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Targeted precision cryotherapy for acne vulgaris

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Abstract

Background: Acne vulgaris poses a significant dermatological challenge, necessitating alternative treatments due to limitations and side effects associated with current therapies. This pilot clinical trial investigated the feasibility and efficacy of precision cryotherapy for acne vulgaris.

Methods: A total of 20 volunteers underwent targeted precision cryotherapy using a carbon dioxide-based device. Treatment outcomes were assessed using various parameters, including Investigator Global Assessment (IGA) score, acne lesion count, erythema index (EI), global evaluation score, and participant satisfaction. Safety monitoring included adverse event reporting and physical examination.

Results: Precision cryotherapy demonstrated a significant reduction (90.25%) in the acne lesion count by week 4, with clinical improvement indicated by IGA score reduction ($p < 0.001$). The EI showed notable improvements at weeks 1, 2, and 4. The global evaluation score demonstrated a 75%–100% clinical improvement at Visit 4. Participants reported high satisfaction (6.75 ± 0.79) with the procedure. No adverse event or discomfort was reported.

Conclusion: Precision cryotherapy effectively improved acne lesions, which was safe and satisfactory for participants. These findings suggest its potential as an alternative therapeutic modality, especially for populations with limited treatment options. Further research is needed to validate the results and explore underlying mechanisms.

KEYWORDS
acne vulgaris, cryosurgery, cryotherapy, sebaceous gland

1 | INTRODUCTION

Acne vulgaris, a nearly universal dermatological condition affecting millions worldwide, remains a multifaceted challenge. Characterized by the formation of comedones, papules, pustules, and nodules, acne vulgaris not only poses significant physical discomfort but carries substantial psychological implications, impairing the quality of life of those who are affected. Traditionally, therapeutic modalities for acne have ranged from topical agents to systemic medications, each with its set of limitations and potential side effects.[1] Oral isotretinoin is currently the most effective option; however, it is mired in controversy related to its teratogenicity, suicidality, and inflammatory bowel disease risks.[2] The prolonged use of oral antibiotics is also problematic because it increases the risk of acquiring resistant bacterial strains.[3] Therefore, alternative methods of attenuating acne lesions are desirable. To reflect this need, the new treatment methods are being clinically implemented. Guo et al. highlighted the effectiveness of a novel photodynamic therapy (PDT) with fewer side effects,[4] while Zdrada-Nowak

et al. demonstrated the enhanced efficacy of a nanotechnology-based topical formulation.[5] Additionally, Zhang et al. found that combining oral probiotics with topical agents significantly improved acne outcomes, suggesting a potential new direction for acne management.[6]

Cryotherapy has a long history in dermatologic fields, widely used for the nonspecific destruction of epidermal lesions such as actinic keratosis or verruca vulgaris.[7] However, the use of conventional cryotherapy with liquid nitrogen spray has been limited for acne treatment due to several drawbacks, including procedural pain and hypopigmentation.[8] Recent advancements in cryotherapy techniques address the shortcomings associated with traditional cryotherapy, presenting a more refined and targeted approach; however, few studies have been conducted on the effect of cryotherapy for acne vulgaris. Therefore, this study was conducted to determine the feasibility of treating acne vulgaris by targeted dermal cooling in a pilot clinical trial with volunteers.

FIGURE 1 Non-contact type cooling device, TargetCool.

2 | MATERIALS AND METHODS

2.1 | Ethics approval

This study was approved by the Institutional Review Board of Chungnam National University Sejong Hospital (IRB No. CNUSH 2023-06-007-004) and followed the guidelines of the Declaration of Helsinki. All the patients provided informed consent before participating in the study.

2.2 | Subjects

This study was conducted at Chungnam National University Sejong Hospital, Sejong, Korea. A total of 20 healthy Korean volunteers older than 20 years with acne lesions (inflammatory and non-inflammatory) on their faces were included. The main exclusion criteria were as follows: (i) treatment history with oral retinoid or chemical peeling during the previous 6 months; (ii) treatment history with oral anti-androgenic contraceptives during the previous 3 months; (iii) treatment history with oral or topical antibiotics, topical retinoids, or systemic steroids during the previous month; (iv) individuals with a history of keloid or hypertrophic scars; (v) individuals with a history of cold urticaria, paroxysmal cold hemoglobinuria, connective tissue disease, and chilblain; and (vi) pregnant or lactating women.

