Effects of Low-Level Laser Therapy on Clinical Characteristics and Laboratory Profiles in Synovitis in patients with Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic disease that requires long-term administration of immunomodulatory drugs, resulting in a greater risk of side effects such as serious infections, malignancies, hepatic or renal dysfunction and cardiovascular diseases. The main treatment for RA is drug therapy and its therapeutic effect has steadily improved. However, problems including side effects such as infection due to suppression of the immune system and off-target effects at other locations such as the liver still exist because it is a systemic rather than a topical therapy.

Despite the effectiveness of anti-rheumatic drugs, further studies are needed to reduce the risk of side effects. It has been revealed that light therapy by laser irradiation could accelerate wound healing and tissue repair, as well as provide relief of pain and inflammation. The purpose of this study was to clarify whether laser irradiation treatment has a therapeutic potential as an adjunctive therapy against RA synovitis. We recruited 15 patients with RA (mean age: 64.9 years old, mean duration of follow-up: 8.5 years). A laser therapy device (Pulse 10, Panasonic Healthcare Inc.) was used for diode laser treatment. The laser was applied at one point over the swollen or tender joint for 5 minutes, over a period of 4 weeks, once a week for a total of 5 sessions. Outcome measures included arthralgia, patients' global assessment, physician's global assessment, the levels of swelling and tenderness of arthritic joints and disability. Also, in addition to laboratory blood tests, serum concentrations of pro inflammatory cytokines were measured.

A total of 26 joints were treated. After the third or 4th treatment with laser irradiation, there was a tendency for the number of swollen and tender joints to decrease. After the 4th treatment, the ADL and VAS scores showed a tendency to decrease significantly. Although no significant difference was observed in the C-reactive protein value, serum concentrations of a matrix degrading enzyme (metalloprotease-3) and a pro inflammatory cytokine (interleukin-6) were significantly reduced after the 5th laser irradiation treatment session. Our results indicate that treatment with laser irradiation may have therapeutic potential as an adjunctive therapy against RA synovitis.

Keywords: Laser Therapy; Rheumatoid Arthritis; Arthralgia; Tumor Necrosis Factor-α; Interleukin 1β; Interleukin-6

Introduction

Rheumatoid arthritis (RA) is characterized by synovial hyperplasia, neoangiogenesis and infiltration of lymphocytes and macrophages into the RA synovium [1-3]. Numerous studies have already demonstrated that synovitis is closely involved in the pathogenesis of RA [4-6]. In RA synovium, large numbers of infiltrating T cells, macrophages, osteoclast precursor cells and synovial fibroblasts can be seen. It has been demonstrated that infiltrating lymphocytes and macrophages in RA synovial tissue produce excessive levels of pro inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 [4-13]. These cytokines form a network and are key participants in the pathogenesis of arthritis. An imbalance of pro inflammatory and inhibitory cytokines may, at least in part, participate in the development of arthritis [13]. In addition, periarticular osteopenia can be observed in the early stage of the disease before the erosion of bone becomes evident [14-18]. Previously, we have demonstrated that infiltrating inflammatory cells in RA synovium may modulate not only inflammation but also bone and cartilage destruction [11]. A therapeutic strategy against synovitis may have the potential to inhibit inflammation, joint pain (arthralgia), and the degeneration of bone and cartilage tissues [9-10]. In this study, we focused on the synovitis to develop a new therapeutic strategy for RA.

In general, currently-available anti-rheumatic drugs to inhibit RA synovitis include non-steroidal anti-inflammatory drugs (NSAIDs), steroids, disease-modifying anti rheumatic
drugs (DMARDs), immune suppressants, or antibiotics. Anti-
rheumatic drugs, such as DMARDs, immune suppressants, and
biologics, exert their therapeutic effects via cellular and
molecular responses of target cells, such as T cells, B cells,
macrophages and synovial fibroblasts [19-22]. In addition to
therapeutic drug responses, these anti-RA drugs are likely to
induce a variety of side effects, such as anemia, vasculitis,
pneumonitis, infection, or liver disorders. Consequently, it is
important to consider the balance between therapeutic effects
and side effects in anti-rheumatic drugs [21,22]. Novel low-
invasive therapies are required to further improve the symptoms
and clinical outcome of RA.

