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ORIGINAL ARTICLE

Photobiomodulation therapy with an 830-nm light-emitting diode for the prevention of thyroidectomy scars: a randomized, double-blind, sham device-controlled clinical trial

Yul Hee Kim[1,2] · Hyeung Kyoo Kim[3] · Jee Woong Choi[1] · You Chan Kim[1]

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Abstract

This randomized, double-blind, and sham device-controlled trial aimed to evaluate the efficacy and safety of home-based photobiomodulation therapy using an 830-nm light-emitting diode (LED)-based device for the prevention of and pain relief from thyroidectomy scars. Participants were randomized to receive photobiomodulation therapy using an LED device or a sham device without an LED from 1 week postoperatively for 4 weeks. Scars were assessed using satisfaction scores, the numeric rating scale (NRS) score for pain, Global Assessment Scale (GAS), and Vancouver Scar Scale (VSS) scores. The scars were also assessed using a three-dimensional (3D) skin imaging device to detect color, height, pigmentation, and vascularity. Assessments were performed at the 1-, 3-, and 6-month follow-ups. Forty-three patients completed this trial with 21 patients in the treatment group and 22 patients in the control group. The treatment group showed significantly higher patient satisfaction and GAS scores and lower NRS and VSS scores than the control group at 6 months. Improvements in color variation, height, pigmentation, and vascularity at 6 months were greater in the treatment group than in the control group, although the differences were not significant. In conclusion, early application of 830-nm LED-based photobiomodulation treatment significantly prevents hypertrophic scar formation and reduces postoperative pain without noticeable adverse effects.

Keywords Photobiomodulation · Light-emitting diode (LED) · Hypertrophic scar · Thyroidectomy · Clinical trial

Introduction

A hypertrophic scar is a firm, raised scar at the site of injury that develops within 4–8 weeks of injury in areas of high tension. It tends to regress spontaneously within a few years; however, if it persists, it may cause pain and cosmetic problems [1]. Thyroidectomy scars have been recently recognized as an important dermatologic concern with a high incidence rate of 31.4% developing hypertrophic scar [2]; unlike other scars, they are located in the exposed area of the anterior neck, resulting in aesthetic and functional problems. Various interventions have been attempted to treat hypertrophic scars over a long time; however, these interventions do not result in complete resolution of the scars and may be associated with adverse events [3, 4].

Skin wound healing after an injury is a process that consists of three sequential phases: inflammation, proliferation, and regeneration [5]. Hypertrophic scar formation can occur owing to an abnormality in these processes. Once scar tissue matures, the surrounding tissue cannot regenerate normal dermal tissue [6]. Therefore, management in the early stages of wound healing before maturation of the scar is the most effective method to prevent hypertrophic scar formation. The most common management strategy comprises the use of occlusive dressing with a silicone gel sheet. However, this approach can induce adverse skin reactions such as persistent pruritus, skin rashes, and skin maceration, which rarely lead to complete resolution and reduce patient compliance [7–9]. To minimize patient discomfort, a topical silicone gel ointment has been tested; its effectiveness in preventing hypertrophic scar formation was noted to be similar to that

✉ You Chan Kim
maychan@ajou.ac.kr

[1] Department of Dermatology, School of Medicine, Ajou University, 164, World cup-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea

[2] Department of Medical Sciences, Graduate School of Ajou University, Suwon, Korea

[3] Department of Surgery, School of Medicine, Ajou University, Suwon, Korea

of the silicone gel sheet [10, 11]. A triamcinolone intralesional injection is often used for the treatment of hypertrophic scars; however, it is commonly associated with adverse events such as cutaneous atrophy, telangiectasia, and permanent hypopigmentation [12]. Recently, several studies have reported the efficacy of laser treatment, such as pulsed dye laser or light therapy, for treating and preventing hypertrophic scars [13]. However, there is no standardized protocol, and this approach is associated with problems related to cost and adverse events, such as pain and post-inflammatory hyperpigmentation [14].