2.3 | Intervention

Targeted precision cryotherapy at 0°C was performed for 3 s for each acne lesion on the face. Cryotherapy was performed three times per week by the same dermatologist during the study with TargetCool (RecensMedical Inc., Hwaseong, Korea) shown in Figure 1. The equipment uses pressurized carbon dioxide (CO_2) as a coolant. The temperature of CO_2 drops below −78°C when the liquid portion of the pressurized CO_2 undergoes adiabatic expansion through the nozzle orifice; this phenomenon is known as the "Joule-Thomson effect." Along with real-time temperature feedback by the infrared temperature sensor, temperature control is achieved by regulating the thermodynamic state of pressurized CO_2 before the expansion. The target area is maintained at a desired temperature and duration by the clinician. The cooling process ensures high reproducibility with each treatment session, allowing precise cryotherapy.

3 | ASSESSMENT

During each visit, the investigator conducted a comprehensive assessment of the facial skin of all participants. Digital photographs of the face were collected before treatment and at each visit. The global severity of all acne lesions was analyzed based on the photographs by an independent dermatologist using the Investigator Global Assessment (IGA) scale (grade 0 = no lesion; grade 1 = nearly clear skin; 2 = mild acne; 3 = moderate acne; 4 = severe acne). The efficacy of acne treatment was evaluated based on the number of acne lesions on clinical photographs, and the mean acne lesion reduction rate was calculated. At each visit, the erythema index (EI) was estimated as an indirect indicator of skin inflammation and used as an objective measure in the assessment of psoriasis severity (PASI). The overall improvement in facial acne was evaluated by the physician using a total of 6 levels of the global evaluation score (grade 0 = 100% improved; 1 = 75%–100% improved; 2 = 50%–75% improved; 3 = < 50% improved; 4 = no change; 5 = worsened). In addition, participants were directly assessed for their satisfaction with the treatment of acne lesions at each visit using grades ranging from grade 1 (very dissatisfied) to grade 7 (very satisfied), allowing subjects to evaluate their satisfaction on a total of 7 levels.

Participants were encouraged to report any discomfort or adverse events, such as pain, erythema, edema, or bruising, experienced during and after the procedure. Physical examination was conducted for safety monitoring.

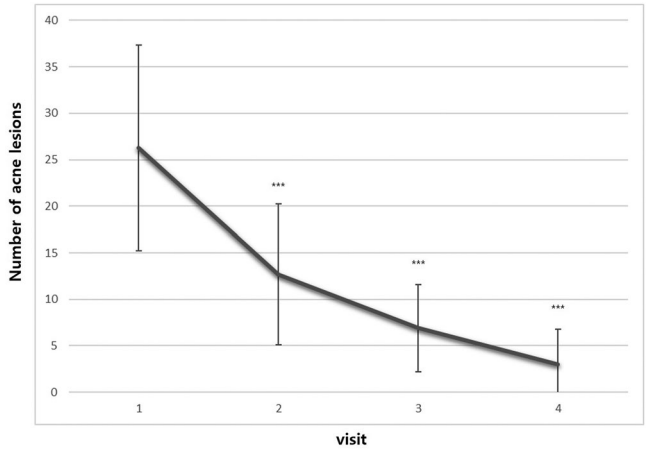

FIGURE 2 Reduction in acne lesion counts following cryotherapy.

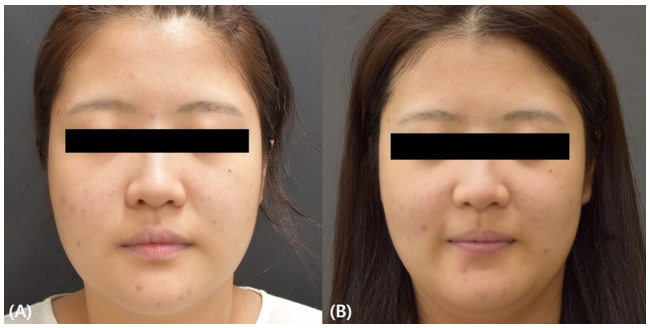

FIGURE 3 Representative case demonstrating noticeable enhancement following cryotherapy.

