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The Effect of Low Level Laser Therapy on Early Onset Rheumatoid Arthritis Patients

Muhamed J. A. Al-Saraj[1] *MSc*, **Zeki Y. Al-Ethary**[2] *MSc*, **Zaid I. Al-Attar**[3] *PhD*

[1]Head of Rheumatology Clinic, Al-Kindy Teaching Hospital, Baghdad, Iraq, [2]Holter Unit, Al-Imamein Al-Kadhimein Medical City, Baghdad, Iraq, [3]Dept. of Pharmacology, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq

Abstract

Background Rheumatoid arthritis (RA) is a systemic chronic, inflammatory disease that may affect many tissues and organs.

Objective To investigate effectiveness and safety of Low-level-laser-therapy (LLLT) in management of early onset RA compared to symptomatic non-steroidal anti-inflammatory drugs (NSAIDS) therapy.

Methods A convenient selection 3 arms single blinded trial conducted in Al-Saraj Center for Rheumatoid Diseases in Baghdad during period between January-May 2017. Thirty-four patients with RA onset below one year were recruited. Disease activity score (DAS28) formula with American College of Rheumatology criteria (ACR20), erythrocyte sedimentation rate (ESR), visual analogue scale (VAS), complete blood count (CBC), C-reactive protein (CRP), rheumatoid factor (RF) were measured. Patients were divided into three groups: group 1 (n=12) received LLLT, group 2 (n=12) received placebo laser and naproxen and group 3 (n=10) received only naproxen. Primary outcomes measured were disease activity using DAS28 score, clinical improvement using ACR20 and pain assessment using VAS. Secondary outcomes measured were remission ACR50 and 70 and inflammatory indicators.

Results LLLT group has shown significant decrease of DAS28 (P=0.02), morning stiffness duration (p=0.05), number of tender joints (p=0.03), number of swelling joints (p=0.04), and VAS (p=0.01) compared to baseline whereas placebo laser group with naproxen and naproxen only group showed only significant reduction in duration of morning stiffness(P=0.04) and (p=0.048) respectively. There was marginal lowering of ESR (P=0.06) in LLLT group but no changes in CRP, RF. There were no reported side effects of LLLT use.

Conclusion Laser therapy is better than NSAIDS in controlling RA symptoms with no associated side effects. Therefore, it is recommended as first-line therapy in early onset RA.

Keywords laser, Low level laser therapy, rheumatoid arthritis, NSAIDS, ESR, Nerve root

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List of abbreviations: ACPAs = Anti-citrullinated protein antibodies, ACR = American College of Rheumatology criteria, AlGaAs = Gallium aluminum arsenide diode laser, CBC = Complete blood count, CRP = C-reactive protein, DAS28 = Disease activity score, DMARDs = Disease-modifying antirheumatic drugs, ESR = Erythrocyte sedimentation rate, LLLT = Low-level-laser-therapy, M±SD = mean±standard deviation, mW = milli watt, NIPH = National Institute of Public Health, RA = Rheumatoid arthritis, RF = Rheumatoid factor, SJN = Swollen joint number, TJN = Tender joint number, VAS = Visual analogue scale

Introduction

Rheumatoid arthritis (RA) is a systemic chronic, inflammatory disease that may affect many tissues and organs, but primarily affects joints causing an inflammatory synovitis that frequently contributes to articular cartilage damage and joint ankyloses

[1-3]. RA may also cause systemic inflammation of the lungs, pericardium, and sclera, as well as nodular lesions, which are most prevalent in skin. While etiology of RA is not fully understood, autoimmunity plays a key role in its chronicity and progression [4,5]. Worldwide, approximately 1% of the population suffers at some point of their life from RA. Females are three times more affected than men with onset most prevalent between 40 and 50 years old, yet can influence any age. RA can be an impaired and debilitating disease as a result of severe progressive loss of control and mobility [6].

