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Low Level Laser Therapy in Rheumatoid Arthritis: Ultrasonographic and Clinical Assessment of Efficacy

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Abstract

Background: There are some conflicting reports in the literature about the effects of Low Level Laser therapy on Rheumatoid Arthritis. The aim of the current study was to investigate the efficacy of Low Level Laser therapy on synovial inflammation in the hand joints of patients with rheumatoid arthritis, via clinical and ultrasonographic evaluations.

Materials and Methods: We recruited 35 patients with rheumatoid arthritis and whose proximal interphalangeal joints had mild or moderate active synovitis. We divided subjects into two groups randomly; 18 participants were determined as the laser treatment group, while 17 patients were determined as placebo group. Laser therapy was applied at a dose of 0.6 J/cm^2 to the joints. Clinical and ultrasonographical assessments were performed.

Results: Both groups had reduction in morning joint stiffness at the end of the treatment and at 3 months after therapy; however, laser therapy caused a significantly higher reduction in morning joint stiffness compared to placebo. While placebo did not reduce Duruöz Hand İndex scores at the end of the treatment laser therapy reduced the scores.

Conclusion: Our results raise the possibility that low-level laser treatment of joints affected with rheumatoid arthritis may be effective, at least in part; however, further studies are needed in order to clarify the efficacy.

Key words: *Low Level Laser Treatment, Rheumatoid Arthritis, synovial inflammation*

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Introduction

Rheumatoid arthritis (RA) is a disease of unknown etiology, characterized by chronic inflammation (especially in diartrodial joints), resulting in joint deformities and accompanied by systemic findings. It leads to inflammation and proliferation in joint synovium at onset, also it creates synovial pannus in time and causes destruction of cartilage, bone tissue and other adjacent tissues, thereby resulting in deformities in the joint (1,2). Although the pathogenesis of the disease has not been clarified to date, it has been suggested that rheumatoid arthritis is a T cell-dependent disease triggered by CD4 + antigen recognizing T cells in synovial tissue. However, no common antigen has been discovered in the synovia of RA patients (3). In another hypothesis, it was suggested that the disease is triggered by abnormal lymphoproliferation, deterioration of peripheral tolerance mechanism and consequently the deterioration of T cell homeostasis (4). The main target of treatment in rheumatoid arthritis is to initiate aggressive therapy to suppress and control inflammatory activity before permanent damage occurs in joints.

Treatment of RA involves pharmacological and non-pharmacological approaches (5). Today there are numerous medication options that are used to control the disease, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease modifying antirheumatismal drugs (DMARD) such as methotrexate, sulfasalazine, gold compounds, antimalarial drugs, leflunomide, azathioprine, penicillamine, , and biologic agents such as etanercept and infliximab (6).

Low-level laser therapy (LLLT) is a treatment which is used as part of rehabilitation programs in the treatment of pain and inflammation caused by RA, similar to many musculoskeletal pathologies (7-9). It was initially defined by Ohshiro and Calderhead in 1981 and has since been used in inflammatory diseases (10). In many studies LLLT has been demonstrated to have dose-dependent positive effects on tissue regeneration (11). However, LLLT induces its effect via stimulation of apoptosis leading to tissue regeneration, which may be a cause of degenerative effects at high doses (12). Although it is stated that LLLT's effects are based on cellular photochemical reactions, the mechanism of its action is still not fully understood (13). Nevertheless, in some limited previous studies, laser treatment has been shown to have positive effects onlaboratory andclinical parameters such as joint pain, joint swelling, morning stiffness, as well as increasing functional capacity (14,15).

The primary pathology in early RA is synovitis and bone damage occurs in proportion to the severity of this synovitis.Although conventional radiographs are used routinely for the detection of progressive joint damage caused by RA, this imaging method is not sensitive to soft tissue changes such as synovitis and cannot detect early erosive lesions. Doppler ultrasonography and conventional B-mode USG have been shown to be more sensitive in the detection of effusions,

synovitis and bone erosions in RA joints when compared with clinical examination and conventional radiography (16,17).