Numerous reports and systemic reviews with meta-analysis
have already demonstrated that laser therapy exhibits an
anti-inflammatory effect in a variety of diseases [23-28]. It is
suggested that laser therapy showed an anti-inflammatory effect
through the mechanism involving the control of pro-inflammatory
cytokine secretion [23-27]. In RA, synovitis induces joint
destructions as well as acute and chronic arthralgia. Treatment
with laser illumination may be expected as an adjunctive therapy
for RA synovitis, although further studies are needed to clarify
possible mechanisms for the therapeutic effect of laser therapy
on synovitis.

Based on the results of our previous in vitro and in vivo
studies, we postulated that light therapy may have potential as an
adjunctive and low-invasive therapy for RA. The purpose of our
clinical study was to clarify whether or not treatment with laser
irradiation has therapeutic potential as an adjunctive therapy
against RA synovitis. We hypothesized that laser irradiation
would have anti-inflammatory and anti-pain effects against
the synovitis in RA. If the light therapy proves effective, it would
enable the doses of NSAIDs, steroids or immune suppressants
to be reduced, resulting in greatly decreased risk of side effects
such as gastric ulcers, osteoporosis or infection.

Patients

Fifteen patients with RA were recruited and received light
therapy by laser irradiation against rheumatoid arthritic joints.
The protocol of this study was approved by the ethical committee
of St. Marianna University School of Medicine (permission
number: 1678) and was conducted in accordance with the 2011
Helsinki declaration and its later amendments or comparable
ethical standards. Informed consent was obtained from all
individual participants included in the study. Table 1 shows the
criteria of patient selection for this study. The mean patient age
was 64.9 years old, with a range from 48 to 78 years. The mean
duration of follow-up was 8.5 years. Six patients showed lower
disease activity as defined by a disease activity score (DAS) score
of less than 2.7 [29]. Nine patients had active disease as defined
by a DAS score of more than 2.7. Table 2 shows patients’ profiles
in this clinical study. All patients had to have received a stable
dose of NSAIDs, steroids, immune suppressants or antibiotics for at least 6 months to participate in the study (Table 3).

<table>
<thead>
<tr>
<th>Table 1: Criteria of the patient selection.</th>
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<tbody>
<tr>
<td>1</td>
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<td>3</td>
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<tr>
<td>4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Patients’ profiles.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of RA patients: 15 (male 2, female 13)</td>
</tr>
<tr>
<td>Mean age: 64.9 years (range, 48 - 78 years)</td>
</tr>
<tr>
<td>Duration of follow-up: 8.5 years (2 - 18 years)</td>
</tr>
<tr>
<td>DAS28 CRP disease activity</td>
</tr>
<tr>
<td>DAS &lt; 2.7 (slight): 6 patients</td>
</tr>
<tr>
<td>DAS 2.7~4.1 (moderate): 7 patients</td>
</tr>
<tr>
<td>DAS 4.1 &lt; (severe): 2 patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Profile of treatment with anti-rheumatic drugs.</th>
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<tbody>
<tr>
<td>Only steroid: 2 patients</td>
</tr>
<tr>
<td>Only methotrexate (MTX): 3 patients</td>
</tr>
<tr>
<td>Steroid + MTX: 9 patients</td>
</tr>
<tr>
<td>Antibiotics (anti-TNF-α) + MTX: 1 patient</td>
</tr>
</tbody>
</table>

*All patients in the present study had been treated with non-steroidal anti-inflammatory drugs.

