SHORT COMMUNICATION

Controlled Single Freezing Cryotherapy for Mild Facial Actinic Keratosis

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Cryotherapy is the treatment of choice for actinic keratosis (AK) and has high efficacy rates (1, 2). However, owing to the inconsistency of cryotherapy, a range of lesion cure rates and various adverse events have been reported (3). Based on the cell death temperature of keratinocytes, treatment parameters, including freeze time, number of freeze-thaw cycles, and margins, have been suggested in the literature to optimize the effects of cryotherapy (4). However, since manual control of cryotherapy cannot be performed with an appropriate and consistent intensity, it is difficult to follow the exact treatment time and to ascertain whether the intended temperature has been attained. Therefore, it is also difficult to predict outcomes and adverse events. To overcome these limitations, temperature- and time-controlled cryotherapy devices (TCD, Cutis-Cool™; RecensMedical, Ulsan, Korea), which use carbon dioxide as a cryogen, have been developed recently. The TCD enables precise and consistent cryotherapy to be performed by setting the treatment parameters, such as the number of freezing cycles, skin surface temperature and spraying time. The TCD administers cryotherapy in a freezing area of approximately 10-mm diameter for a set time at a constant intensity to reach the set skin surface temperature (5). (Video S1). The aim of this study was to evaluate the efficacy and safety of the TCD for mild facial AK and establish cornerstone cryotherapy parameters for mild facial AK.

MATERIALS AND METHODS

This study retrospectively analysed the medical records and clinical photographs of patients diagnosed with mild facial AK and treated with the TCD who visited the Kyungpook National University Hospital, a tertiary referral centre in South Korea, between May 2020 and November 2021. The patients were diagnosed clinically or histologically with mild facial AK (slightly palpable and more felt than seen) (6) and treated with the TCD at –20°C for 20 s in a single freeze-thaw cycle. Freezing areas overlapped by 20% while sufficiently covering the entire target lesion. After 4 weeks of treatment, the treatment response of lesions was evaluated using medical records and clinical photographs. Complete remission was defined as the disappearance of the lesion on skin biopsy or no lesion remaining on the clinical photographs, with a smooth surface when touched by a finger. The treatment was repeated every 4 weeks until complete remission was achieved. Four weeks after the first treatment (4WFT), the cure rate and adverse events were assessed. The cure rate, recurrence rate, adverse events, and cosmetic outcomes were assessed 12 and 24 weeks after the last treatment (12WLT and 24WLT, respectively). All adverse events that occurred were recorded as responses to open-ended questions, and pain after treatment was assessed using a visual analogue scale (VAS 0–10). Cosmetic outcomes were assessed by the patients themselves and by 2 dermatologists using clinical photographs and graded as follows: excellent: no or mild redness or change in pigmentation; good: moderate redness or a change in pigmentation; fair: slight-to-moderate scarring, atrophy, or induration; poor: extensive scarring, atrophy, or induration. Patients who did not visit the hospital for regular follow-ups or for whom clinical photographs were not taken were excluded. This study was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH 2022-02-003).

RESULTS

Twenty-three patients with a total of 38 lesions were included in this retrospective study. The mean age of the patients was 75.7 years, and Fitzpatrick skin phototypes III (8.7%) and IV (91.3%) were predominant. The mean ± standard deviation (SD) treatment number was 1.13 ± 0.5. Of the total 38 lesions, 3 were retreated, 2 of which were treated 3 times in total and 1 lesion was treated 2 times in total. Complete remission rates at 4WFT, 12WLT, and 24WLT were 92.1%, 97.4%, and 94.6%, respectively (**Fig. 1**). Recurrence occurred in only 1 lesion (2.6%) at 12WLT and in 2 lesions (5.4%) at 24WLT. Serious adverse events were not observed. Only pain (100%; mean ± SD VAS score, 3.84 ± 1.76) during or