Photobiomodulation is a treatment modality involving the use of low incident levels of visible to near-infrared light to alter biological activity by inducing nonthermal effects on exposed cells or tissues [15]. Photobiomodulation has been reported to reduce inflammation, promote wound healing, and treat neurological disorders and pain [16]. Several small studies have reported that photobiomodulation at both red and near-infrared wavelengths of light-emitting diode (LED) promoted wound healing; moreover, in vitro studies have demonstrated that red and near-infrared wavelengths of LED phototherapy can suppress fibroblast proliferation, which is important in the formation of hypertrophic scar [13, 17–20]. However, this approach required frequent treatments and visits to the hospital, which can reduce the compliance and satisfaction of patients. In addition, the prevention of thyroidectomy scars using photobiomodulation with home-based LED has not been previously reported. Therefore, this study aimed to investigate the use of photobiomodulation therapy with home-based 830-nm LED for the prevention of thyroidectomy scars for the first time concerning efficacy, safety, and pain relief.

Methods

Study design

This study was a single-center, randomized, sham device-controlled, double-blind clinical trial conducted at the Department of Dermatology, Ajou University Hospital, Suwon, Korea, over a 1-year period (March 2020 to March 2021). This trial was approved by our institutional review board (AJIRB-DEV-DE2-19–445). Written informed consent was obtained from each participant before their inclusion in the study.

Sample size calculation

A previous study was referred to calculate the sample size for this trial [18]. To demonstrate that the treatment group had a lower Vancouver scar scale (VSS) score than the control group, the sample size was calculated with the assumption that $\sigma^2 = 2.25$ with a difference of 1.5 between the treatment group and the control group. Accordingly, the authors decided to recruit approximately 20 participants in each group, accounting for a 20% drop-out rate.

Participant selection

Adults over 18 years of age who had undergone thyroidectomy performed by the same surgeon were included in this study. The exclusion criteria were as follows: history or family history of keloid formation, history of more than one thyroidectomy surgery, use of other treatments for scars, other skin diseases, and other diseases that may affect wound healing (e.g., diabetes).

Randomization and blinding

Participants were randomized to receive photobiomodulation therapy using either an 830-nm LED device or a sham device on their post-thyroidectomy wound using a randomization system. Both devices were outwardly indistinguishable, and a researcher who was not an outcome assessor distributed devices to participants according to random numbers. Throughout the study, both the participants and outcome assessors maintained their double-blind status.

Treatment protocol

Each participant was treated with PAEAN (WON TECH Co, Ltd., Daejeon, Korea), a curved 830-nm LED-based photobiomodulation device that was applied around the neck. The device consists of 14 LEDs of 830 nm and 4 LEDs of 650 nm for visual effects. The device for the treatment group emits 830-nm LEDs normally, while the device for the control group does not. The devices in the treatment and control groups emitted 650-nm light to indicate that light was being applied. The device was used daily for 30 min, involving nine cycles with each cycle including 80 s on and 100 s off. The 10th cycle (final cycle) involved 180 s on. The entire area of the LED on the neck was 14 cm^2. The 14 LEDs of 830 nm (bandwidth ± 20 nm) for the treatment group delivered a nominal irradiance of 5 mW/cm^2 for 900 s, resulting in a total dose of 4.5 J/cm^2. The 4 LEDs of 650 nm (bandwidth ± 7 nm) for the treatment and control groups delivered a nominal irradiance of 0.5 $mW/cm^2/s$, giving a total dose of 0.13 J/cm^2; the authors assumed that the amount of output energy for visual effects was small enough to be neglected. Thus, the effects of the 650-nm LEDs in the sham device on the scars in the control group could be excluded as potential confounders.

PAEAN was made of curved lines that fit along the flexion of the anterior neck, leading to parallel and even irradiation of the thyroidectomy scar (Supplementary Fig. 1). It has

been reported that, during the process of wound healing, the proliferative phase lasts for 2 to 4 weeks after the injury, while the remodeling phase varies greatly from 4 weeks to 2 years after the injury [5]. Controlling the inflammatory and proliferative stages of wound healing is important for preventing hypertrophic scar formation [21]. Thus, the authors assumed that a 4-week treatment period was sufficient for this purpose, and the period of photobiomodulation therapy was set accordingly. Patients used the device daily for 4 weeks from 1 week postoperatively at home, and an additional topical scar gel was applied daily before sleeping for 6 months after the surgery. All patients used the same protection glasses while using the device to protect their eyes from LEDs. The patients were trained and understood how to use the device when they received the device, and they contacted the researchers immediately if they had any questions while using the machine to hear the explanation. No other treatment was attempted during the study period.