The primary diagnosis starts with history and physical examination in association with laboratory tests especially rheumatoid and anti-citrullinated protein antibodies (ACPAs) and X-rays [7]. Different therapeutic protocols are available. Physical exercise, brace, splint, and occupational therapy are used with non-pharmacological care. The goal of therapy is firstly to achieve pain relief, and secondly to avoid potential joint damage and the resultant impairment if the condition continues untreated. These two goals do not necessarily coincide: while pain killers do accomplish the first goal, the long-term outcomes are not affected [8]. Analgesia and anti-inflammatory medications, including steroids, are used to relieve the symptoms, while anti-rheumatic disease-modifying medicines (DMARDs) are also used to slow or interrupt the underlying immune response, produce long-lasting symptomatic remissions [9] and avoid long-term damage. DMARDs influence biological measures such as levels of erythrocyte sedimentation rate (ESR) and hemoglobin and autoantibody and reduce the risk of bone and cartilage harm. The new generation of biologics has recently expanded therapeutic choices [10].

Low-level light therapy (LLLT) also known as cold laser, low power laser, bio-stimulation, photo-biomodulation, is a medical technique in which the low-level laser is used to stimulate or inhibit the cellular function. LLLT precipitates a complex series of cellular-level physiological interactions that reduce acute inflammation, reduce pain and speed up tissue healing [11] and effectiveness in treating chronic and acute pain associated many inflammatory diseases has been reported [12]. The role of LLLT in RA has been investigated, however, results are contradicting [13-15]. This study aimed to investigate the effectiveness and safety of LLLT in the management of early onset RA in a sample of Iraqi patients, applying different ways to alleviate disease activity and improve pain including acupuncture points, trigger points, nerve supply and referring pain points.

Methods

Study design

This is a convenient randomized clinical trial conducted at Al-Saraj Center for Rheumatoid Diseases during the period between January-May 2017. The trial was registered at National Institute of Public Health (NIPH) Clinical Trials of Japan (rctportal.niph.go.jp), with a Unique ID number (UMIN000042632). The study protocol was approved by the Scientific and Ethical Committee in Al-Kindy College of Medicine, University of Baghdad.

Patients and groups

Thirty-four patients diagnosed with RA according to revised criteria for RA classification in 1987 [16] when they showed at least four of these seven criteria: 1) morning stiffness; 2) arthritis of three or more joint area; 3) arthritis of hand joints; 4) symmetrical arthritis; 5) rheumatoid nodules; 6) serum rheumatoid factor; 7) radiographic changes, given that these criteria have been present for at least 6 weeks and not exceeding one year. Patients with 2 clinical diagnoses were excluded. None of the participants had extra articular involvement such as rheumatoid nodules or Felty syndrome or skin or cardiovascular.

Fifteen (44.1%) of patients were classified as moderately active disease DAS28 (3.2-5.1) and 19 (55.9%) had severely active disease DAS28 (>5.1). Patients were conveniently randomized to three groups so that each group contain

approximately equal rate of disease severity as shown in Table 1; first, group1 (n=12) received LLLT, second, group 2 (n=12) received placebo laser and naproxen and the third, group 3 (n= 10 patients) who received only naproxen.

Table 1. Distribution of patients in three groups according to disease activity score DAS28

Activity DAS28	Group 1	Group 2	Group 3	Total
Moderate (3.2-5.1)	5 (14.7%)	5 (14.7%)	5 (14.7%)	15 (44.1%)
Severe (>5.1)	7 (20.6%)	7 (20.6%)	5 (14.7%)	19 (55.9%)
Total	12 (35.3%)	12 (35.3%)	10 (29.4%)	34 (100%)

Intervention

Patients in group 1 received 20 sessions of LLLT, in the form of 2 courses separated by 10 days free, each course contains 10 sessions of LLLT divided as 3 sessions per week. Each session included four steps: 1) Irradiate the point of pain, which the patient complains from the most for 15 min. 2) Irradiate the acupuncture points according to (HAND laser acupuncture treatment protocol) for 15 min [(17)]. 3) Irradiate the site that might be the origin of the referring pain to the figures and wrist according to anatomical map of trigger points for 15 min [(18)]. 4) Lastly irradiate the site of C7, C6 and C5 at the side of the pain for one minute each.

Two laser apparatuses were used for therapy in this study; Gallium aluminum arsenide diode laser (AlGaAs), 830 nm, maximum output power 300 mW used for the first 3 steps [(15)] and Helium-Neon Laser of wave length 632,8 nm, continuous emission, output power 7.3 mW applied in step four of a session [(19)].

Patients in group 2 received deactivated placebo laser courses (electrical transcutaneous simulator) with naproxen 1000 mg/day in two divided doses.

