Effect of Low-level Laser Therapy on Propylthiouracil-induced Hypothyroidism Model Mice: A Pilot Study

In Kwon Mun^{1,*}
 Won Sang Yoo^{2,*}
 Sang Joon Lee¹
 Phil-Sang Chung¹
 Seung Hoon Woo¹

¹Department of Otorhinolaryngology-Head and Neck Surgery, Dankook University College of Medicine, Cheonan, Korea

²Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Korea

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Correspondence

Seung Hoon Woo
 Department of Otorhinolaryngology-Head and Neck Surgery, Dankook University College of Medicine, 119 Dandae-ro, Dongnam-gu, Cheonan 31116, Korea
 Tel.: +82-41-550-1781
 Fax: +82-41-550-7837
 E-mail: lesaby@hanmail.net

*These authors contributed equally to this study.

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Background and Objectives

Hypothyroidism is the most common endocrine disease. On the other hand, there is no treatment that can improve the thyroid function. Low-level laser therapy (LLLT) can improve the cellular activity. The effect of hypothyroidism is not obvious. This study examined the effects of LLLT on the thyroid gland function of a propylthiouracil (PTU)-induced hypothyroidism mouse model.

Materials and Methods

Twenty-five male ICR mice were distributed into five groups of five animals each: Negative control (none PTU animal) and positive control (PTU animal) of unirradiated animals, and three experimental groups with LLLT (3J, 6J, and 12J). Each mouse was exposed to a distinct dose of a 632-nm laser once a week for three rounds. The positive control group and three LLLT groups were induced into a hypothyroidism state by PTU administration. The animals' thyroid-stimulating hormone and thyroxine levels were measured using an ELISA kit, and their thyroid tissue was harvested and analyzed after sacrifice at the end of the experiment. The hormone level and morphological changes in the tissue of the five groups were compared.

Results

The thyroid hormone levels in the control group and LLLT groups were similar. On the other hand, the thyroid tissue of the LLLT groups showed some morphological changes that were similar to those of iodine deficiency thyroid.

Conclusion

LLLT did not affect the thyroid gland function in PTU-induced hypothyroidism mice.

Key words

Hypothyroidism; Propylthiouracil; Low-level laser therapy; Mice

INTRODUCTION

Hypothyroidism is a relatively common chronic disease and the most common endocrine disease worldwide. Most cases of hypothyroidism are primary, and autoimmune thyroiditis is the most common cause in populations of adequate iodine intake.¹⁻³ Levothyroxine monotherapy remains the current standard treatment for patients with primary hypothyroidism.⁴ However, this treatment simply replaces insufficient thyroid hormone and does not normalize thyroid cell function. Therefore, patients with hypothyroidism must continue to take their medications daily. Additionally, thyroid function tests should be performed regularly to maintain adequate drug dose.⁵ Because of these limitations, improved treatments to normalize thyroid function are needed.

Low-level laser therapy (LLLT) is the application of light to biologic systems using narrow spectral widths ranging from 600 to 1100 nm. LLLT can cause biochemical and physiological effects in various enzymes, cells, and tissues. Because of its numerous beneficial effects, LLLT has recently been introduced for clinical use in various fields. For example, LLLT is known to improve the healing of damaged tissues; enhance bone, skin, and muscle recovery;⁶⁻⁹ relieve pain,¹⁰ and reduce the inflammatory response.¹¹ Moreover, LLLT is known to be effective in the treatment of autoimmune diseases,^{12,13} potentially owing to the induction of anti-inflammatory effects. Because most cases of hypothyroidism have an autoimmune background,¹ LLLT may have therapeutic effects on hypothyroidism.

Antithyroid antibody production through B cells and T cell-mediated cytotoxicity cause inflammation and injury of thyrocyte. Due to these injuries and inflammation, autoimmune hypothyroidism occurs.¹⁴ If LLLT can boost recovery of damaged thyrocyte and promote cellular function, it could be a paradigm-shifting treatment method. However, only a few studies were conducted about the effects of LLLT on hypothyroidism. Therefore, we designed this pilot study to examine the histological and evaluated whether this approach could have applications in the treatment of hypothyroidism.