Assessment

Scar evaluation was performed on day 1 and 1, 3, and 6 months postoperatively in the treatment group and control group; however, the measurement data from postoperative day 1 were excluded from the analysis considering the inflammation and bleeding seen immediately after surgery. High-resolution digital photographs were taken at each visit. The VSS (Table 1) and Global Assessment Scale (GAS) scores for the final cosmetic results were measured by two independent dermatologists, who were blinded to group assignment. The VSS is used to assess four variables: vascularity, height, pliability, and pigmentation; the score ranges from 0 to 13 [22]. The GAS is used to evaluate the overall improvement at 6 months, using a 4-point scale (GAS; poor = 1, fair = 2, good = 3, and excellent = 4) [23]. Patients reported their satisfaction and overall postoperative pain at 6 months. A 4-point scale (unsatisfied = 1, slightly satisfied = 2, satisfied = 3, and very satisfied = 4) was used to assess satisfaction for overall treatment outcomes. Pain was evaluated using an 11-point numeric rating scale (NRS), with 0 representing "no pain" and 10 representing "worst pain imaginable" [24]. Complaints of adverse events reported at any time during the study period were recorded.

For objective evaluation, the authors used a 3D skin imaging device (Antera 3D™; Mirvax Limited, Dublin, Ireland), and the means of height, hemoglobin, and melanin values were calculated by selecting regions to match the linear scar shape. The mean height was calculated by dividing the volume of scar elevation by the affected scar area, as measured by the Antera 3D™. The authors set the values obtained at 1 month as baseline values and evaluated each measurement according to baseline values to detect changes in individual scars.

Table 1 Vancouver Scar Scale score

	Scar characteristic	Score
Pigmentation	Normal	0
	Hypopigmentation	1
	Hyperpigmentation	2
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pliability	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Ropes	4
	Contracture	5
Height	Flat	0
	< 2 mm	1
	2–5 mm	2
	> 5 mm	3
Total score	13	

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences 21.0 (SPSS; IBM Corp., Armonk, NY, USA). Results are expressed as mean and standard deviation or median and interquartile range. The Friedman test was used to analyze changes in a scar over time. The Student *t*-test and Mann–Whitney *U* test, corrected with Bonferroni adjustment, were used to compare the two groups. Notable results were presented in figures and tables with more detailed numerical values. *P* values < 0.05 indicated a significant difference.

Results

Forty-four patients who underwent thyroidectomy from March to September 2020 at our institution were recruited in this prospective study based on the inclusion and exclusion criteria. They were randomized to either of the two groups; one patient in the treatment group was lost to follow-up. The final number of patients was 21 in the treatment group and 22 in the control group (Fig. 1). No significant differences were found between the treatment and control groups at baseline in terms of demographic variables (i.e., sex and age), Fitzpatrick skin type, and surgery method (Table 2).

The median patient satisfaction score at 6 months postoperatively was significantly higher in the treatment group than in the control group (median 4, interquartile range (IQR) 3–4 vs. median 3, IQR 2–3, $p = 0.008$, Fig. 2A). The median

