

## SHORT REPORT

# Split-face comparative trial of 785-nm picosecond neodymium: yttrium-aluminum-garnet laser and precision cryotherapy combination treatment for facial benign pigmented lesions

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## Abstract

Cryotherapy (or cryosurgery) has been performed to treat various skin lesions in the field of dermatology; however, to the best of our knowledge, no study has investigated its efficacy and safety for benign pigmented lesions. Therefore, we conducted a split-face study to evaluate the efficacy and safety of cryotherapy in the treatment of benign pigmented lesions. A total of five subjects were included. Picosecond laser therapy was performed to treat the whole face and cryotherapy for half the face. Four weeks after completing the treatment sessions, patients showed more clinical improvement on the laser and cryotherapy combination treatment side than on the laser-only side, with no adverse events. Our study demonstrated that cryotherapy is a potential adjuvant therapeutic modality for benign pigmented lesions.

## KEYWORDS

cryosurgery, cryotherapy, laser, pigmentation

## 1 | INTRODUCTION

Cryotherapy has been performed for various skin lesions since the first cryogens were developed.<sup>1–3</sup> Recently, cryotherapy has been performed in dermatology for body contouring by non-invasive fat removal with selective cryolysis.<sup>4</sup> However, there has been a lack of studies investigating the role of cryotherapy in the treatment of pigmentations, which are cosmetically important. Herein, we report cases of cryotherapy as a potential treatment for pigmented lesions.

### 1.1 | Case reports

Five healthy Asian participants aged 20–40 years with Fitzpatrick skin types III and IV were enrolled. The effectiveness and safety of cryotherapy were assessed using a split-face comparison. The whole face of all patients was treated with a 600-ps pulse using a 785-nm

neodymium: yttrium-aluminum-garnet laser (Helios IV 785™; Laseroptek, Seongnam, Republic of Korea). A total of 1000 pulses of laser therapy were administered using a single-parameter diffractive optical element (DOE) with a fluence of 0.2 J/cm<sup>2</sup>, spot size of 5 × 5 mm, and frequency of 10 Hz. Immediately after laser treatment, cryotherapy was performed on half the face. We used a newly developed portable cryotherapy device (CryoVIVE®, RecensMedical, Ulsan, Republic of Korea), which uses CO<sub>2</sub> gas for contact cooling, and a thermo-sensor enabled real-time monitoring of the temperature and duration (Figure S1). We set the temperature to 0–1°C, allowed for slow cooling, and equally applied cryotherapy on half the face. Cryotherapy was performed for 3–4 min, and freezing and thawing were repeated. A total of 5–6 treatment sessions with 2-week intervals were performed for each patient. During the treatment period, all patients were educated to use the same cosmetic products that they had been using before the treatment and to avoid other laser treatments and skincare or esthetic procedures.

Photographs of each subject were taken at baseline, before every treatment session, and after 4 weeks of treatment using an imaging