TNF (tumor necrosis factor)

**Laser Irradiation**

All laser irradiation treatments were applied over a period of 4 weeks, once a week for a total of five sessions. A laser therapy
device (Pulse 10, Panasonic Healthcare Inc., Japan) was used
for treatment with a diode laser [30]. The wave length of this
machine was 830 nm, peak output power was 10 W, and power
density was 6–7W/cm². The product used in the current study
can produce the pulsed laser light with peak output power
of 10W (20 milliseconds, irradiation energy 1/second) by
intervals of 180 seconds, which enables to suppress the strong
thermal effect and to transmit the laser light into the deeper
tissue at the same time. The laser was applied at one point
over the swollen or tender joint for 5 minutes. Outcome measures
included arthralgia, patients global assessment, physicians
global assessment, the levels of swelling and tenderness of
arthritic joints and disability. The level of joint pain was
evaluated by visual analog scale (VAS). The VAS is a standard 10-
cm horizontal scale. The patient indicates the severity of pain
by placing a mark between terminal points designated “No pain”
and “Pain as bad as it could be.” The VAS is scored from 0 (no
pain) to 10 (pain as bad as it could be).
In general, it is well known that the VAS found in the Stanford Health Assessment Questionnaire was found to be the most useful available measure for routine clinical use. However, some patients could not complete this scale without assistance. Therefore, it has been developed a brief pain scale for regular use, based on the frequency of pain in the same 8 activities of daily living (ADL) used to assess difficulty, dissatisfaction, and change in status [31].

The patient was asked: “How often is it painful for you to . . .” for each of the 8 ADL (a, b, c, d, e, f, g, h) described below:

a) Dress yourself, including tying shoelaces?
b) Get in and out of bed?
c) Lift a full cup or glass to your mouth?
d) Walk outdoors on flat ground?
e) Wash and dry your entire body?
f) Bend down to pick up clothing from the floor?
g) Turn regular faucets on and off?
h) Get in and out of a car?

And then, four response options were presented and were scored as follows: never = 0, sometimes = 1, most of the time = 2, and always = 3. The total ADL pain score was the mean score for the 8 responses [31,32].

In addition to laboratory blood tests, serum concentrations of biomarkers for inflammation [C-reactive protein (CRP), pro inflammatory cytokines (TNF-α, IL-1, IL-6)] and matrix degrading enzyme [matrix metalloprotease (MMP)-3] were measured. The schedule of analysis is summarized in (Table 4).

<table>
<thead>
<tr>
<th>Table 4: Schedule of analysis.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Check of patient profile</td>
</tr>
<tr>
<td>Laser irradiation</td>
</tr>
<tr>
<td>Objective analysis of arthritis</td>
</tr>
<tr>
<td>Subjective analysis of arthritis</td>
</tr>
<tr>
<td>Check of side effects</td>
</tr>
<tr>
<td>Laboratory tests</td>
</tr>
<tr>
<td>Bloodtest</td>
</tr>
<tr>
<td>CRP</td>
</tr>
<tr>
<td>ESR</td>
</tr>
<tr>
<td>Cytokines (blood sample)</td>
</tr>
<tr>
<td>MMP-3</td>
</tr>
<tr>
<td>IL-1β</td>
</tr>
<tr>
<td>TNF-α</td>
</tr>
<tr>
<td>IL-6</td>
</tr>
<tr>
<td>Diagnostic imaging</td>
</tr>
<tr>
<td>DAS28</td>
</tr>
</tbody>
</table>

○Before irradiation, ● After irradiation, △ Before irradiation as necessary, ▲ After irradiation as necessary CRP (C reactive protein), ESR (erythrocyte sedimentation rate), MMP (matrix metalloprotease-3), IL (interleukin), TNF (tumor necrosis factor)

Results

Table 5: Laser-irradiated joints

<table>
<thead>
<tr>
<th>Finger joints</th>
<th>3 patients</th>
<th>8 joints</th>
</tr>
</thead>
<tbody>
<tr>
<td>thumb CM joint</td>
<td></td>
<td>2 joints</td>
</tr>
<tr>
<td>index finger PIP joint</td>
<td></td>
<td>3 joints</td>
</tr>
<tr>
<td>middle finger PIP joint</td>
<td></td>
<td>3 joints</td>
</tr>
<tr>
<td>Wrist joints</td>
<td>5 patients</td>
<td>7 joints</td>
</tr>
<tr>
<td>Elbow joints</td>
<td>1 patient</td>
<td>1 joint</td>
</tr>
<tr>
<td>Shoulder joint</td>
<td>1 patient</td>
<td>1 joint</td>
</tr>
<tr>
<td>Knee joints</td>
<td>3 patients</td>
<td>5 joints</td>
</tr>
<tr>
<td>Ankle joints</td>
<td>2 patients</td>
<td>4 joints</td>
</tr>
<tr>
<td>Total</td>
<td>15 patients</td>
<td>26 joints</td>
</tr>
</tbody>
</table>

CM (carpometacarpar)
PIP (proximal interphalangeal)

A total of 26 joints were treated (Table 5). Relatively more PIP finger and wrist joints were involved in comparison to large joints.