There are some conflicting results in the literature about the effects of LLLT on RA joints (18-20). However, the effects of LLLT have been evaluated with only clinical and laboratory parameters, and USG imaging methods have not been utilized in these studies. On the other hand, objective data that can be obtained from ultrasonography may be important in evaluating the efficacy of this treatment in RA. Thus, we aimed to investigate the efficacy of LLLT treatment on synovial inflammation in the hand joints of patients with RA, via clinical and ultrasonographic evaluations.

Materials and Methods

This study was conducted in the Department of Physical Medicine and Rehabilitation. Local ethics committee approved the study and 35 patients with Rheumatoid Arthritis (RA) who were diagnosed according to the American College of Rheumatology (ACR) 1987 criteria, and had mild or moderate active synovitis of the proximal interphalangeal joints as measured by the modified synovitis activity index were recruited (21).

The modified synovitis activity index has been previously defined as: 1-inactive: there is no temperature increase or pain –with or without mild swelling in the joint, 2-mild active: pain and swelling are both present, 3-active: when all three symptoms (swelling, pain and heat) are present (21). Patients who had changes in NSAID or corticosteroid medications within 30 days of laser therapy, or changes in disease-modifying anti-rheumatismal drug (DMARDs) treatments within 3 months before laser therapy, Patients who had severe hand deformities that would influence grip strength, neurologic or orthopedic disease, pregnancy, and those with vasculitis effecting finger joints were excluded from the study.

All patients were informed about possible effects and side effects of the treatment and their personal consent was documented prior to the study. This study was designed as a randomized, double-blind and placebo-controlled study. We divided subjects into two groups randomly, a closed envelope was given to the patients which determined their group (placebo or laser treatment). While 18 participants were determined as the laser treatment group, 17 were defined as the placebo group. The local ethical committee of our university approved the study protocol and all participants signed the written informed consent form.

Laser therapy

For the application of laser therapy, a Ga-Al-As diode laser device with 50 mW output at 830 nm wavelength was used (Endolaser 476, EnrafNonius, The Netherlands). LLLT (Low-level laser therapy) was performed by using a full contact technique at right angle and lateral approach techniques to the each of the PIP joints (consistent with modified synovitis activity index) of patients.The laser therapy was given at a dose of 0.6 J/cm^2 for 2 minutes to each joint. A total of 15

sessions of this treatment was applied, taking the overall laser dose to 9 J/cm^2. The same treatment protocol was applied to 17 patients in the placebo group, showing the device in working condition, but without applying the laser treatment to the treated area. All treatments were given once a day, five days a week, for a total of 15 sessions, and were performed by the same researcher.

Clinical evaluation

The demographic data of patients such as age, sex, disease duration and medications were recorded, a detailed clinical evaluation was performed and disease activity scores (DAS-28) were determined (22). All patients continued their standard drug treatment protocols in the same way during treatment and the follow-up period. Clinical evaluations were performed before and after the treatment, and at the 3rd month. Visual analog scale (VAS) for pain, hand grip strength, joint circumference measurement, range of motion, number of tender joints, number of swollen joints, Duruöz hand index score (DHİ), and morning stiffness were evaluated. LLLT treatment was applied to all joints with synovitis, and the 2nd PIP joint was evaluated for joint circumference and ROM measurement in all patients. All clinical assessments were performed by a specialist blinded to the study protocol.

Pain level measurement was performed by VAS, first described by Boachi-Adjei et al. Patients were asked to mark their pain levels on the 100 mm VAS scale. Zero showed no pain and 10 showed the most extreme pain imaginable (23). Hand dynamometer was used in order to determine the grip strength of the hand, while the elbow was positioned at 90 degrees flexion and the forearm was in the pronation position. The measurement was performed three times and the mean value of these results were taken. The PIP joint circumference was measured by an Arthrocirometer, and a goniometer was used to measure ROM. Additionally, DAS-28 was done for tender and swollen joints and findings were marked on the DAS-28 diagram (22).In order to evaluate the functional status of joints, we used the Duruöz hand index (DHİ). DHİ includes 18 items which assess dexterity-associated activities (cooking, dressing, personal hygiene, office work and others). Scores between 0-5 are given to each item and overall total score obtainable is 90. High scores show functional insufficiencies (24).