MATERIALS AND METHODS

Animals

In this study, we used 6-week-old Institute of Cancer Research (ICR) male mice (N = 25). The body weights of the mice ranged from 31 to 33 g (average: 32 ± 0.71 g). The weight of each animal was measured at least every

3 days. Hypothyroidism was induced by anti-thyroid drug. Propylthiouracil (PTU) (Sigma-aldrich, Inc., St. Louis, MO, USA) was diluted in drinking water to 1 mg/ml and then administered 2 mg to each subject daily for three weeks.¹⁵

Twenty-five mice were randomly assigned to five equal groups according to the application of antithyroid drug and LLLT. The first 5 mice were not exposed to either antithyroid drug or LLLT (negative control [NC] group). The next 5 mice were exposed to the antithyroid drug but not to LLLT (positive control [PC] group). Finally, the remaining 15 mice were exposed to both antithyroid drugs and LLLT, with 5 mice each exposed to 3, 6, or 12 J/cm² radiation.

This study was approved by the Institutional Review Board (IRB) of Dankook University of Medicine, Cheonan, Korea. All of the experiment protocols on animals were conducted in accordance with the Institutional Animal Care guidelines of Dankook University of Medicine, Cheonan, Korea.

LLLT protocol

The three LLLT groups were treated with a 632-nm laser (CyT-ML 630; CyTroniQ Co. Ltd., Cheonan, Korea) on days 1, 7, and 14. One hour before laser treatment, the mice were anesthetized with an intramuscular injection of ketamine hydrochloride (Yuhan Co., Seoul, Korea). The thyroid gland was exposed using a 1-cm incision created with sterilized surgical scissors and a knife (Fig. 1). Mice in 632-nm laser the PC group were not exposed to the laser but were subjected to anesthesia and surgery, as the LLLT groups. During anesthesia, mice in the LLLT groups

Fig. 1. Laser therapy preparation. (A) Both thyroids of mouse were exposed after anesthesia with sterilized scissors and knife (B) Both thyroids next to trachea were exposed (white arrow). Laser was directly irradiated on thyroids.

were exposed to the laser, targeted to both lobes of the thyroid gland for 1.5 min (3 J/cm² group), 3 min (6 J/cm² group), or 6 min (12 J/cm² group). The total irradiation doses were 9, 18, and 36J, respectively. After irradiation, the incised skin was closed with nonabsorbable polyamide sutures.

Monitoring of thyroid hormone levels

Serum thyroid-stimulating hormone (TSH) and thyroxine (T4) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits with collected blood serum. Blood collection was performed using the retro-orbital blood collection method. Due to some limitations at the experimental stage, the blood collection was performed on only one representative mouse in each of the 5 groups, not all mice. Collections were performed on days 1, 7, and 21. Analyses were performed using a mouse TSH ELISA Kit (cat. no. CSB-E05116m; CusaBio, Houston, TX, USA) and a mouse T4 ELISA Kit (cat. no. CSB-E05083m; CusaBio), according to the manufacturer's instructions.

Histological evaluation

On day 21, all 25 mice were euthanized by cervical dislocation, and thyroid glands were excised, fixed in 4% formalin, and embedded in paraffin blocks. Samples were then sectioned with a microtome at a thickness of 5 µm and stained with hematoxylin and eosin (H&E). After staining, photomicrographic morphologies were analyzed. The longest diameters of the follicles were measured and compared between each group.

Statistical analysis

Wilcoxon signed-rank tests were used to compare the levels of hormones after the first LLLT with the level of hormones after the third LLLT. Kruskal-Wallis tests were used to compare thyroid hormone levels between groups. The results of parametric tests are expressed as means ± standard deviations. Results with *p* values of less than 0.05 were considered significant. All statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA).