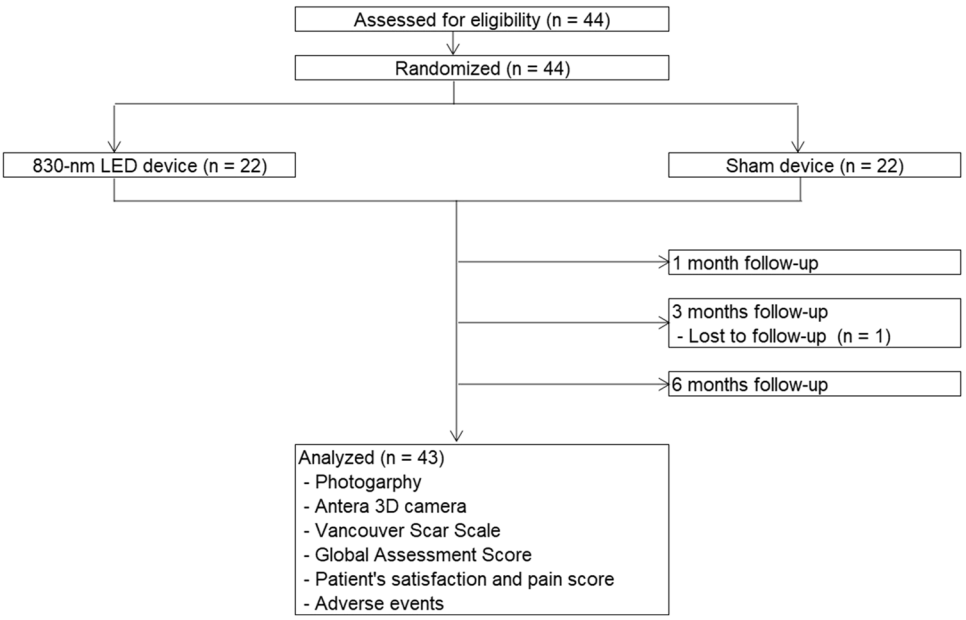

Fig. 1 Flow diagram of the study design

Table 2 Demographic and clinical characteristics of the study population

Characteristics	Treatment group	Control group	p^a
Case no	21	22	
Sex, *N* (%)			0.444
Female	14 (66.7)	17 (77.2)	
Age, mean (SD), years old	42.0 (7.08)	46.9 (10.74)	0.083
Fitzpatrick skin type, median (IQR)	4 (1)	3 (1)	0.449
Operation method, *N* (%)			0.16
Total thyroidectomy	6 (28.6)	4 (18.1)	
Partial thyroidectomy	15 (71.4)	15 (68.2)	
Others	0 (0)	3 (13.6)	

SD, standard deviation; *IQR*, interquartile range

[a]Student *t*-test and Mann–Whitney *U* test

overall pain NRS score at 6 months was significantly lower in the treatment group than in the control group (median 0, IQR 0–1 vs. median 1, IQR 0.75–2, $p = 0.005$, Fig. 2B). Furthermore, this trend in the pain NRS scores was the same at all measured timepoints, i.e., 1, 3, and 6 months postoperatively (Supplementary Fig. 2). The median GAS score was significantly higher (median 4, IQR 3–4 vs. median 3, IQR 2–3, $p = 0.002$, Fig. 2C) and the median VSS score was significantly lower (median 0, IQR 0–2 vs. median 2, IQR 2–4, $p = 0.004$, Fig. 2D) in the treatment group than in the control group. Figure 3 represented the clinical photographs comparing the treatment and control groups at 1 and 6 months of follow-up.

We measured the values of color variation, height, melanin levels, and vascularity of thyroidectomy scar using the Antera 3D™. The values for height were collected as absolute values at subsequent follow-ups based on preoperative skin; by contrast, for color variation, melanin levels, and vascularity, the change ratios were calculated by dividing the values at 6 months by the baseline values (at 1 month) postoperatively. The mean change ratios for color variation (mean ± standard deviation (SD); -17.32 ± 3.21 vs -14.08 ± 3.75, $p = 0.52$, Fig. 4A), height (mean ± SD; -16.09 ± 9.88 vs -5.05 ± 7.11, $p = 0.37$, Fig. 4B), melanin levels (mean ± SD; -10.8 ± 1.11 vs -7.97 ± 1.47, $p = 0.13$, Fig. 4C), and vascularity (mean ± SD; -25.56 ± 2.39 vs -24.62 ± 3.17, $p = 0.81$, Fig. 4D) after 6 months (comparison: baseline) tended to indicate greater improvement in the treatment group than in the control group, but no significant differences were noted.

No significant adverse events, such as heating sensation, pain, and skin rash, were reported during the study period.