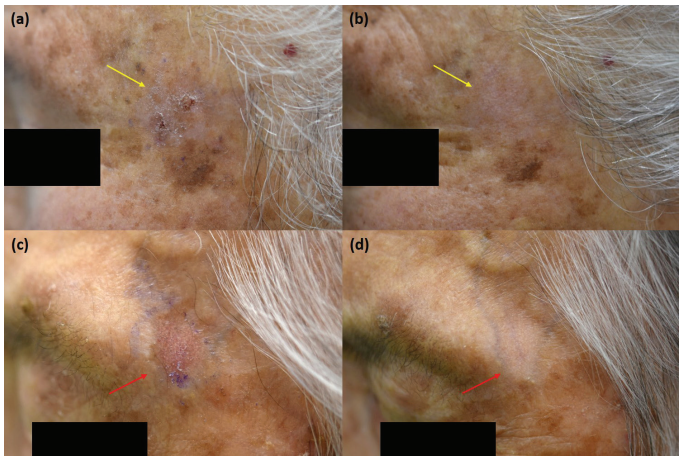

Fig. 1. (a) Solitary hyperkeratotic walnut-sized mild actinic keratosis on the left temple before treatment. (b) Complete lesion remission 24 weeks after single treatment (*yellow arrow*). (c) Solitary hyperkeratotic erythematous bean-sized mild actinic keratosis on the left temple before treatment. (d) Complete lesion remission 24 weeks after single treatment (*red arrow*).

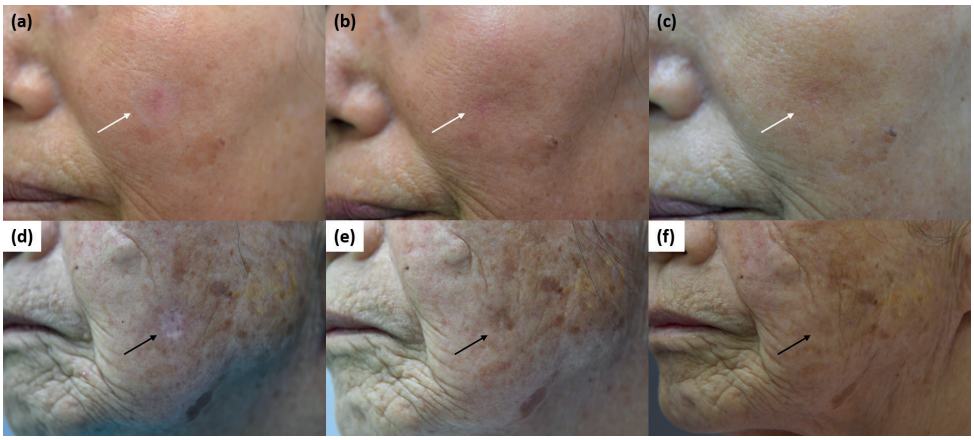

Fig. 2. (a) Erythema at the maximal state 4 weeks after the first treatment. Improvement of erythema at (b) 12 weeks and (c) 24 weeks after the last treatment (*white arrow*). (d) Hypopigmentation 4 weeks after the first treatment. Improvement of hypopigmentation at (e) 12 weeks and (f) 24 weeks after the last treatment (*black arrow*).

immediately after the treatment, erythema, and hypopigmentation were observed. The erythema rate decreased significantly from 31.6% at 4WFT to 5.3% at 12WLT to 0.0% at 24WLT, whereas the hypopigmentation rate decreased slightly from 23.7% to 23.7% to 10.0% (**Fig. 2**). As for the cosmetic outcomes at 24WLT, 91.3% of the patient responses were good or excellent (34.8% and 56.5%, respectively), and 100% of the investigator assessments demonstrated good or excellent results (30.4% and 69.6%, respectively).