Patients in group 3 received naproxen 1000 mg/day in two divided doses.

Outcome's measurement

The main three outcomes measured were disease activity using DAS28 and clinical improvement using ACR20% and pain assessment using visual analogue scale (VAS). DAS28 formula which is a composite score derived from the assessment of 4 measures [(20)]: 1) count the number of swollen joints (out of the 28), 2) count the number of tender joints (out of the 28), 3) ESR and 4) patients' global assessment of health by a questionnaire. The final score is calculated by a special formula, a DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission [(20)].

Clinical improvement was further measured according to criteria of ACR20% (20) by assessing 2 parameters; 1) equal or more than 20% improvement in tender joint number (TJN); 2) equal or more than 20% improvement in swollen joint number (SJN). A positive ACR20% should have fulfill both above parameters in addition to ≥20% in three of the following five parameters: patient pain assessment, patient global assessment, physical global assessment, patient self-assessment disability and acute phase reactant ESR and C-reactive protein (CRP).

VAS is estimated using a scale between 0 and 10 cm, for which 0 represents no pain and 10 represents maximum pain (unbearable) using a questionnaire filled by the patient [(21)].

Secondary outcomes included ACR remission criteria measured by fulfilling five or more of the following criteria for at least 2 consecutive months: morning stiffness <15 min, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling, ESR <30 mm/hr in females and <20 mm/hr in males. Complete blood count (CBC), ESR, CRP, liver function test,

renal function test, rheumatoid factor (RF) and X ray for affected joint were obtained for each patient at baseline and after 10 weeks [20].

Statistical analysis

Statistical analysis was done using IBM SPSS version 20 (IBM, Armonk, NY, USA). The results were presented in mean± standard deviation or range as necessary. Comparison between means was calculated using Student-t test and ANOVA test with post-hoc test as indicates implementing $p<0.05$ as a significance level.

Results

The mean age of participants was 49.6 ranged between 28 and 69 years, most of them were women (73.5%) as shown in table 2 and figure 1, female:male ratio was 2.77:1.

Table 2. Age and gender distribution of study groups

Variable		No.	%
Age categories	20-40	7	20.6
	41-60	22	64.6
	>60	5	14.7
Gender	Male	9	26.5
	Female	25	73.5
Total		34	100

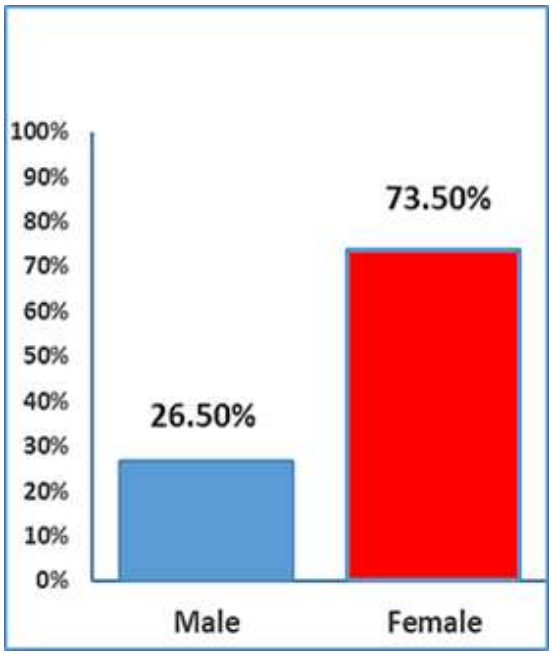

Figure 1. Distribution of patients according to gender

At base line assessment, DAS28, ESR, morning stiffness, TJN, SJN and VAS were not significantly different between study groups. RF was positive in only 56% of the patients shown in figure 2.