TABLE 1 Changes in the erythema index following cryotherapy treatment.

	V1	V2	V3	V4
Mean	3.10	1.95	1.55	0.95
SD	0.72	0.94	0.69	0.60
Minimum	2	1	1	0
Maximum	4	4	3	2
Median	3	2	1	1
***p*-Value**		< 0.001	< 0.001	< 0.001

Abbreviation: SD, standard deviation.

3.1 | Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data are presented as the mean ± standard deviation. Descriptive statistics were used to analyze demographic characteristics (age and sex). The analysis of efficacy variables was conducted with a significance level of $\alpha = 0.05$, and depending on the nature of the variables, paired *t*-test or Wilcoxon rank–sum test was performed. Additionally, the 95% confidence interval for the difference between time points was provided.

4 | RESULTS

4.1 | Enrolled patients

A total of 20 patients (M:F = 4:16) were enrolled in this study. No patients were lost to follow-up until the end of the study. The mean age was 31.4 ± 5.79 years. All the patients had Fitzpatrick skin type III or IV. The mean IGA score at baseline was 3.50 ± 0.61. The mean acne lesion count at baseline was measured as 26.25 ± 11.07. The mean EI at baseline was evaluated as 3.10 ± 0.72.

4.2 | Treatment outcomes

To assess the efficacy in improving acne lesions following cryotherapy, acne counts were continuously measured at 1, 2, and 4 weeks after cryotherapy intervention. The mean number of acne lesions was 26.25 ± 11.07 at baseline, which was decreased to 3.00 ± 3.77 after 4 weeks ($p < 0.001$). Figure 2 shows the statistically significant decrease in lesion counts observed at weeks 1, 2, and 4 compared with the baseline. Reduction rates were 53.86%, 75.16%, and 90.25% at weeks 1, 2, and 4, respectively, compared with week 0.

At Visit 1, the average IGA score of participants was 3.5 ± 0.61, indicating the enrollment of patients with moderate to severe acne. Upon reassessment of the IGA score at week 4, the mean IGA score was significantly decreased to 1.10 ± 0.64, demonstrating a statistically significant reduction ($p < 0.001$). Notably, participants who achieved total clearance with an IGA score of 0 were included, demonstrating the therapeutic efficacy of cryotherapy in achieving lesion-free outcomes. A representative case is shown in Figure 3.

To assess the efficacy in improving erythema associated with acne lesions, EI measurements were continuously performed at 1, 2, and 4 weeks after cryotherapy to determine the reduction from week 0. Statistical analysis revealed significant improvements in scores at weeks 1, 2, and 4 compared with the baseline, indicating a significant reduction in erythema (Table 1).

In a subjective assessment by the investigator of the degree of improvement in acne lesions, a clinical improvement of 50%–75% was observed at Visit 2, reflected by a score of 1.80 ± 0.62. At Visit 4, the score was further decreased to 1.00 ± 0.56, demonstrating a clinical improvement of 75%–100%. Notably, some participants achieved a score of 0, indicating 100% clearance at Visit 4. Even for participants showing slower improvement, the maximum score recorded was 2, corresponding to a 50%–75% improvement. The results demonstrated clinical improvement across subjects.

Participants were instructed to assess their satisfaction with the improvement in their skin condition following the procedure on a 7-point scale (higher scores indicating higher satisfaction). At the 4-week posttreatment evaluation, the satisfaction score for the procedure was 6.75 ± 0.79, indicating a high level of satisfaction (approaching "very satisfied").

4.3 | Safety outcomes

Throughout the study, there were no reports of side effects, adverse reactions, or any harmful incidents, including post-inflammatory hyper- or hypopigmentation. Additionally, there were no reports of pain or discomfort during the procedure.

5 | DISCUSSION

The pathogenesis of acne is typically attributed to several mechanisms, including increased sebum secretion, excessive keratinization of hair follicles, colonization by *Cutibacterium acnes*, and inflammatory reactions.[9] Efforts to reduce acne occurrence involve multifaceted approaches aimed at regulating the progression of these mechanisms.