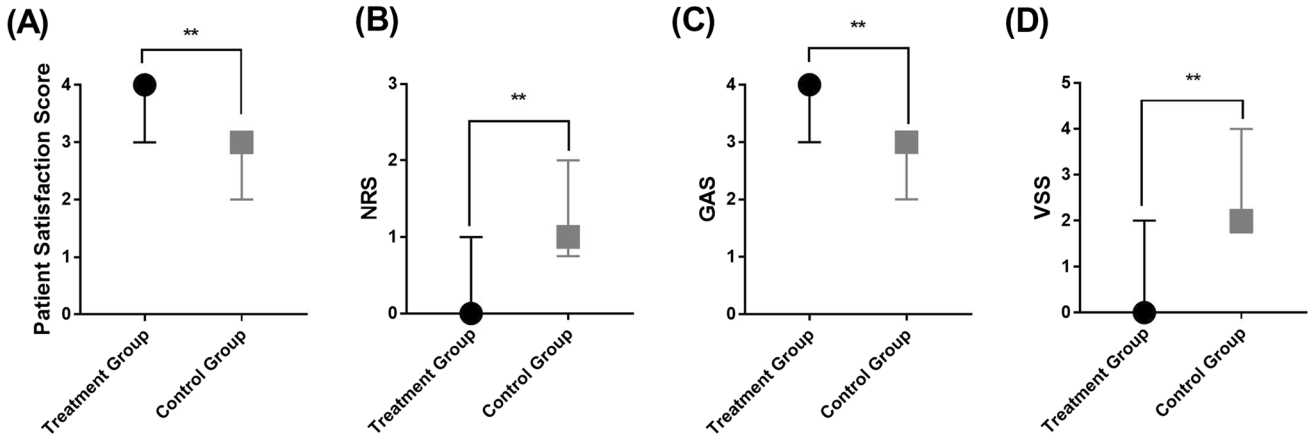

Fig. 2 Comparative results between the treatment group and the control group. **A** Patient satisfaction scores, **B** Pain Numeric Rating Scale (NRS) scores, **C** Global Assessment Scale (GAS) scores, and **D** Vancouver Scar Scale (VSS) scores at 6 months. All results were different between the two groups. Data were analyzed by the Mann–Whitney *U* test and expressed as medians and interquartile range. Lines above bars indicate statistical comparisons with significant differences between categories (**$p < 0.01$)

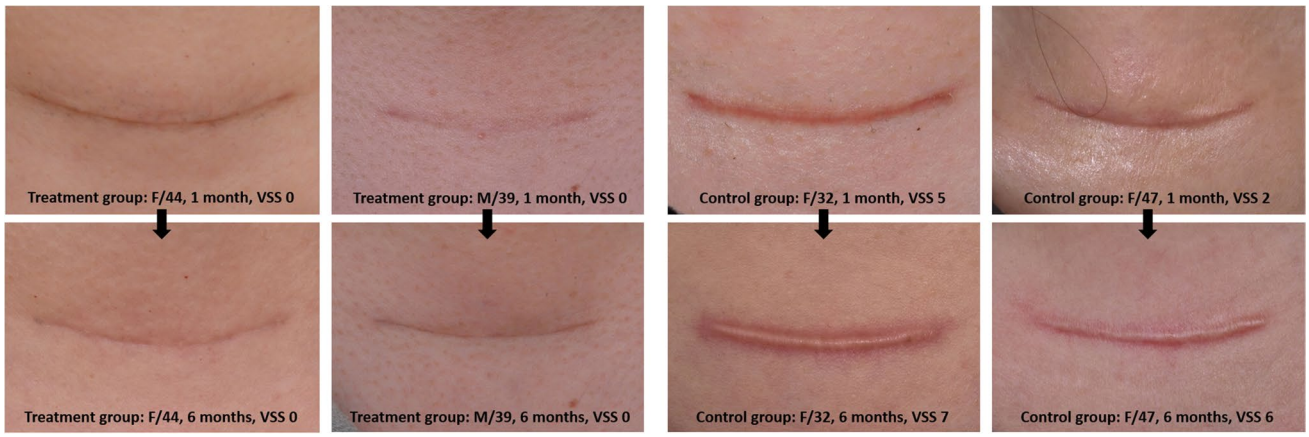

Fig. 3 Representative clinical photographs comparing the treatment and control groups at 1 and 6 months of follow-up