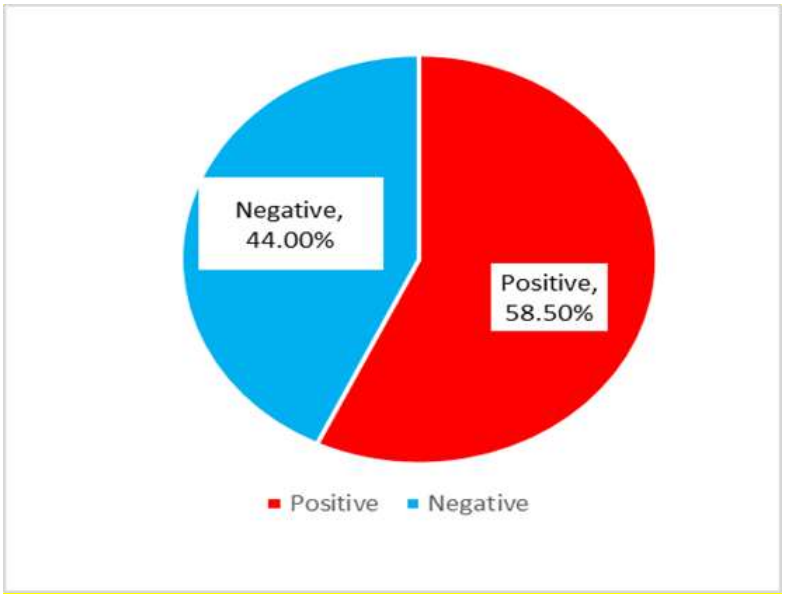

Figure 2. Distribution of patients according to presence of rheumatoid factor

Patients in group 1 showed a significant reduction of DAS28 score after completing the LLLT courses (P=0.02) as well as all the clinical parameters, morning stiffness (P=0.05), number of tender joints (P=0.03), number of swelling joints (SJN) (P=0.04) and VAS (P=0.01) (Table 3), whereas the improvement in patients of group 2 and 3 was limited to the duration of morning stiffness P=0.04, 0.048 respectively.

Marked positive dynamics of clinical parameters were observed in group 1 patients; there was 27% reduction in TJN, 23% reduction in SJN and 26% lower VAS compared to reduction by 11% in TJN, 11% in SJN and 11% in VAS observed in group 2 and 16%, 10% and 13% in group 3. Similarly, there DAS28 score reduced by 12% compared to 3% and 7% in group 2 and 3 respectively.

Table 3. Changes in clinical parameters before and after treatment in study groups (M±SD)

Parameter	Group 1 (n=12)		Group 2 (n=12)		Group 3 (n=10)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
DAS28	5.65±0.57	4.98±0.57*	5.62±0.7	5.47±0.7	5.57±0.6	5.2±0.5
ESR	43.8±n8.83	36±7.5	44.5±9.25	40.1±7.9	44.07±9.9	40.5±10.3
Morning stiffness	120.7±8.2	97.6±7.6*	122±8.7	105±7.4*	119.5±8	107.1±5.8*
TJN	8.0±2.0	5.83±1.9*	7.66±2.0	6.83±2.2	7.8±2.0	6.4±2.0
SJN	8.16±1.9	6.33±1.7*	8.33±1.83	7.42±1.95	7.8±1.8	7.0±1.8
VAS (mm)	47.1±10.7	34.7±11.4*	49.16±9.3	43.75±9.7	48.5±9.5	42±12.4

*Significant differences before and after treatment in p<0.05. Abbreviations: disease activity score (DAS); tender joint number (TJN); swelling joint number (SJN), visual analogue scale (VAS).

ESR on the other hand reduced by 17% in group 1 (P=0.06), 10% in group 2 and 8% in group 3. It is clear that LLLT group showed the highest resection rate, however, the change was not significant. In terms of CRP and RF, there was no significant change in in all groups. Furthermore, 70% percent of patients received LLLT showed positive ACR20 whereas none in the other two group achieved ACR20; however, none of the study groups achieved remission according to criteria of ACR.

Most importantly, no side effect has been reported by group 1 patients during and after treatment whereas 25 % and 20% of group 2 and 3 respectively complained of gastrointestinal symptoms at some point during the study, (Figure 3).