Ultrasonographic assessment

A Toshiba Aplio (Toshiba Medical Systems Co, Ltd, Tokyo, Japanese) USG device was used for ultrasonography. B-mode USG was used to measure synovial thickness, spectral Doppler USG was used to count color flow signals (cfs), and duplex USG was used to measure resistance index (RI). Images of the second PIP joint, which were affected in all patients, were obtained as standard. A linear probe with 7.5 Mhz signal was used for synovial thickness measurement from the dorsal side of the joint for horizontal images. The synovium was recognized by its hypo echogenic appearance relative to other soft tissues. The vascular density in the joints were counted by cfs and was staged via the Klauser method as follows:

Grade 0: cfs is absent, Grade 1: 1-4 cfs, Grade 2: 5-8 cfs Grade 3: more than 9 cfs(25,26). Resistance index (RI) was measured by the strongest doppler signal received from the vessel and was calculated automatically with the formula, (maximum systolic velocity - end diastolic velocity) / maximum systolic velocity. When cfs could not be obtained, RI was accepted as "1".

Statistical analyses

Data were analyzed using SPSS v15.0 (SPSS Inc., Chicago, IL) statistics software. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test, and values were presented as frequency and percent values (%) for categorical data and as mean ± SD (standard deviation) for continuous data. The comparison of categorical variables was performed using the Pearson Chi-square and Fisher's exact tests. Continuous variables were compared with the Mann-Whitney U test or the Student's t-test and One Way Repeated Measures Analysis of Variance (ANOVA), depending on normality of distribution and the number of groups compared. Also, the Friedman test was used to compare the distribution of related variables in >2 group comparisons (before treatment, 1st day and 3rd month). The level of statistical significance was set at $p<0.05$.

Results

The laser therapy group was comprised of 18 patients and the placebo group was comprised of 17 patients.There were no statistical differences between groups in terms of age, gender, disease duration, DAS 28 scores and Rheumatoid factor positivity (Table 1).

Table 1. Sociodemographic characteristics of the groups.

	Laser group (n=18)	**Placebo group (n=17)**	***p***
Gender (M/F)	11/7	11/6	>0.05*
Age (year)	49.80±14.02	55.20±10.97	>0.05*
Disease duration (year)	7.02±5.66	8.97±6.83	>0.05*
DAS- 28	5.10±0.88	4.47±0.86	>0.05*
RF (+)	16/18	16/17	>0.05*
Total number of treated joints	5.22±0.56	5.08±0.35	>0.05*

All patients were using methotrexate and NSAIDs, 20 patients were using sulfasalazine (10 in the laser, 10 in the placebo group), 20 patients were using antimalarial drugs (9 in the laser, 11 in the placebo group), 28 patients were using corticosteroids (16 in the laser, 12 in the placebo group).

Friedman analyses showed that both Laser therapy and placebo reduced the morning joint stiffness at the end of the treatment and at 3 months after therapy ($p<0.0001$, $p<0.05$ respectively). Besides, laser therapy significantly reduced morning joint stiffness compared to placebo ($p<0.05$). Placebo did not reduce DHİ scores at the end of the treatment while laser therapy reduced DHİ scores at the end of the treatment ($p<0.05$); however, it did not cause any change in DHİ scores at 3 months after laser therapy ($p>0.05$). Additionally, DHİ scores were similar between the placebo and laser groups at 3rd month evaluation ($p>0.05$).

Laser therapy significantly reduced the number of swollen joints after 3 months from treatment ($p<0.001$), whereas, in the placebo group, the number of swollen joints at the end of the same period did not show significant reduction ($p>0.05$). Interestingly there were no significant differences between the groups regarding the number of regressed swollen joints, neither on the 1st day after treatment nor at the 3rd month.