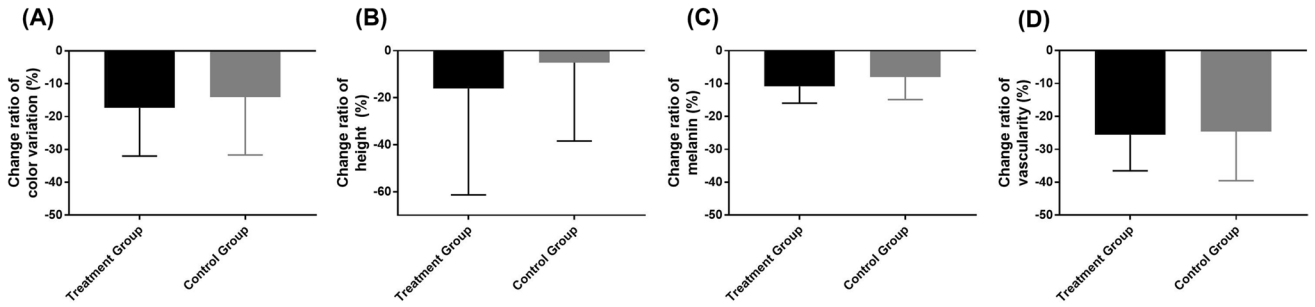

Fig. 4 Comparison of changes in scar-related values obtained using the Antera 3D™. **A** Color variation, **B** height, **C** melanin, and **D** vascularity at 6 months. Data were analyzed by Student *t*-test and expressed as means and standard deviation

Discussion

Multiple studies have reported the efficacy of laser- and light-based treatment for wound healing [13]. Among them, photobiomodulation, especially that with red and infrared wavelengths of LED, has shown efficacy for wound healing and prevention of skin scarring [19, 25]. Various data have established the efficacy of 830 nm in enhancing wound healing [19]. Postoperative scars, such as those due to thyroidectomy, result from deep wounds that involve the skin and the subcutaneous layer; thus, special attention is needed as these can develop into hypertrophic scars more frequently than other superficial scars [26]. The 830-nm LEDs penetrate deeper than other near-infrared wavelengths; thus, 830-nm LEDs were expected to be more effective in pain attenuation and healing of deep wounds, including postoperative scars involving subcutaneous layers [20]. Park et al. reported that 830-nm LED photobiomodulation therapy was effective for the prevention of hypertrophic scars post-thyroidectomy in Asian adults [18]. However, the treatment protocol of this study required patients to visit dermatologic clinics daily in the first week and three times a week for the next 3 weeks; therefore, patients needed to visit the hospital frequently, resulting in increased economic and time burdens and reduced compliance with treatment in clinical practice. To our knowledge, the present study is the first to evaluate the efficacy of home-based 830-nm LED-based photobiomodulation for the prevention of thyroidectomy scars. Furthermore, this study used various subjective and objective measures to evaluate the improvement in these scars.

Patient satisfaction was higher and postoperative pain was lower in the treatment group than in the control group. Given the double-blind design of this study, these results may be considered reliable, with relatively less bias. In interviews regarding patient satisfaction, patients responded that the device was convenient to use at home and saved transportation and medical expenses, resulting in less time and economic burdens. They also reported lower pain and fewer side effects with this treatment than those with other treatments, such as triamcinolone intralesional injection and pulsed dye laser therapy, which contributed to higher satisfaction.

