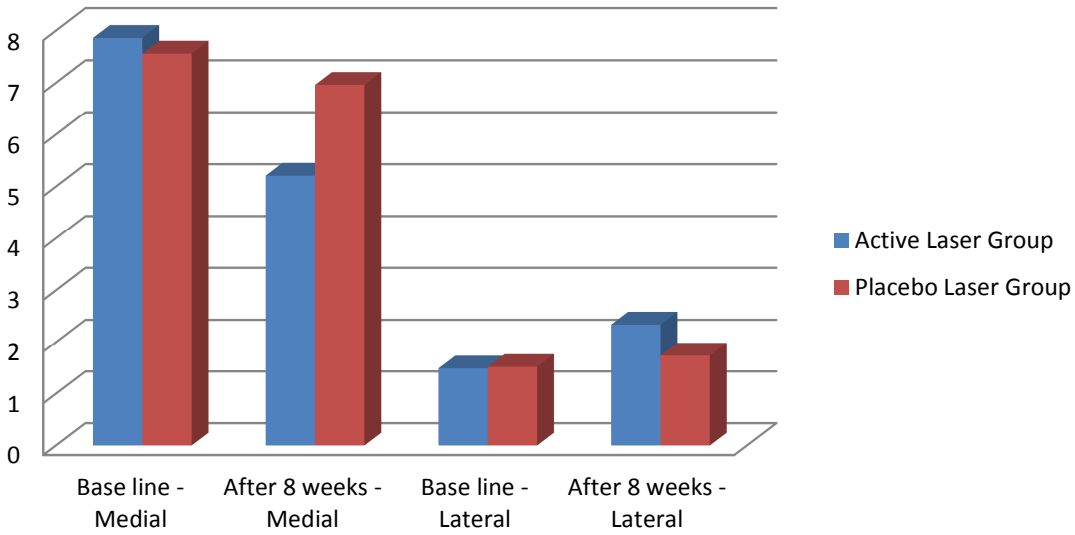
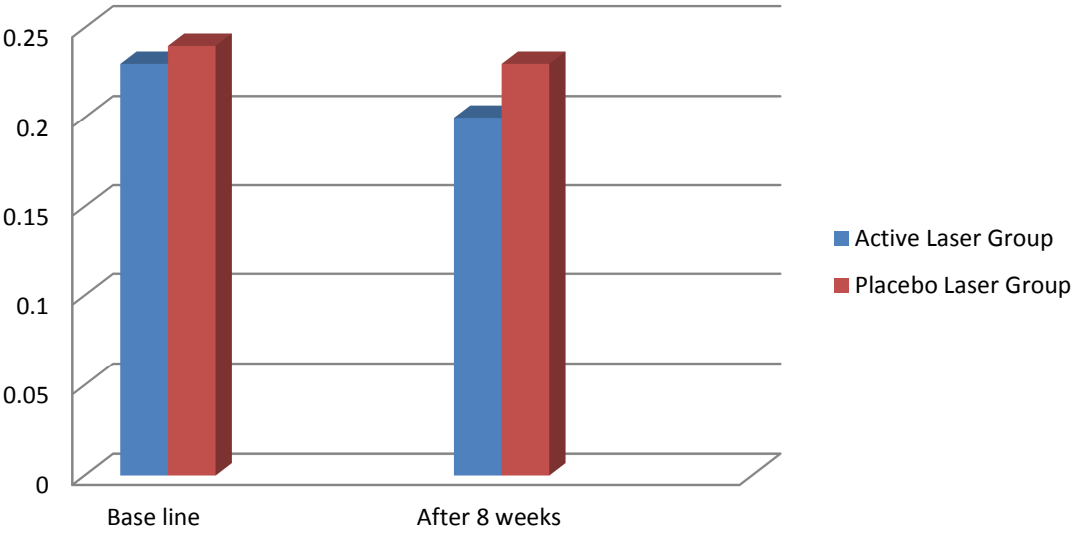


Fig-3: Pre (base line) and post (after 8 weeks) values of CTX-II (µg/mmol) of Active and Placebo Laser groups



CONCLUSION

In conclusion, the low level laser therapy is helpful in modifying the biochemical components and leads to make changes in the cartilage level which subsequently improve the quality of life of OA patients.

The major study limitations were the small number of patients and the absence of a control group, which would allow us to assess the natural course of the disease and absence of follow up.

Future studies should increase the number of patients, include a control group, and add a group which receives only exercise from the very beginning and a long-term follow-up assessment. Ultimately, it might be feasible to include Low level laser therapy in the management protocol of patients with knee OA.

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