RESULTS

Weight differences

All 25 mice were approximately 32 g at the beginning of the experiment. The bodyweight of mice in the NC group was gradually increased throughout the experiment period. Through this, it was confirmed that there was no problem in the laboratory conditions. In contrast, the weights

of mice in the other four groups with PTU administration were similar throughout the experimental period without significant differences from the baseline measurements. Therefore, at the end of the experiment, mice in the NC group (38 g) weighed significantly more than mice in the other four groups (33–35 g). However, there were no significant differences in body weight in mice in the PC group and three LLLT groups (Fig. 2).

Thyroid hormone level

Baseline hormone levels did not differ among the groups; the TSH level was 1.50 ± 0.11 µIU/mL, and the T4 level was 274.8 ± 6.1 ng/mL. On day 7, hormone levels were measured before the second round of LLLT. Mice in the NC group showed hormone levels similar to those at baseline. In contrast, in the PC group and three LLLT groups that were administered PTU, TSH levels were elevated (8.59 ± 1.45 µIU/mL), and T4 levels decreased (84.5 ± 25.9 ng/mL). This suggested that hypothyroidism was successfully induced. The last hormone level measurement was performed on the last day of the experiment. The hormone levels in the NC group remained similar to those at baseline. There was no significant difference throughout the experiment between the PC and the three LLLT groups in both TSH and T4 levels. (*p* = 0.380 and 0.183, respectively). However, these four groups showed elevated T4 levels (122.3 ± 43.7 ng/mL) compared with those on day 7. Accordingly, a decline in TSH levels was observed in all groups except the 6J group (3J: 6.52 µIU/mL, 6J: 9.11 µIU/mL, 12J: 6.78 µIU/mL). Thyroid function in the three LLLT groups improved after all three rounds

Fig. 2. Weight changes through experiment period. Negative control (NC) group showed gradual increase of weight. Positive control (PC) group and three low level laser therapy group showed much slower weight gain than NC group. Red arrows: low-level laser therapy performed.

of laser radiation compared with that on day 7. However, improvements in both TSH and T4 were not statistically significant ($P = 0.285$ and 0.109 , respectively). In addition, the PC group also showed improved thyroid function (TSH: $7.85 \mu\text{IU/mL}$, T4: 111 ng/mL), suggesting that there may be other reasons for the improvement in addition to LLLT (Figs. 3, 4).

Fig. 3. TSH levels of PC and three low-level laser therapy group. The measurements were done at the start of experiment, week 1, and week 3.

Histological evaluation

Thyroid gland sections were stained with H&E. The thyroid follicles in the NC group (Fig. 5A) showed different shapes and sizes. Each follicle was lined with cuboidal epithelial cells enclosing an internal lumen occupied by a homogeneous colloid. The PC group (Fig. 5B) showed larger follicles than the NC group and stroma with moderate edema and hemorrhage. The 3J LLLT group (Fig. 5C) showed similar histological findings as to the PC

Fig. 4. T4 levels of PC and three low-level laser therapy group. The measurements were done at the start of experiment, week 1, and week 3.

Fig. 5. Photomicrography of thyroid tissue after hematoxylin & eosin (H&E) staining. (A) Negative control (NC) group showed various size of follicles. Homogenous internal colloid can be observed. (B) PC group showed enlarged follicle size. Moderate edema and hemorrhage can be seen in stroma. (C) 3J low-level laser therapy (LLLT) group showed similar findings with PC group. Slightly smaller size of follicle than PC. (D) 12J LLLT group. Follicle sizes were similar to NC group. Heterogenous internal colloid, some depletion can be observed. Vacuolar change of epithelial lining cells. Black bars: $100 \mu\text{m}$.

group. However, the thyroid follicles in this group were relatively smaller than those in the PC group. In the 12J LLLT group (Fig. 5D), follicle sizes were similar to those in the NC group. Some follicles showed depletion of colloids and vacuolar degenerative changes in their epithelial lining cells. The mean diameter was $51.38 \pm 19 \mu\text{m}$ in negative control, $80.28 \pm 22.50 \mu\text{m}$ in positive control, $57.78 \pm 26.39 \mu\text{m}$ in 3J LLLT group and $55.28 \pm 17.61 \mu\text{m}$ in 12J LLLT group. The follicle size between negative control and positive control showed statistically significant difference ($p=0.02$), while the other three groups showed no significant difference between each other.

