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ORIGINAL ARTICLE

Efficacy and safety of the innovative cold atmospheric-pressure plasma technology in the treatment of keloid: A randomized controlled trial

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Abstract

Background: Keloid (KD) treatment is challenging for both physicians and patients. It can be functional debilitating and psychologically distressing. Available current therapeutics modalities give inconsistently effective results.

Objectives: To evaluate the efficacy and safety of innovative cold atmospheric plasma (CAP) technology in the treatment of keloid.

Methods: This prospective, randomized control trial, the assessor-blinded trial, includes 18 patients with keloids. The keloid lesion was divided into two halves. One side was randomly treated with CAP technology biweekly on the same treated side for five sessions with a follow-up 30 days after finishing the final treatment. Another half was left untreated as a control. Efficacy assessment using POSAS, VSS, Patients' satisfaction scale, Antera 3D® skin imaging system. The safety assessment using VAS and adverse effects monitoring was completed.

Results: Objective assessment using Antera 3D® skin imaging system (Miravex, Dublin, Ireland) showed statistically significant improvement (p-value <0.05) on the treated side compared with the untreated side in all parameters, color, melanin, hemoglobin, texture, except for volume. POSAS, patient, and observer overall opinion score, and patient and observer total score in the summary of all rated characteristics, comparing the treated and untreated areas, showed a statistically significant reduction in all parameters after two treatments (*p-value <0.05). VSS showed statistically significant improvement after the second treatment and continued to the last follow-up. Most patients rated satisfaction scales up to 72.2% as moderate improvement, 11.1% as great improvement, 11.1% as slight improvement, and 5.6% as no change. The adverse effect was only a small scab in one patient.

Conclusion: CAP technology could be considered an alternative treatment for keloid offering mild-to-moderate improvement with minimal side effects.

KEYWORDS
cold atmospheric plasma, keloid, scar

Abbreviations: KD, Keloid; CAP, cold atmospheric plasma; POSAS, Patient and observer scar assessment scale; VSS, Vancouver scar scale; VAS, Visual Analog Scale; 3D, 3-dimensional.

1 | INTRODUCTION

Keloid (KD) classically presented clinically as a firm, rubbery nodules in the area which previously injured or inflamed.[1,2] The main characteristic of KD extends beyond the initial margins of the areas of trauma. It can be symptomatic as painful, itching, or burning. KD occurred from an abnormal wound healing process in response to skin injury or inflammation.[3] The pathogenesis of KD can be possibly implicated by overactive keloid fibroblasts inducing excessive amounts of collagen and growth factors.[4] Histologic findings showed large dense, abnormal, hyalinized collagen bundles, so-called keloidal collagen, and numerous fibroblasts. KD affects patients' quality of life, especially in excessive scarring, which is contracting or restricting movement. There is no best single treatment for KD, and multiple treatments are available with inconsistent success. The most common modalities include corticosteroid, intralesional therapy, occlusive dressing, compression therapy, cryotherapy, radiotherapy, laser therapy, surgical excision, and combination.[1,5]

Cold atmospheric plasma (CAP) technology is a novel therapeutic method.[6] It has been recently used for several indications, including muscle regeneration, infections, blood coagulation, cancer treatment,[7] and wound healing aids in treating pressure ulcers, unhealed chronic ulcers, diabetic ulcers, burn scars, and various types of scars.[8–20] Studies on CAP also showed that mild CAP inactivates microorganisms and improves wound healing via increased integrin expression, modulating adhesion molecules and matrix metalloproteinase 9.[21,22] CAP was previously discovered that it suppresses cell migration, induced cell growth arrest, and delay tumor invasion in cancer models.[23,24] Because of its tumor-suppressive ability of CAP, it could possibly reduce skin hypercellular conditions associated with KD. Furthermore, the therapeutic effects of CAP on KD cells have recently been described as suppressing cell migration of keloid fibroblasts (KFs) in vitro but enhancing cell migration of normal fibroblasts (NFs). This study supported the inhibitory mechanism of CAP on cell migration and collagen production in KFs by regulating signal pathways.[25] Recent progress in understanding CAP technology and property elicited its application in treating various conditions, possibly leading to a new therapeutic strategy for KD. This study aimed to establish the positive effects of CAP on KD in humans.

