Analgesic Efficacy of Low Intensity Laser Therapy in a Monosodium Iodoacetate-induced Osteoarthritic Rat Model

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Abstract. [Purpose] This study evaluated the analgesic efficacy of low-intensity laser therapy (LILT) in a monosodium iodoacetate (MIA)-induced arthritis rat model. [Subjects and Method] Thirty Sprague–Dawley rats were randomly divided into 3 groups with 10 rats each: the normal, control, and LILT groups. The LILT group was treated with LILT using a gallium–aluminum–arsenide diode laser during the 3 weeks. Each group had 10 rats. All treatments were applied once a day, 5 days a week, for a total experimental period of 21 days. Weight-bearing shift, paw withdrawal threshold (PWT), and paw withdrawal latency were used as outcome measures. [Results] The hind paw weight-bearing shift, PWT, and paw withdrawal latency of rats in the control group were significantly lower than those in the normal group. In the LILT group, the weight-bearing shift, PWT, and paw withdrawal latency were significantly greater than those in the control group. [Conclusion] LILT reduces pain related behaviors of MIA-induced osteoarthritis in rats.

Key words: Low intensity laser, Osteoarthritis, Pain

INTRODUCTION

Osteoarthritis (OA) one of the most common forms of degenerative arthritis, is caused by a progressive loss of articular cartilage, new bone formation at the joint margins, and synovial proliferation. It is also involves the subchondral bone, ligaments, synovial membrane and periarticular muscle. OA can result in a loss of joint function, disability, chronic pain, and diminished quality of life1–3. Pain is the predominant clinical feature in OA patients and often involves hyperalgesia, referred pain, and ongoing pain; it is also the driving factor for visiting a primary care physician4, 5. Knee OA is generally classified as inflammatory nociceptive and neuropathic pain. Regarding the mechanism of neuropathic pain in knee OA, it is highly possible that knee joint pain occurs in association with damage to nerves innervating subchondral bone because of its weight-bearing surface in late stage OA6. However, the pathophysiology associated with OA, especially in the knee joint, involves complex structural changes; moreover, the pain related to OA is poorly understood7.

Knee OA patient pain is primary treated with lifestyle changes, followed by pharmacological interventions including acetaminophen, non-steroidal anti inflammatory drugs, topical agents, and intra-articular steroid injection8, 9 as well as non-pharmacological interventions such as transcutaneous electrical nerve stimulation10, microwave diathermy11, and exercise12. These interventions currently aim to provide symptomatic relief of the pain and inflammation associated with osteoarthritis to increase joint function.

Intra-articular space injection of monosodium iodoacetate (MIA) induces chondrocyte death in the articular cartilage of both rodent and non-rodent species13. The pathological OA rat model involves injecting MIA into the rat femoral-tibial joint space, this model produces a linear pathology similarities to that of human OA14, 15 as well as significant pain-related behavior16, 17. This model is an established and well-characterized preclinical model of osteoarthritis.

Low-intensity laser therapy (LILT) has numerous clinical benefits such as improved tissue metabolism, pain reduction via reduce inflammation, blocked nerve sensitivity via the anagogic effect, and nerve regeneration at the tissue level18–20. Low-level laser photons can penetrate deep into the body through the skin, muscles, tendons, ligaments, nerves, and even bones, in order to pinpoint and target painful and damaged areas21. LILT is also used to control pain in different musculoskeletal conditions. Therefore, LILT is a commonly recommended physical therapy to treat arthritis22, 23. However, the results of experimental and clinical studies on LILT are conflicting despite its widespread use.

Therefore, the present study was designed to investigate the effectiveness and mechanisms of LILT on the attenuation of OA pain behavior in a rat model.
METHODS

This study involved 30 male Sprague–Dawley rats, each weighing 150–160 g. The rats were housed at a temperature of 25.0 °C ± 1.0 °C and a humidity level of 50 ± 5% with a 12-h light-dark cycle; they had free access to food and water. The general health of the animals was monitored. A total of 30 rats were used in this study, and they were randomly divided into 3 groups of 10 rats after MIA-induced arthritis (Table 1). All experimental procedures in this study were reviewed and approved by the Ethical Review Committee of Dongshin University.

After the rats were acclimatized for 1 week, they were given a single intra-articular injection of MIA via the infrapatella ligament of the left knee at a dose of 4.8 mg dissolved in 60 µL sterile saline. The rats of the normal group were given a single intra-articular injection of equal volume of sterile saline. Substantial inflammation of the synovial joints was observed in the MIA-injected rat up to 5 days after the MIA injection.

A gallium–aluminum–arsenide diode laser with the following characteristics was used for LILT: wavelength, 850 nm; power output, 200 mV; wave pulse, 16 Hz; and spot area, 0.07 cm². The therapeutic point was positioned medial to the patellar ligament, and the treatment was applied on the joint surface of the femur. The LILT group was treated with 3.6 J/cm² for 20 s in the periartricular region of both hind paws 5 times per week over 21 days following arthritis induction. The researchers wore protective eyeglasses during the laser treatment for safety. In the control group, the diode laser was applied in the same way, but the device was turned off during therapy sessions.