DISCUSSION

Several studies have reported that LLLT is effective in various fields, including treatment of alopecia,¹⁶ vestibulopathy,¹⁷ and ophthalmic diseases.^{18,19} However, the mechanism of LLLT has not been fully elucidated. Current research has shown that the effects of LLLT involve the absorption of photons from the laser to cytochrome c oxidase in cells, leading to stimulation of the electron transport chain and promotion of ATP production. In cells in which metabolism was promoted by LLLT, the production of inflammatory response mediators decreases.^{20,21} This anti-inflammatory effect may be exploited, resulting in therapeutic effects on autoimmune diseases, such as rheumatoid arthritis, psoriasis, and autoimmune thyroiditis.^{12,13}

Most studies of the effects of LLLT on the thyroid gland have been conducted in animals with normal thyroid function. In contrast, in the current study, we analyzed the effects of LLLT on the thyroid gland in a PTU-induced hypothyroidism mouse model. There are several methods to induce hypothyroidism in animal models. Among these approaches, antithyroid drugs, such as methimazole and PTU, are commonly used.²² Methimazole and PTU cause a hypothyroid state by inhibiting the thyroid peroxidase (TPO) enzyme that converts iodide to iodine, a form that can be used to produce thyroid hormone.²³ This mechanism is similar to the anti-TPO antibody, which is an important cause of primary hypothyroidism.²⁴ For this reason, we used a PTU-induced hypothyroidism model in this study.

Hypothyroidism induced mice by PTU shows weight loss compared to control group.^{15,22} Likewise, in this study, PTU administered PC and three LLLT groups showed significant weight loss compared to the NC group. This suggests that hypothyroidism induction was successful in this study. However, there was no significant body weight difference between PC and LLLT groups, which means

that LLLT could not inhibit weight loss by PTU. In the PC and 6J groups, after the second and third rounds of LLLT, more than 0.5 g weight loss was observed in only 1 day (Fig. 2) (second round: 33.6 and 34.12 g decreased to 32.6 and 33.51 g, respectively; third round: 33.75 and 34.25 g decreased to 33.25 and 33.5 g, respectively). This sudden weight loss after LLLT suggested that the mice experienced stress due to the procedures required for laser irradiation.

Several studies have evaluated morphological changes in healthy thyroid gland caused by LLLT. For example, Parrado et al.²⁵ studied morphological changes in the thyroid after irradiation with a 904-nm laser (total dose, 46.8 J/cm^2) in mice with normal thyroid function. Through quantitative measurement, a significant increase in capillary volume was reported. This morphological change could alter thyroid function. After morphological changes of thyroid gland induced by LLLT were reported by Parrado et al, studies on the effects of LLLT on thyroid function were conducted. Luciane et al.²⁶ irradiated normal male mice with a 780-nm laser three times (4 J/cm^2 dose each) and measured hormone levels after 24 h, 48 h, 72 h, and 1 week. There were no significant changes at 24, 48, or 72 h; however, after 1 week, T4 and triiodothyronine (T3) levels were significantly increased compared with those in the control group. Weber et al.²⁷ irradiated normal male rabbits with an 830-nm laser seven times. Dose per times were 5 J/cm^2 , 10 J/cm^2 , and 20 J/cm^2 . T3 and T4 levels were measured four times throughout the experiment. The T3 level showed a significant increase compared to the control group, but the T4 level did not.