After the 3rd or 4th treatment with laser irradiation, there was a tendency for the number of swollen and tender joints to decrease (Figures 1A & 1B). Regarding ADL (pain) score and VAS of pain, after the 4th treatment, the scores showed a tendency to decrease significantly, suggesting a therapeutic effect of laser irradiation on the rheumatoid synovitis (Figures 2A & 2B). Although no significant difference was observed in the CRP value, serum concentration of matrix metalloprotease MMP-3 was significantly decreased after the 5th laser irradiation treatment (Figures 3A & 3B).

We observed that serum concentrations of pro inflammatory cytokines TNF-α and IL-6, but not IL-1 β, were decreased after the 5th laser irradiation (Figures 4A-4C). These pro inflammatory
Cytokines are mainly produced by synovial fibroblasts, infiltrating T cells and macrophages. We conclude that the laser irradiation against the arthritic joints directly inhibits the production of pro-inflammatory cytokines from synovial tissue.

**Figure 1:** Number of swollen and tender joints.

A: number of swollen joints that received laser irradiation.

B: number of tender joints that received laser irradiation.

After the treatment with laser therapy, there was a tendency to decrease the number of swollen and tender joints. Number of swollen and tender joints were significantly decreased after the 3rd ~4th treatment with laser irradiation (* P<0.05 compared to the initial phase, **P<0.01 compared to the initial phase).

**Figure 2:** Pain score and visual analog scale.

A: pain score (ADL score).

B: visual analog scale (VAS). After the treatment with laser therapy, arthralgia was improved. Both pain score and VAS were significantly decreased after the 3rd ~4th treatment with laser irradiation (* P<0.05 compared to the initial phase, **P<0.01 compared to the initial phase).
In the present study, we carried out a clinical trial with a device for laser therapy to clarify whether or not treatment with laser irradiation has therapeutic potential for RA patients. Our present study indicates that there is a tendency for the number of swollen and tender joints to decrease after laser irradiation treatment. The arthralgia was also improved by the treatment. Interestingly, we observed that the laser therapy was more effective in fingers and wrist joints than in other large joints such as shoulder, elbow and knee joints (Table 6), although it still unknown why there was difference in therapeutic effects between small joint and large joints.

### Table 6: Therapeutic effects (after the fifth treatment).

<table>
<thead>
<tr>
<th>Illuminated site</th>
<th>Swelling</th>
<th>Tenderness</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger</td>
<td>8 joints</td>
<td>4/8</td>
<td>5/8</td>
</tr>
<tr>
<td>Wrist</td>
<td>7 joints</td>
<td>4/7</td>
<td>5/7</td>
</tr>
<tr>
<td>Elbow</td>
<td>1 joint</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Shoulder</td>
<td>1 joint</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Knee</td>
<td>5 joints</td>
<td>1/5</td>
<td>2/5</td>
</tr>
<tr>
<td>Ankle</td>
<td>4 joints</td>
<td>2/4</td>
<td>3/4</td>
</tr>
</tbody>
</table>

**Discussion**

In the present study, we carried out a clinical trial with a device for laser therapy to clarify whether or not treatment with laser irradiation has therapeutic potential for RA patients. Our present study indicates that there is a tendency for the number of swollen and tender joints to decrease after laser irradiation treatment. The arthralgia was also improved by the treatment. Interestingly, we observed that the laser therapy was more effective in fingers and wrist joints than in other large joints such as shoulder, elbow and knee joints (Table 6), although it still unknown why there was difference in therapeutic effects between small joint and large joints.
In our study, scores of joint symptoms (number of swollen joints and tender joints), pain score, and VAS gradually decreased with the advance of laser treatment and showed a tendency to decrease significantly after the 4th treatment. This suggests that the laser irradiation to the arthritic joint may reduce the level of synovitis, such as synovial hyperplasia and infiltration of inflammatory cells into synovial tissue, in rheumatoid arthritic joint. The laser treatment may have a potential to decrease the level of inflammation in RA joints. Anti-inflammatory effect of laser irradiation may accumulate according to increase in the laser irradiation number of times, and then joint symptoms may show a tendency to decrease significantly after the 4th treatment. Although further studies are needed to clarify the issue, we would like to conclude that the laser irradiation have an anti-inflammatory effect against rheumatoid synovitis.