Tactile sensory thresholds were determined using calibrated von Frey filaments. The development of mechanical allodynia was assessed using von Frey monofilaments described previously24. Von Frey monofilaments were applied to the plantar surface of both hind paws for 3 s. Once a withdrawal reflex was established, the paw was retested with the next descending von Frey monofilament until no response occurred. The lowest monofilament weight that elicited a withdrawal reflex was recorded as the paw withdrawal threshold (PWT). When the instrument was activated, a fine plastic monofilament advanced at a constant speed and touched the paw in the proximal metatarsal region.

The method of Hargreaves et al.25 was used to assess paw withdrawal latency to a thermal noxious stimulus as described previously26. Baseline latencies were established at 20 s to allow a sufficient window for the detection of possible hyperalgesia. A maximal cutoff of 30 s was used to prevent tissue damage. Hind paw withdrawal latency and withdrawal threshold differences were assessed on days 1, 7, 14, and 21 after LILT.

Hind-limb weight bearing was measured using an incapacitance tester that included a dual-channel weight average. On day 21, the rats were carefully placed in a plastic chamber. The force exerted by each hind limb was averaged over a 3-s period. The mean of 3 readings was recorded. The percentage of weight distributed onto the treated (i.e., ipsilateral) hind limb was calculated using the following equation: (weight on left leg/weight on right leg) ×100.

Data analysis was performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). All the data are expressed as the mean ± SD of 3 replicates. Differences between 2 groups were tested by one-way ANOVA followed by Dunnett’s post hoc analysis when a significant difference was detected. P values less than 0.05 at a 95% confidence level were considered significant.

RESULTS

As shown in Table 2, the paw withdrawal threshold decreased significantly in the MIA-induced arthritic group compared to the normal group (p<0.05). The PWT of the LILT group increased significantly after 7 days compared with that of the control group (p<0.05). The effects of LILT on the withdrawal latency of MIA-induced arthritic rats are shown in Table 3. The LILT group had significantly longer withdrawal latency than the control group assessed at 14 and 21 days after LILT began (p<0.05). The effects of LILT on the hind-limb weight-bearing of MIA-induced arthritic rats are shown in Table 4. The hind-limb weight-bearing rate of the ipsilateral limb was significantly lower in the MIA-treated groups than the normal group (p<0.05). After 21 days, the LILT group exhibited significant recovery of hind-limb weight bearing (p<0.05).

DISCUSSION

The present study investigated the therapeutic effects of LILT on the PWT, paw withdrawal latency, and weight-bearing shift in a MIA-induced OA rat model. The results indicate that daily treatment of OA rats with LILT significantly improved joint mobility and decreased the secondary tactile allodynia, mechanical hyperalgesia, and the hind-limb weight-bearing of the affected knee joint.

Knee OA is a common chronic degenerative disease characterized by loss of articular cartilage components, and affects the entire joint structure including the synovial membrane, fat pad, and subchondral bone27. MIA injection has been reported to cause joint pathology by the inhibiting glycolysis, thereby targeting avascular cartilage and causing chondrocyte death similar to human OA40. Normally quiescent chondrocytes as well as synovial cells respond to repetitive excess mechanical loading via stress-induced intracellular signals that mediate the production of

### Table 1. Experimental group design

<table>
<thead>
<tr>
<th>Group (Total n=30)</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Normal group (n=10)</td>
<td>Non-arthritis group</td>
</tr>
<tr>
<td>Control group (n=10)</td>
<td>Placebo laser therapy for 20 second at the peri-articular area after MIA-induced arthritis</td>
</tr>
<tr>
<td>LILT group (n=10)</td>
<td>LILT 3.6 J/cm² for 20 seconds at the peri-articular area after MIA-induced arthritis</td>
</tr>
</tbody>
</table>

*Low Intensity Laser Therapy
proinflammatory mediators such as cytokines and cartilage-degrading proteinase\(^{28}\).