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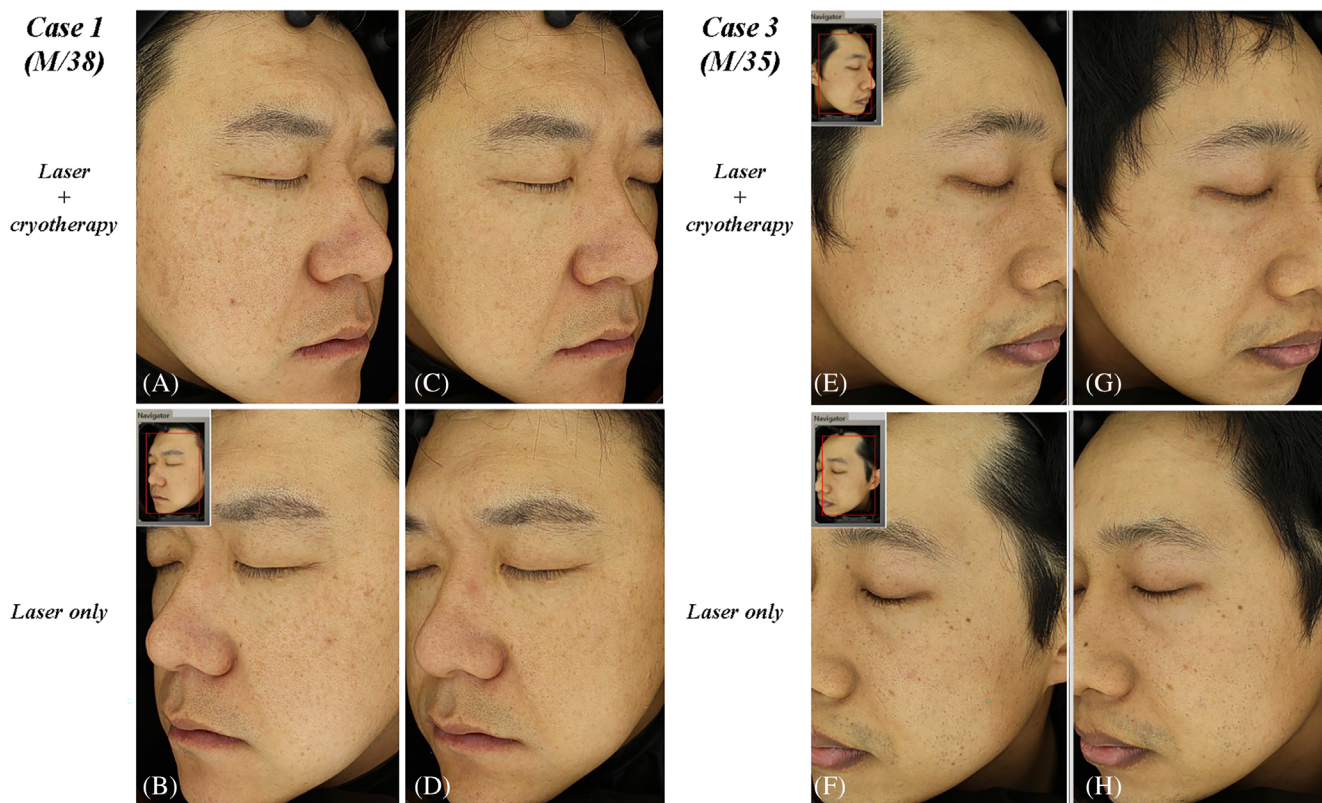
tool (Mark-Vu<sup>®</sup>; PSI PLUS, Suwon, Republic of Korea). Two independent evaluators assessed the photographs of the patients and reached a consensus using a five-point grading scale at 4 weeks after completing all sessions (poor, Grade 1 = no improvement; mild, Grade 2 = 1%–25% improvement; moderate, Grade 3 = 26%–50% improvement; good, Grade 4 = 51%–75% improvement; and excellent, Grade 5 = 76%–100% improvement). Patient satisfaction was assessed 4 weeks after completing all sessions (1, unsatisfied; 2, slightly unsatisfied; 3, neutral; 4, slightly satisfied; and 5, satisfied). Any adverse events, such as dyspigmentation, pain, erythema, blistering, and edema, were observed and reported by both subjects and physicians during the laser treatment and at each visit. Written informed consent was obtained from all patients for the publication of their images and case details.

## 2 | DISCUSSION

In the field of dermatology, cooling that is not for therapeutic purposes is commonly employed to protect the epidermis and skin during treatment.<sup>5</sup> Cooling is used for therapeutic purposes in actinic keratosis, warts, superficial tumors, and even malignant lesions by non-selective tissue destruction, in terms of “cryosurgery” or “the

cryosurgical technique.”<sup>6,7</sup> Single or multiple freeze/thaw cycle(s) induce irreversible damage to cells when the tissue temperature reaches far below the freezing point of the tissue water.<sup>8</sup> A relatively recent application of cryotherapy is cryolipolysis. With the concept that lipid-rich tissues are more susceptible to cold injury than the surrounding water-rich tissues, an applicator set at a specific cooling temperature for a preset time period targets adipocytes while sparing the skin, nerves, vessels, and muscles.<sup>4</sup> However, there are insufficient studies or reports investigating the efficacy of cryotherapy on benign pigmented lesions. Although some studies have reported on the use of cryotherapy for lentigines, concerns of adverse events, including depigmentation and burns, remain.<sup>9,10</sup> Hypopigmentation is one of the most common adverse effects of cryotherapy; it indicates that melanocytes can be destroyed by cryotherapy. At the same time, it is plausible that the application of cryotherapy can extend to benign pigmented lesions.