1.1 | Aim of the study

The aim of this study is to evaluate the efficacy and safety of CAP technology in the treatment of KD.

2 | MATERIALS AND METHODS

2.1 | Subject design

This study is a prospective randomized, assessor-blinded, controlled clinical trial of patients with KD treated with novel technology of cold atmospheric-pressure plasma. The protocol was approved by the Institutional Review Board committee of Human Rights Related to Research Involving Human Subjects, Mae Fah Luang university hospital EC 20106–20. The purpose of the study, study design, and risk of adverse effects were explained to all subjects. Written consent was obtained from all patients before participation.

Eighteen healthy subjects aged 20–40 years who were diagnosed with KD located on the shoulder, arm, breast, abdomen, and chest area were enrolled. Subjects were excluded if they were pregnant or planning a pregnancy and lactation, gained or lost weight ≥5 kg of their starting weight during the study, were malnutrition, have had connective tissue diseases, autoimmune disorders, diabetes mellitus, Cushing syndrome, polycystic ovarian syndrome, thyroid disorder, any uncontrolled systemic diseases, and bleeding disorders. Subjects were excluded if they had active dermatitis or infection within the same treatment area or concurrently participating in another investigational research study, including current use of corticosteroid topically/orally or any anabolic hormone intake or concomitant/ongoing adjunctive skin treatment, laser therapy, chemical peeling, dermabrasion, within 12 months before study initiation. Subjects with a previous history of skin treatment by isotretinoin and retinoid within the past 6 months were excluded.

2.2 | Intervention

Each selected KDs lesions were equally divided into half. (Figure 1) The selected treated side was randomly generated by Spin and Wheel application on iPhone, and the treated areas were the same for five biweekly treatments. Another side was left untreated as a control. One centimeter from the center of the lesion from both sides was left undone as a blank area to eliminate the unseen effects of CAP treatment. Plasma treatment with BIOplasma® system, rounded-floating electrode-DBD type, at 50% energy setting for 5–15 min per session until the endpoint of mild erythema was reached. A total of five-biweekly treatments were completed at D1, D15, D30, D45, D60, and a follow-up visit at D90 (30 days after finishing the final treatment). After the procedure, bland white petrolatum jelly was applied. Subjects were instructed to avoid irritation or use soap or cleansers on the treated lesions. They were also informed not to apply any other creams or moisturizers on the treated area.

2.3 | Evaluation of efficacy subjective evaluation

The patient and Observer Scar Assessment Scale (POSAS) has been effectively used to analyze the different scar types with a reliable outcome. It was used for subjective scar assessment in this study in response to the treatment in two parts: the assessment from the patients, the Patient Scar Assessment Scale (PSAS), and the assessment from the observers, Observer Scar Assessment