Various studies have demonstrated that photobiomodulation reduced pain in those with musculoskeletal disorders, such as chronic neck pain, back pain, and arthritis [27, 28]. In the dermatological domain, photobiomodulation has been reported to be effective for pain relief in herpes labialis and oral mucositis [29, 30]. Only a few studies have reported on postoperative pain relief, such as that after inguinal herniation surgery and cesarean surgery [31, 32]. The mechanism underlying pain relief after photobiomodulation is as follows: peripheral nerves, which are located superficially in the skin, can be easily exposed to the wavelengths emitted by the LED; with a sufficient dose, irradiation can inhibit the action potential of nerves and cause an approximately 30% nerve block within 10–20 min, resulting in analgesic effects [33]. Photobiomodulation is also considered helpful for pain relief by reducing the concentration of inflammatory markers, such as cyclooxygenase-2 and prostaglandin E2 [34]. Moreover, as previously mentioned, wavelengths of 830 nm penetrate deeper into the subcutaneous layer than other wavelengths, exerting further effects to the sensory nerve in the skin. To our knowledge, this study is the first to demonstrate that 830-nm LED-based photobiomodulation reduces postoperative and overall pain at 6 months at the thyroidectomy scar. In addition to the conventional mechanisms for pain relief through photobiomodulation, the authors assume that photobiomodulation inhibits the proliferation of fibroblasts to reduce fibrosis, thereby reducing the pliability and stretching pain of the scar and surrounding tissues [17]. Therefore, photobiomodulation is considered to help relieve pain at postoperative wounds involving injury to subcutaneous layers, including thyroidectomy scars.

Wound healing is a complex mechanism involving various factors. A previous in vitro study revealed that infrared photobiomodulation inhibited the proliferation of fibroblasts, which play an important role in wound healing and skin fibrosis [17]. Another study showed that photobiomodulation modulated the expression of insulin-like growth factor 1 and transforming growth factor (TGF)-β1 during striated muscle repair [35]. TGF-β1 plays a key role in collagen overproduction and excess deposition by fibroblasts during scar formation, and photobiomodulation is expected to have a similar effect on TGF-β1 in hypertrophic scar [26]. In addition, early intervention before the scar enters the remodeling phase may show better cosmetic results than treatment after scar maturation. Our study also demonstrated similar results, showing a significant improvement in GAS and VSS scores in the treatment group, compared with those in the control group. The change ratios of color variation, height, vascularity, and pigmentation were much lower in the treatment group than in the control group at 6 months; however, no significant differences were noted. There may be several explanations for these results. First, the "pliability" of the scar accounts for a high percentage of the VSS score, but this is not measured by the Antera 3D™. Although the texture and rigidity of the scar play an important role in the cosmetic outcomes of hypertrophic scars, the Antera 3D™ may not measure these important outcomes, as it only measures the levels of hemoglobin and melanin, not pliability. Second, the protocol for the assessment using the Antera 3D™

has not yet been established; therefore, compared with the VSS, its use as a universal scar assessment tool may still be limited. In addition, the Antera 3D™ may not evaluate the overall characteristics of the scar if the wound is larger than the device. Thus, the VSS may be considered a more widely used and reliable tool for scar assessment, because the standard tool for objective measurement of scars has not yet been established.

This study has some limitations. First, because the patients used the device at home, it was not possible to determine whether the patients used it appropriately, despite providing sufficient education regarding device use. Second, we did not calculate the effect size of some variables due to performing the nonparametric test. However, our study has several strengths. First, the participants were randomized, and the study was double-blinded, with fewer biases for both patients and researchers. Second, no other interventions, except the scar gel, were used, and no statistical demographic differences existed between the two groups, and the surgical procedures were performed by the same surgeon. These factors resulted in reliable results. Third, this study included a relatively long follow-up period of 6 months, compared with previous studies, to evaluate changes in scars in the same patients. Finally, the LED device could be used conveniently at home for 30 min a day, which resulted in patient satisfaction and cost-effectiveness. In addition, the device was curved to fit the anterior neck structure to ensure that all scar points received the same amount of light.

In conclusion, the results of this study demonstrated that early application of 830-nm LED-based photobiomodulation for 4 weeks following thyroidectomy was effective in the acceleration of wound healing, resulting in preventing hypertrophic scar formation and relieving pain. In addition, this home-use LED device was relatively comfortable, safe, and cost-effective. However, more studies comparing the outcomes of hypertrophic scars among different treatment periods are needed to determine the most optimal period for an 830-nm LED-based photobiomodulation. Furthermore, further studies are needed to evaluate the mechanisms by which 830-nm LED-based photobiomodulation is involved in the prevention of hypertrophic scars and related pain relief.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10103-022-03637-6.

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Declarations

Ethical approval The study was approved by the institutional ethics committee from Ajou University Medical Center of Suwon, Korea (AJIRB-DEV-DE2-19–445).

Conflict of interest The authors declare no competing interests.

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