Pain fibers are present in the synovium, ligaments, bone, muscle and meniscus of the knee. The MIA model of OA, in which a single injection of the irreversible NADPH inhibitor, sodium monooiodoacetate, is made into the joint space, provides a model of the painful and structural components of human OA in rodents. In the MIA-induced OA model, synovial inflammation occurs during the first week after MIA treatment and resolves 1 week later\(^{29}\). In addition, the contribution of neuropathic pain and other neurologic mechanisms to the development of pain in this model remain to be elucidated. The significant decrease in PWT observed in the present study indicates tactile allodynia pathogenesis, which is consistent with a previous study\(^{30}\). This decrease is considered to result from allodynia derived from central sensitization; the increase in afferent signaling from the joint nociceptors to the spinal cord neurons results in increased sensitivity of the spinal cord neurons to input from the joint, rendering the spinal cord neurons hyperexcitable\(^{31}\). LILT can relieve pain, induce collagen proliferation, have anti-inflammation effects, enhance circulation and stimulates peripheral nerves\(^{32}\). In 1994, Stelian et al. randomly assigned 50 patients with knee OA to receive treatment with red (630 nm), infrared (830 nm) or placebo laser light emitters\(^{33}\). They observed significant functional improvement and pain reduction in the laser therapy groups, but not in the control group. On the basis of these results, they concluded that low-power laser therapy is effective for pain relief and improving functional ability. Tascioglu et al.\(^{34}\) used a gallium–aluminum–arsenide laser with a wavelength of 830 nm for the treatment of knee OA. However, they found no significant difference between laser and placebo-treated groups with respect to any measure of pain score including the visual analogue scale\(^{35}\).

The present study has some limitations. First, MIA-induced OA is chemically induced animal model. Further research should study by other OA pathological model to clarify the details. Second, the pain behavioral evaluation for tactile allodynia with von Frey hairs can be somewhat inaccurate and depends on the subjective responses of the animals. To analyze the behavior of rats objectively to analyze their behavior by using other methods such as evaluating weight-bearing in free-moving animals, as well as response to heat and direct measurement of pressure on the knee\(^{36,37}\). Third, our present study had a small sample size. Therefore, further investigation with a larger sample size may be needed to clarify whether analgesic effect actually occurred.

The present results demonstrate that treatment with LILT increased paw withdrawal latency and threshold on day 14 after MIA-induced OA. In addition, the hind-paw weight shift recovered on day 21 after LILT. Therefore, the present results indicate that LILT exerts an analgesic effect by reducing the synovial inflammation induced by MIA injection, which causes peripheral and central sensitization\(^{37}\). More trials with laser subject numbers are needed to precisely determine the optimal treatment procedure for LILT as well as possible interactions regarding the treatment of chronic pain associated with OA.

### References


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**Table 2. Effect of low intensity laser therapy on the paw withdrawal threshold in MIA-induced arthritis rats (g)**

<table>
<thead>
<tr>
<th></th>
<th>1 day</th>
<th>7 days</th>
<th>14 days</th>
<th>21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td>20.50 ± 5.80</td>
<td>21.60 ± 5.68</td>
<td>23.80 ± 4.64</td>
<td>24.90 ± 3.48</td>
</tr>
<tr>
<td>Control group</td>
<td>5.60 ± 1.58*</td>
<td>5.60 ± 1.63*</td>
<td>5.60 ± 1.27*</td>
<td>5.40 ± 1.35*</td>
</tr>
<tr>
<td>LILT(^)* group</td>
<td>5.60 ± 1.58</td>
<td>6.60 ± 1.65</td>
<td>9.00 ± 1.05**</td>
<td>10.90 ± 3.11**</td>
</tr>
</tbody>
</table>

\(\text{LILT}\) data were presented as mean ± SD, \(*: p<0.05\) as compared to normal group, **: \(p<0.05\) as compared to control group

**Table 3. Effect of low intensity laser therapy on the paw withdrawal latency in MIA-induced arthritis rats (s)**

<table>
<thead>
<tr>
<th></th>
<th>1 day</th>
<th>7 days</th>
<th>14 days</th>
<th>21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td>12.70 ± 3.65</td>
<td>12.40 ± 2.22</td>
<td>13.80 ± 1.93</td>
<td>14.60 ± 1.26</td>
</tr>
<tr>
<td>Control group</td>
<td>3.00 ± 0.61*</td>
<td>3.02 ± 0.73*</td>
<td>3.40 ± 0.70*</td>
<td>3.95 ± 0.89*</td>
</tr>
<tr>
<td>LILT(^)* group</td>
<td>2.87 ± 0.70</td>
<td>4.45 ± 1.23</td>
<td>6.60 ± 1.26**</td>
<td>9.30 ± 2.58**</td>
</tr>
</tbody>
</table>

\(\text{LILT}\) data were presented as mean ± SD, \(*: p<0.05\) as compared to normal group, **: \(p<0.05\) as compared to control group

**Table 4. Effects of low intensity laser therapy on hind-limb weight bearing rate of the ipsilateral limb in MIA-induced arthritis rats on 21 days**

<table>
<thead>
<tr>
<th></th>
<th>Hind-limb weight bearing rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td>96.96 ± 10.00 %</td>
</tr>
<tr>
<td>Control group</td>
<td>50.15 ± 4.74* %</td>
</tr>
<tr>
<td>LILT(^)* group</td>
<td>63.13 ± 3.62** %</td>
</tr>
</tbody>
</table>

\(\text{LILT}\) data were presented as mean ± SD. \(*: p<0.05\) as compared to normal group, **: \(p<0.05\) as compared to control group