Friedman analyses showed that the two treatments (Laser and placebo) significantly reduced VAS scores, the number of tender joints, synovial thickness, and improved grip strength at the 3rd month after treatment compared to initial findings ($p<0.005$ for each); however, both treatments caused a similar impact on these parameters; there were no significant differences between the two groups in terms of VAS, the number of tender joints, synovial thickness, and grip strength after treatment ($p>0.05$ for each parameter) (Table 2 and Table 3). There were also no significant differences between the post-treatment results of the groups in terms of PIP circumference, PIP ROM, RI, and Klauser stage ($p>0.05$ for each). Also there were no significant differences between the before and after treatment comparisons of the placebo and laser groups ($p>0.05$ for each parameter) (Table 2 and Table 3).

Table 2. Results of parameters at baseline, at the end of treatment and 3 months after treatments.

		Baseline	End of treatment	3 months after treatment	*P*
Morning stiffness (min)	Laser group	96.33±68.52	22.67±19.68	25.33±25.60*	**<0.001**
	Placebo group	93.67±68.57	51.33±49.06	58.00±34.29	**<0.05**
Swollen joint count	Laser group	5.33±3.24	4.07±2.94	3.80±1.93	**<0.01**
	Placebo group	3.20±1.32	2.87±1.46	2.61±1.35	>0.05
VAS (mm)	Laser group	66.00±23.16	43.67±17.27	50.67±22.82	**<0.05**
	Placebo group	64.67±15.64	50.00±19.73	50.67±11.63	**<0.05**
Tender joint count	Laser group	6.80±4.50	5.67±4.29	5.40±3.96	**<0.05**
	Placebo group	6.93±5.08	5.91±4.10	5.23±2.99	**<0.05**
Grip strength (Barr)	Laser group	0.33±0.18	0.38±0.18	0.39±0.20	**<0.05**
	Placebo group	0.28±0.07	0.32±0.08	0.34±0.07	**<0.05**
Circumference of PIP joint (cm)	Laser group	6.80±0.93	6.40±2.06	6.53±2.10	>0.05
	Placebo group	6.53±1.25	6.13±0.83	6.07±0.70	>0.05
ROM of PIP joint (degree)	Laser group	82.33±17.61	90.33±11.41	89.00±15.37	>0.05
	Placebo group	86.67±12. 2	74.33±13.74	87.00±9.21	>0.05
DHİ scores	Laser group	29.67±9.12	27.60±8.73	29.47±17.15	**<0.05**
	Placebo group	28.87±9.37	28.73±9.64	27.60±8.10	>0.05
Synovial thickness (mm)	Laser group	3.87±1.75	3.54±1.03	3.12±0.67	**<0.01**
	Placebo group	3.33±0. 7	3.07±0.59	2.83±0.46	**<0.05**
Resistance index	Laser group	0.68±0.16	0.70±0.20	0.75±0.16	>0.05
	Placebo group	0.69±0.13	0.74±0.16	0.74±0.14	>0.05
Klauser stage	Laser group	2 ±0.925	1.73±0.961	1.60±0.828	>0.05
	Placebo group	1.80 ±0.774	1.66 ± 0.899	1.60±0.507	>0.05

Discussion

The results of our study show that LLLT may cause significant but limited improvements in the clinical findings of patients, but not in ultrasonographic findings. Morning stiffness was one of these clinical parameters that was significantly reduced by LLLT in comparison with the placebo group. Also, LLLT caused a significantly higher reduction in DHİ scores at the end ofthe treatment; however, long term DHİ scores were similar. An interesting finding of our research was, while LLLT significantly reduced the number of swollen joints, placebo did not; however, after 3 months from the treatments, the number of regressed swollen joints were similar in both groups. We think that this can be explained with the small sample size of our study. Another main goal for this study was to compare the effects of LLLT and placebo with the help of ultrasonography findings. However, the impact of the two treatment modalities on the USG findings of RA patients (such as resistance index and Klauser stage) were similar, and we did not find any differences between the placebo and LLLT

groups in terms of other clinical findings. Therefore, our results demonstrate that LLLT has limited beneficial effects in RA patients, which are only evident in the early period of treatment.