Newer precision cryotherapy devices are attracting attention in dermatological treatment due to their ability to control the target temperature. Previous studies have reported the anti-inflammatory effects and reduction of oxidative stress induced by cryotherapy,[10] which has demonstrated efficacy in inflammatory skin conditions such as atopic dermatitis[11,12] and psoriasis.[13,14] In this study, spot cryotherapy was applied to acne lesions, which showed a rapid therapeutic effect. After a single treatment, over 50% of the lesions were improved at the 1-week follow-up visit, highlighting the efficacy of the treatment. Targeted precision cryotherapy demonstrated convenience and efficiency comparable to those of procedures such as intralesional steroid injections while offering the advantage of avoiding discomfort or pain associated with injection treatment.

Based on prior findings showing that cold stimulation restores microflora and normalizes the excessive keratinization of hair follicles, it is reasonable to infer the applicability of cryotherapy for acne lesions.[15,16] The potential mechanisms of cryotherapy for acne include enhancement of dermal microcirculation, improvement in sebum evacuation, and modulation of the immune response.[7,17,18] It has been observed that cold has an initial inflammatory effect; however, after 24–48 h, an anti-inflammatory effect becomes evident, and faster reabsorption of the lesion occurs.[8] Considering the greater vulnerability of lipid-containing cells to cold injury,[19] controlled local skin cooling may allow the selective harm of sebaceous glands. Burge et al. reported that mild freezing injury led to the contraction and deterioration of sebaceous glands.[20] Additionally, 24 h after superficial cryotherapy, inflammatory cell infiltration and partial damage to sebaceous gland cells were observed.[21] Ray Julian et al. found that damage induced by cooling resulted in a 20% decrease in sebum output over 2 weeks, with minimal harm to adjacent tissues.[7]

Based on the findings of this study, no cases of pain, side effects, or downtime were observed either during or after the procedure. Particularly, a rapid improvement in inflammatory acne lesions was noted, consistent with a previous clinical report in Korea.[8] Furthermore, erythema was effectively attenuated, and no instances of pigmentary changes or discoloration were noted post-procedure. Cryotherapy is also suitable for concurrent use with intralesional steroid injections, which are commonly performed for nodulocystic acne and are known for causing significant pain. Cryotherapy can help alleviate the pain associated with steroid injections, making it appropriate for combined use.[22] Considering the efficacy and safety profile of this treatment, it could be considered as an alternative therapeutic modality that is effective for individuals such as pediatric and adolescent patients or pregnant women, for whom the utilization of oral medications, topical agents, or injection therapies might be constrained.

Some limitations in this study should be acknowledged. First, the sample size was small, limiting the generalizability of the results. Additionally, the study only analyzed short-term follow-up data from 4 weeks, which may not be sufficient for a comprehensive assessment of long-term effects. Considering the potential for future large-scale studies and preclinical investigations, mechanistic insights supporting the effects of cryotherapy may be further validated.

In conclusion, the treatment of acne using a targeted precision cryotherapy device effectively ameliorated acne lesions. The use of the device was safe, as demonstrated by the absence of side effects such as post-inflammatory hyper/hypopigmentation or scar formation.

Cryotherapy was performed with the equipment capable of providing rapid, controlled, precision cooling in a very short period of time, approximately 2–3 s.

The graph illustrates a significant reduction in the number of acne lesions after cryotherapy treatment. Each data point represents the mean lesion count at various time points posttreatment, and error bars indicate standard deviations. Statistical analysis revealed a significant decrease in lesion counts, suggesting the efficacy of cryotherapy in improving acne lesions (*** $p < 0.001$).

A side-by-side comparison of clinical photos before (a) and after (b) cryotherapy treatment for acne vulgaris was performed. Panel (a) shows the baseline condition of acne lesions, and panel (b) shows the post-cryotherapy outcome, demonstrating a visible reduction in the severity of preexisting lesions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical considerations and the privacy of research participants.

REFERENCES

1. Park KY, Han HS, Hong JY, Seo SJ, Lee SJ. Gold nanoshell-mediated photothermal therapy for acne vulgaris. *Dermatol Ther*. 2020;33(1):e13189.
2. Prevost N, English JC. Isotretinoin: update on controversial issues. *J Pediatr Adolesc Gynecol*. 2013;26(5):290–293.
3. Tzellos T, Zampeli V, Makrantonaki E, Zouboulis CC. Treating acne with antibiotic-resistant bacterial colonization. *Expert Opin Pharmacother*. 2011;12(8):1233–1247.