Unlike these reported studies mentioned above, in this study the thyroid hormone levels showed no differences between LLLT group and PC group. To establish a hypothesis about the reason for this result, thyroid hormone synthesis procedure should be considered. First, iodide (I^-) is absorbed into the follicular lumen through the Sodium-Iodine symporter and pendrin. Thereafter, iodide is oxidized to Iodine (I_2) by TPO and binds to thyroglobulin (Tg) which is secreted from the follicular cell to the follicular lumen. The generated monoiodothyronine and diiodothyronine are coupled by TPO to generate T3 and T4. After T3 and T4 binding Tg is absorbed into the follicular cell through endocytosis, Tg is decomposed by the lysosome and only T3 and T4 are secreted to serum. In the final stage, endocytosis and secretion are influenced by cellular activity. Since LLLT can increase cell activity, it can be thought that it affects the ability to secrete thyroid hormones. However, in this study, thyroid hormone levels showed no difference. This is thought to be because TPO

Fig. 6. Schematic image of thyroid hormone synthesis procedure and effects of PTU and Low-level laser therapy. Although cellular activity is increased by LLLT (green arrow), there is no hormonal change because PTU (red arrow) prevents iodination of thyroglobulin (Tg) (TPO: thyroid peroxidase, MIT: monoiodothyronine, DIT: diiodothyronine, T3: triiodothyronine, T4: thyroxine).

was inhibited by PTU. Which results in a lack of iodine. Accordingly, T3 and T4 could not be synthesized. Cellular activity increased due to LLLT. However, the process that LLLT can promote during the production mechanism of thyroid hormone is located after the process that PTU suppresses. Therefore, LLLT could not inhibit the action of PTU, so there was no T3 and T4 to secrete (Fig. 6). Morphological change also supports this hypothesis. In LLLT groups, decreased follicular size, colloid depletion, and vacuolar changes in epithelial cells were observed according to the laser irradiation dose. These changes are similar to those seen when iodine deficiency thyroid is stimulated with high TSH for a long time. Cellular activity increased with high TSH, but iodine supply was insufficient, which is the same situation as in this study. Therefore, it can be confirmed that if TPO does not function normally, the serum hormone level cannot be increased only by increasing cellular activity due to LLLT.

Hopefully, there is a series of study that showed LLLT can reduce the required dosage of levothyroxine in hypothyroidism patients. In their pilot study,²⁸ fifteen hypothyroidism patients with thyroid hormone supplement therapy were selected as subjects. All patients received total 10 times application of LLLT, twice a week (830 nm, 50 mW, 38-108 J/cm²). After 9 months, the required dosage of levothyroxine is significantly decreased from 96 ± 22 μ g/day to 38 ± 23 μ g/day (p -value < 0.0001). Seven patients did not even need any supplements. Due to this successful result,

follow-up randomized controlled study was conducted.²⁹ Forty-three hypothyroidism patients with thyroid hormone supplement therapy were selected as subjects. They were randomly assigned to LLLT group (10 sessions, 830 nm, 50 mW, 707 J/cm², N = 23) or placebo group (N = 20). The results showed a significant difference in required dosage of levothyroxine between the LLLT group (38.59 ± 20.22 μ g/day) and the placebo group (106.88 ± 22.90 μ g/day, p -value < 0.001). Lower level of anti-TPO antibody ($p = 0.043$) was also noted in the LLLT group. This is thought to be due to LLLT's inhibition effect of secreting proinflammatory cytokines such as tumor necrosis factor alpha and interferon gamma.

In conclusion, it was confirmed that no matter how much LLLT increases the activity of thyroid cells, the increased activity alone is impossible to normalize the thyroid function. Based on the result of this pilot study, LLLT's effect on thyroid autoantibodies should be examined in following studies to evaluate the potential of LLLT as a treatment for primary hypothyroidism.

CONFLICT OF INTEREST

Seung Hoon Woo is the Editor-in-Chief of the journal but was not involved in the review process of this manuscript. Phil-Sang Chung is an editorial board member of the journal but was not involved in the review process of this manuscript. Otherwise, there is no conflict of interest

to declare.

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