Although there are some studies in the literature investigating the impact of LLLT on RA, our study differs from those with the addition of USG findings to clinical assessments.. As previously mentioned, the efficacy of LLLT in RA is still debated; however, the majority of studies have suggested the presence of positive effects. Palmgren et al. used the Ga-Al-As laser at a lower dose (3.6 J / cm^2) and, similar to our results, found a reduction in morning stiffness in the laser-treated group compared to the placebo group (15). Also consistent with our results, Brosseau and colleagues also reported that LLLT reduced morning stiffness and pain in RA patients (27). In addition to these studies, in a meta-analysis the same researcher concluded that LLLT should be considered for short term relief of pain and morning stiffness in patients with RA, particularly since it has few side effects (28). However, there is a common point in all these studies; although marginal benefits have been shown, the exact mechanism of these effects are still unclear. The results and findings of the major studies in this field show that LLLT utilization in patients with RA is beneficial with reductions in pain and morning stiffness, when applied for a minimum of four weeks. However, as mentioned before, there are conflicting results in the literature and conclusive evidence does not yet exist (28).

In some of the studies which showed positive effects of LLLT on RA symptoms, it has been claimed that LLLT decreases inflammation in RA through different mechanisms of action. For instance, Attia et al. associated the effectiveness of laser therapy to its effects in alleviating oxidative stress and inflammation, improving antioxidant and energy metabolic status, while also suppressing disease activity in RA patients (29). In other experimental research conducted by Alves et al., LLLT was suggested to decelerate disease progression in the early and late phases of RA, by ameliorating inflammatory activation (30). This suggestion is supported by Zhang and colleagues who showed LLLT application resulted in anti-inflammatory effects by reducing CCL2 gene expression (31). Besides these studies, Yamaura et al. have reported that radiation at 810 nm (5 J/cm^2) decreases the mRNA level of TNF-alpha and IL-1beta in RA synoviocytes. In another study, the application of radiation at 25 J/cm^2 dose was also shown to decrease the intracellular levels of TNF-alpha, IL-1beta, and IL-8 protein, but did not affect the levels of seven other cytokines/chemokines(32). Although we did not measure inflammatory parameters in this study, it is feasible to speculate that, in the current study, the significant reduction in pain scores with LLLT application may have been associated with these anti-inflammatory properties. But this speculation is controversial because of the similarities in the pain levels of the two groups.

Besides these studies, there are a few studies that have reported no efficacy with LLLT treatment in patients with RA. In a study by Heussler et al., which also used

a Ga-Al-As laser with 12 J/cm^2 dose for 12 sessions, it was reported that there were no significant differences between the LLLT and placebo groups in swollen joint count (33). Similar to this research, Bliddal et al. also did not find any positive effects with LLLT treatment (6 J/cm^2 dose, for 3 weeks,one application every other day) (14). There are also some other studies which have applied different laser methods, dosage and duration which have not found any significant positive effects of LLLT on RA (19,34). However, the variation in laser type, dose and duration may be associated with the lack of significant results, and also limit the comparability of these studies.

Additionally, the number of tender joints, synovial thickness and grip strength were among other parameters that were found to have been improved by both LLLT and placebo in our study. However, the small sample size of this study may have caused the lack of statistical significance when these parameters were compared. Another possible explanation for conflicting results may be associated with the nature of RA progression which involves relapsing and remitting phases. Although we did not allow the inclusion of patients that had any changes in treatments, this natural course of the disease may lead to unmodifiable variations in the findings.

Our study has some certain limitations, the few number of participants was the primary limitation; however, the rigid inclusion/exclusion criteria of the study limited the number of patients that could be included in the study. Secondly, although we evaluated the effects of LLLT with radiologic methods (USG) in addition to clinical findings, we did not measure biochemical markers of inflammation. The lack of these results limit our ability to draw conclusions regarding the possible anti-inflammatory properties of LLLT therapy.

Conclusion

In the light of the literature and our findings, although available data about the impact of LLLT in RA is controversial to say the least, we believe our findings (similar to the majority of studies) point to a limited but positive effect of LLLT in RA joints. Considering the short-term differences between the placebo and control groups in our study, we believe LLLT may be most effective when swift amelioration of symptoms are required in the short term. In order to clarify the role of LLLT and its effects on RA synovitis, studies with an increased number of patients and extensive biochemical investigations are required.

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