4. Guo Y, Zeng Mi, Yuan Y, et al. Photodynamic therapy treats acne by altering the composition of the skin microbiota. *Skin Res Technol*. 2023;29(1):e13269.
5. Zdrada-Nowak J, Stolecka-Warzecha A, Odrzywołek W, Deda A, Błońska-Fajfrowska B, Wilczyński S. Hyperspectral assessment of acne skin exposed to intense pulsed light (IPL) intense pulsed light in acne treatment. *Skin Res Technol*. 2023. 29(6):e13338.
6. Zhang X, Zhang Z, Tao H, etal. Comprehensive assessment of the efficacy and safety of a clay mask in oily and acne skin. *Skin Res Technol*. 2023;29(11):e13513.
7. Ray Jalian H, Tam J, Vuong LN, et al. Selective cryolysis of sebaceous glands. *J Invest Dermatol*. 2015;135(9):2173–2180.
8. Rho N-K. Revisiting the role of local cryotherapy for acne treatment: a review and update. *J Clin Med*. 2022;12(1):26–43.
9. Knutsen-Larson S, Dawson AL, Dunnick CA, Dellavalle RP. Acne vulgaris: pathogenesis, treatment, and needs assessment. *Dermatol Clin*. 2012;30(1):99–106, viii-ix.
10. Kaminsky A. Less common methods to treat acne. *Dermatology*. 2003;206(1):68–73.
11. Lee EH, Lee HJ, Park KD, Lee WJ. Effect of a new cryotherapy device on an itchy sensation in patients with mild atopic dermatitis. *J Cosmet Dermatol*. 2021;20(9):2906–2910.
12. Kwack MH, Song CH, Lee S, Ha GU, Kim G-H, Lee WJ. Effect of a temperature-adjustable cryotherapy device on mice with lysophosphatidic acid-induced pruritus. *Ann Dermatol*. 2023;35(5):381–385.
13. Nouri K. Cryotherapy for psoriasis. *Arch Dermatol*. 1997;133(12):1608–1609.
14. Shamsadini S, Varesvazirian M, Shamsadini A. Cryotherapy as a treatment for psoriasis. *Dermatol Online J*. 2005;11(2):21.
15. Dzubow LM. Histologic and temperature alterations induced by skin refrigerants. *J Am Acad Dermatol*. 1985;12(5 Pt 1):796–810.
16. Knaggs HE, Holland DB, Morris C, Wood EJ, Cunliffe WJ. Quantification of cellular proliferation in acne using the monoclonal antibody Ki-67. *J Invest Dermatol*. 1994;102(1):89–92.
17. Kotova TG, Tsybusov SN, Kochenov V I, Tcyganov MI. Application of cryogenic methods in skin diseases of different etiology. *Dermatol Surg Proced*. 2018;47–86.
18. Lee Y, Kim S, Kim J, Song S, Lee W, Lee J. Tissue-remodelling M2 macrophages recruits matrix metallo-proteinase-9 for cryotherapy-induced fibrotic resolution during keloid treatment. *Acta Derm Venereol*. 2020;100(17):1–8. adv00306.
19. Gage AA, Meenaghan MA, Natiella JR, Greene GW. Sensitivity of pigmented mucosa and skin to freezing injury. *Cryobiology*. 1979;16(4):348–361.
20. Burge SM, Dawber RPR. Hair follicle destruction and regeneration in guinea-pig skin after cutaneous freeze injury. *Cryobiology*. 1990;27(2):153–163.
21. Ma J, Yu X, Lv J, et al. Cryotherapy mediates histopathological and microstructural changes during the treatment of skin and subcutaneous tumors in dogs. *Cryobiology*. 2021;98:164–171.
22. Park SJ, Shin SH, Koh YG, Kim G-H, Rho NK, Park KY. Cold anesthesia for pain reduction during intralesional steroid injection for nodulocystic acne. *J Cosmet Dermatol*. 2023;22(12):3375–3378.

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