Because the laser light spreads rapidly within the human body, a greater output of laser light is required in order to deliver the light to deeper biological tissue. For laser therapy, the device (Gallium-Aluminium-Arsenide Diode) we used in the current study can produce pulsed laser light with a peak output power of 10 W, which simultaneously reduces the strong thermal effect and allows transmission of the laser light into deeper tissue. The device can deliver the laser light more deeply while maintaining average irradiation energy of 1 W which is equivalent to that of conventional laser devices [30]. In deep parts of the body, the intensity of the laser light becomes very low due to diffusion. Sufficient laser light intensity and irradiation energy are achieved by fast switching of the 10 W high-power laser element. By irradiating the high-power laser light periodically, it is possible to transmit laser light into deeper tissue while providing enough cooling time to suppress unnecessary heat generation. Therefore, we believe that the device we used for laser therapy can be safely used to treat synovitis in RA.

Our results showed that the serum concentration of MMP-3, but not CRP, was significantly decreased after the laser irradiation treatments. CRP is produced by the liver in response to inflammation/immune reaction. MMP-3, that is a highly-sensitive marker of joint destruction, is mainly produced by synovial tissue. Laser irradiation against the arthritic joint may directly influence the production of MMP-3 from the inflammatory synovium, but not the production of CRP from liver tissue. We believe this is the reason why the decrease caused by light irradiation was observed in the serum level of MMP-3, but not the CRP value.

Our study also showed that the serum level of pro-inflammatory cytokine IL-6 was significantly decreased after the 5th treatment with laser therapy. In addition, the serum level of pro inflammatory cytokine TNF-α tended to decrease after laser irradiation, although no significant difference was observed in comparison with the initial phase. These findings suggest that the laser irradiation may have an anti-inflammatory effect in RA synovitis. In RA, it is well known that infiltrating lymphocytes and macrophages in RA synovial tissue produce excessive levels of pro inflammatory cytokines, such as TNF-α, IL-1 and IL-6. These cytokines form a network and are key participants in the pathogenesis of arthritis. The laser irradiation may influence the production of pro inflammatory cytokines from infiltrating lymphocytes and macrophages. In contrast, no significant
difference in the serum level of IL-1β was observed by laser irradiation in our present study. Among these pro-inflammatory cytokines, TNF-α and IL-6 seems to be stronger in participation as a pathogenic factor than IL-1 in RA. Indeed, biologics targeting TNF-α and IL-6 are widely used to treat in patients with RA.

In conclusion, from the results of the current study, we conclude that treatment with laser irradiation may have therapeutic potential as an adjunctive therapy against RA synovitis. Future developments in light therapy may be able to provide a new therapeutic choice to a patient with RA. This method may show promise as an adjunctive therapy with no side effects over the short term in inpatients and which could allow outpatient to carry out treatment at home. Further studies are needed to clarify the exact therapeutic effect of laser irradiation on rheumatoid synovitis. We are now trying to prepare for a new double-blind randomized controlled trial to analyze the effect of light irradiation therapy on synovitis in patients with rheumatoid arthritis.

Acknowledgement

We would like to thank M. Suzuki, S. Mogi, M. Tamaki, and J. Tamate for excellent technical assistance.

Compliance with ethical standards

a. Ethical approval

This study was independently reviewed and approved by the ethics board of St. Marianna University School of Medicine and was conducted in accordance with the 2011 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Conflict of Interest / Funding

This study was supported by Panasonic Healthcare co. Ltd, Japan. The sponsor had no control over the interpretation, writing, or publication of this work. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

systematic review and network meta-analysis. Cochrane Database Syst Rev 3.


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