DISCUSSION

Cryotherapy parameters for AK differ depending on the clinical grade of the lesions (1). Mild or moderate AK corresponding to grades I and II in Olsen's classification is generally treated with a freezing time of 5–20 s, with 1 freeze-thaw cycle and a margin of <2 mm (1, 4). For thicker and larger lesions, a longer freezing time is required (1). However, the manual cryotherapy makes it difficult to follow the guidelines because of its inconsistent intensity. Moreover, despite the fact that low temperature is an important mechanism of action in cryotherapy, there is no standard treatment temperature for cryotherapy, and a few studies have reported varying treatment responses (cure rate 66.7–100%) (**Table I**; 7–14). However, with the TCD, it was possible to deliver precise and consistent cryotherapy by controlling the treatment temperature and time. Therefore, we attempted to obtain effective and safe treatment parameters using the TCD. In an unpublished pilot study, we noticed that performing cryotherapy at –20°C for 20 s in a single freeze-thaw cycle is more effective than performing at other parameters, while minimizing the side-effects of treating mild facial AK. Therefore, we attempted to confirm that these parameters are effective and safe for the treatment of mild facial AK. The current study confirmed that the parameters were sufficiently effective, and the cure rates were not inferior to those reported in previous studies (Table I). However, care must be taken when comparing the cure rates of the current study with those of previous studies. Each previous study had a different follow-up period (minimum 1 week; maximum 8.5 years; mean ± SD 11.38 ± 25.4 months), did not specify the freezing method or time, and had varying severities of AK (Table I).

As cryotherapy intentionally damages tissue for secondary healing, it has potential complications and adverse events (4). During cryotherapy, localized burning pain occurs immediately and usually ends within 1 h, followed by erythema and oedema (4). After 12–36 h, serous or haemorrhagic vesicles develop, and after 1–2 weeks, crust forms (1, 4). Owing to the susceptibility of melanocytes to freezing, hypopigmentation

Table I. Summary of recent studies on the efficacy of cryotherapy in actinic keratosis

Study	Severity of AK	Freeze time	Temperature	Freeze-thaw cycle, *n*	Follow-up time	Cure rate (%)
Lubritz et al. (7), 1982	N/S	N/S	N/S	N/S	1–8.5 years	98.8
Szeimies et al. (8), 2002	Mild, moderate, severe	Mean of 24 s	N/S	2	12 weeks	75.3
Freeman et al. (9), 2003	Mild, moderate	Based on the diameter of lesion: < 10 mm, mean of 12 s 10–20 mm, mean of 16 s >20 mm, mean of 26 s	N/S	1	12 weeks	68.3
Thai et al. (2), 2004	Mild, moderate	2 s–1 min 30 s	N/S	1	12 weeks	67.2
Morton et al. (10), 2006	Mild, moderate	Mean of 16 s	N/S	2	12 weeks, 24 weeks	75.0, 85.0
Krawtchenko et al. (11), 2007	N/S	20–40 s	N/S	1	6 weeks	68.0
Kaufmann et al. (12), 2008	Mild, moderate	Mean of 20 s	N/S	2	24 weeks	88.0
Hauschild et al. (13), 2009	Mild, moderate	5–10 s	N/S	1	12 weeks	76.6
Goldberg et al. (3), 2010	N/S	5–10 s	–5 °C	1	1 week, 6 weeks	66.7, 100.0
Zane et al. (14), 2014	Mild, moderate, severe	10–20 s	N/S	1	12 weeks, 1 year	78.2, 66.8
Current study	Mild	20 s	–20 °C	1	12 weeks, 24 weeks	97.4, 94.6

N/S: not specified.

or hyperpigmentation can develop (15). In the current study, it is noteworthy that less hyper/hypopigmentation occurred after this treatment despite Fitzpatrick skin phototypes III–VI, which are prone to develop post-inflammatory pigmentation. The TCD resulted in only mild adverse events, including pain, erythema, and hypopigmentation, which were all acceptable to the patients and investigators. No serious adverse events were observed, suggesting that TCD treatment at –20 °C for 20 s is safer and more predictable than the existing cryotherapy methods.

In conclusion, TCD treatment at –20°C for 20 s is an effective, safe, and predictable treatment for mild facial AK. This study will help establish standard cryotherapy parameters for AK with other severities or at other sites.

The authors have no conflicts of interest to declare.

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