We conducted a split-face study with whole-face laser treatment considering the experimental nature of our study, as there has been no parameter for treatment with cryotherapy alone. Picosecond lasers have been reported to be safe and effective in the treatment of pigmented lesions.<sup>11</sup> Compared with laser treatment alone, laser and cryotherapy combination treatment significantly improved pigmented lesions on the face in five patients (Figure 1). Additionally, patient



**FIGURE 1** Case 1. (A, B) Before treatment. Multiple pigmented macules and patches on the face. (C, D) Four weeks after six treatment sessions, more clinical improvement of the lesions was observed on the (C) laser and cryotherapy combination treatment side (“excellent”) than on the (D) laser-only side (“moderate”). Case 3. (E, F) Before treatment. Multiple pigmented macules and patches on the face. (G, H) Four weeks after five treatment sessions, more clinical improvement of the lesions was observed on (G) the laser and cryotherapy combination treatment side (“excellent”) than on the (H) laser-only side (“mild”)

**TABLE 1** History of the five subjects and the outcomes of split-face treatment

	Sex/age (years)	Fitzpatrick skin type	Comorbidity	Total treatment sessions	Treatment response		Patient satisfaction		Side effects
					Laser + cryotherapy	Laser only	Laser + cryotherapy	Laser only	
Subject 1	M/38	4	None	6	5	3	5	4	None
Subject 2	F/30	3	None	5	3	1	4	3	None
Subject 3	M/35	4	None	5	5	2	5	3	None
Subject 4	M/32	4	None	6	4	2	4	3	None
Subject 5	F/28	3	None	5	4	2	5	4	None

satisfaction was higher with combination therapy than with laser therapy alone without any adverse events (Table 1). Despite its complex effects, one plausible mechanism of cryotherapy in our study is that the freezing response varies among different cell types in the epidermis and dermis. Cryotherapy, at  $-20^{\circ}\text{C}$  is widely considered lethal for all cells as it leads to cell necrosis. In this clinical trial, we set the target temperature to  $0$ – $1^{\circ}\text{C}$ , which is relatively higher than that suggested by Anderson et al. to induce melanocyte loss while sparing the surrounding keratinocytes.<sup>12</sup> In their attempts to determine the parameters to induce selective melanocyte death, Anderson et al. demonstrated that epidermal melanocytes can be selectively killed by topical application of cold temperatures (less than  $-7.5^{\circ}\text{C}$ ) to the skin for  $\geq 10$  min. However, because post-inflammatory hyperpigmentation or hypopigmentation tends to occur in darker-skinned patients with greater frequency and severity, we supposed that there was a risk of applying temperatures colder than  $-7.5^{\circ}\text{C}$  for several minutes without a standard parameter.<sup>13,14</sup> Two suggested mechanisms of injury associated with cryosurgery were the immediate effects of freezing on the cells and delayed effects in the warming cycle. Irreversible damage to the treated tissue occurs because of intracellular ice formation. The degree of damage depends on the cooling rate and the minimum temperature achieved. Inflammation develops during 24 h after treatment, further contributing to the destruction of the lesion through immunologically mediated mechanisms. Therefore, we evenly applied cryotherapy to half the face using a portable device and delayed cooling, ensuring that ice crystals were not formed by fast freezing/slow thawing. With the existing cryotherapy technology, the cooling temperature is uncontrollable and the therapeutic temperature cannot be achieved instantly. These limitations of the current cryotherapy technology can result in inadvertent tissue damage as well as variable treatment outcomes. The device used in our study allows the cryotherapy protocol to be predetermined and controlled in an unprecedentedly precise and rapid manner. As soon as the treatment begins, the desired temperature is achieved instantaneously, without depending on one's experience or skill to manually adjust the application distance and duration. Because of the precise temperature

control, it serves as a safer, more effective, and reliable cryotherapy option for physicians and patients.

Despite the effects of cryotherapy in our study, the number of subjects included was small. In addition, we did not make use of equipment such as a mexameter, which reflects objective color changes. Further studies are recommended to standardize the maximum cooling temperature, duration of treatment, and freeze/thaw cycles of cryotherapy. Nevertheless, we believe that our study suggests cryotherapy to be a potential modality for the clinical treatment of benign pigmented lesions.

We found that clinical improvement of pigmented lesions and satisfaction of subjects were higher on the laser and cryotherapy combination treatment side than on the laser-only side. Further well-designed studies involving more patients and a longer monitoring period are recommended to evaluate the therapeutic effect and safety of cryotherapy alone on pigmented lesions.

#### CONFLICT OF INTEREST

Gun-Ho Kim is Chief Executive Officer of RecensMedical Inc.

#### AUTHOR CONTRIBUTIONS

**Jae Wan Park:** Conceptualization, methodology, original draft, investigation. **Hye Sung Han:** Validation, investigation, original draft. **Young Gue Koh:** Validation, investigation, supervision. **Suk Bae Seo:** Review and editing manuscript, investigation, supervision. **Gun-Ho Kim:** Conceptualization, methodology, review and editing manuscript. **Kui Young Park:** Conceptualization, methodology, review and editing manuscript.

#### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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