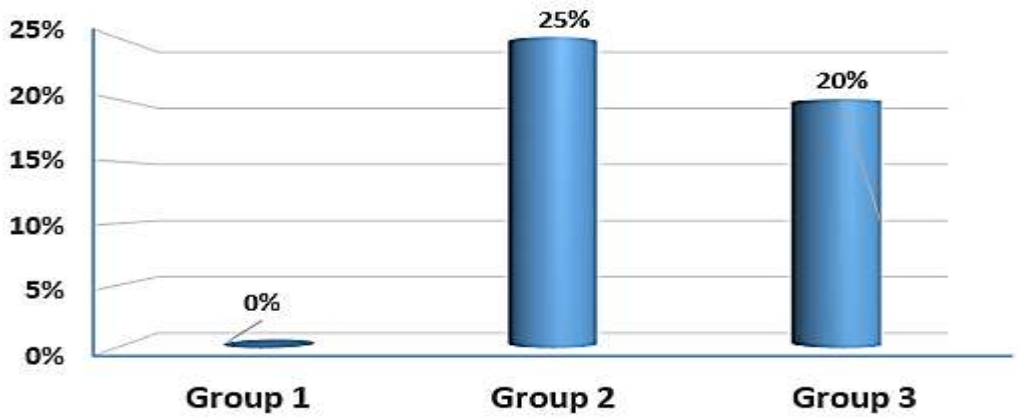

Figure 5. Side effects reported in patients during and after therapy (in percentages)

Discussion

RA is a progressive autoimmune inflammatory disease associating with pain and movement limitation. LLLT has been suggested as an alternative noninvasive therapeutic procedure in RA about 20 years ago [13] and was a focus of research for couple of decades. To our knowledge, this is the first study in Iraq to investigate the effect of LLLT on recent onset RA using four different steps targeting affected joints and relevant nerve root and including several assessment scores and parameters that have not been investigated before such as DAS 28 and ACR20.

In our cohort, the female:male ratio was 2.77:1 which lies within the reported range 2-2.5:1 [22]. We have demonstrated that the intervention group exhibited significant improvement of disease activity (17% reduction in DAS28 score, P=0.02) and clinical parameters including morning stiffness, joint swelling, tenderness and pain, whereas the other 2 groups have not. A metanalysis conducted by Brosseau et al. pooled data form five placebo-controlled trials with a total of 222 patients, with 130 randomized to laser therapy concluded that LLLT reduced pain by 1.10 points (95% CI: 1.82, 0.39) on VAS relative to placebo, reduced morning stiffness for duration by 27.5 minutes (95%CI: 2.9 to 52 minutes) and increased tip to palm flexibility by 1.3 cm (95% CI: 0.8 to 1.7). Other outcomes such as functional assessment, range of motion and local swelling in aforementioned metanalysis were not different between groups [14]. Further, studies used other limbs, as control depicted no significant difference in stiffness duration, or pain RR 13.00 (95% CI: 0.79 to 214.06). Unlike all previous studies, for each patient in the intervention group we targeted four sites including nerve roots, which might explain the significant improvement we illustrated in clinical aspects.

LLLT is non pharmacological medical technique works through generating extremely pure light with no evident side effects. The effect of LLLT is related to photochemical reactions in the cells rather thermal [14]. Light can simultaneously target many cascades of immune system activation in comparison with drugs, so photo-biomodulation can modulate cellular dysfunctions by initiating self-organization phenomena and finally and subsequent healing [12]. ESR is a phase reactant and serve as an indicator of disease activity and patient follow up [20]. We have reported 17% reduction in ESR and 12% reduction in DAS28 after completing the LLLT therapeutic plan suggesting inflammatory modulation effect beside the pain relief. Although the ACR20% was achieved by 70% of LLLT treated patients, the effect was not enough to induce remission and DMARDS remained an important aspect of RA management.

We have not reported any side effect in patient received LLLT. By contrast, 25% of patients in group 2 and 20% of those in group 3 complained of gastrointestinal side effect of NSAID suggesting LLLT as an alternative symptomatic and therapeutic substitute for patients with NSAID contraindication such as those with bronchial asthma, hypertension, or heart diseases.

In conclusion, laser therapy has a positive role in lowering parameters DAS28 and can promote a modest improvement of symptoms and signs according to ACR20. Laser therapy is better than non-steroidal anti-inflammatory drugs in improving clinical features of RA with no side effects.

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Author contribution

Study design and execution conducted by Dr. Al-Saraj and Dr. Al-Attar. Dr. Al-Attar and Dr. Al-Ethary generated the data and drafted the first manuscript. Dr. Al-Attar revised the manuscript.

Conflict of interest

Authors declare no conflict of interest.

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Correspondence to Dr. Zaid I. Al-Attar
E-mail: zaidattar@kmc.uobaghdad.edu.iq
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