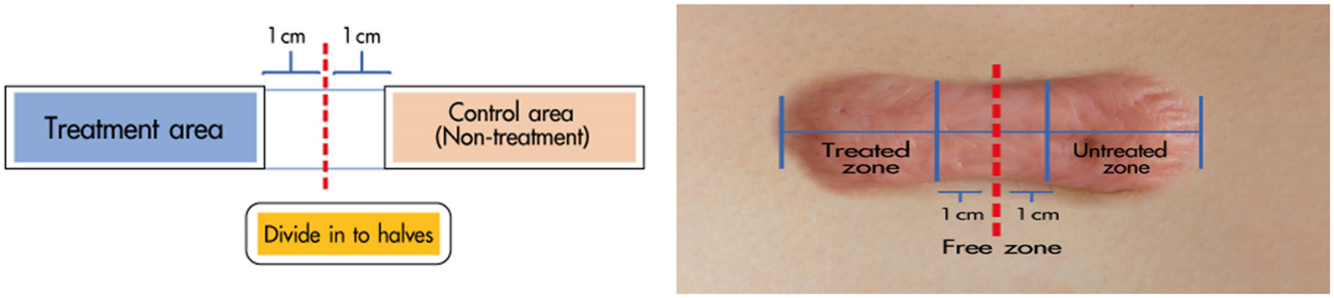

FIGURE 1 Selected KDs lesions were equally divided into halves. One side was randomly selected to be treated, while another was left untreated as a control. One centimeter from the center of the lesion from both sides was left undone as a blank area to eliminate the unseen effects of CAP treatment.

Scale (OSAS). In this study, observers were two-blinded dermatologists with over 15 years of experience. The perception of pain, itching, color, stiffness, thickness, and irregularity relative to the surroundings were rated by patients for PSAS. The vascularity, pigmentation, thickness, relief, pliability, and surface area were assessed by two blinded dermatologists for OSAS. The assessment was done at baseline, before treatment, and 30 days after finishing the final treatment. Both evaluate six characteristic features of pathological scarring on a scale from 1 to 10, then add up to one total score. (minimum six points; maximum 60 points) The numerous scores correlate to the severity of the scar.[26] In addition, all patients rated the patient's satisfaction score at D90, 30 days after the last treatment session. The improvement was graded as grade 0 = symptoms worse than no treatment; grade 1 = symptoms do not change, grade 2 = a slight improvement in symptoms, grade 3 = moderate improvement, grade 4 = greatly improved symptoms, grade 5 = extremely improved symptoms.

2.4 | Objective evaluation

Color, pigmentation, redness, texture, and volume were evaluated using Antera® 3D Skin imaging system (Miravex, Dublin, Ireland) on treated and non-treated controlled areas at baseline before each treatment and 30 days after finishing the final treatment.

2.5 | Evaluation of safety

A universal pain scale (VAS scale) for pain assessment was recorded immediately after each treatment. Treatment adverse effects immediately and after each treatment were recorded.

2.6 | Photographic documentation

All digital 2D and 3D photographs were captured using Antera® skin imaging system (Miravex, Dublin, Ireland), a novel advanced imaging tool for skin analysis and assessment. The pictures were taken under uniform conditions of body position, camera angle, and lighting at baseline before each treatment visit and 30 days after the final treatment. This imaging system incorporated with matching technology allows the highest before and after comparison accuracy. The software will automatically find the corresponding site, compare two images to one another, and generate the report details, including the comparison between images. It showed skin imaging in different parameters, such as surface topography, redness, pigmentation, color, and volume. They were assessed before each biweekly treatment for five sessions and at a follow-up date after 30 days of the last treatment.

2.7 | Statistical analysis

Statistical analysis was performed on SPSS program version 23.0. Intraclass correlation coefficients (ICC) were used to assess the reliability of the measurement scales between the two blinded evaluators. Measures of central tendency were obtained as means and standard deviation (Mean ± SD) in the case of quantitative data and continuous data. For continuous data to compare between the baseline, treatment, and follow-up visit and endpoint visit, repeated measure, analysis of variance (ANOVA) test was applied to compare between the visit, if the data are a normal distribution. In the case of non-normal distribution, non-parametric, repeated measure Friedman test was used. Kolmogorov–Smirnov test was used to test the normal distribution of data. Paired *t*-test or Wilcoxon-signed rank test (non-normal type) was examined between each pair of significant differences. The statistical significance level is considered at a p-value <0.05. All data used a dependent *t*-test to analyze for comparison within the group and an independent *t*-test for comparison between groups.

3 | RESULTS

Eighteen patients completed the study. The subjects were female more than male. The mean age was 31.06 ± 5.66, ranging from 21 to 40 years old. The mean keloid duration was 9.27 ± 7.66. Most of the KD (11 out of 18) were caused by acne. The rest were caused by vaccination, shaving, pierced navel, and after surgery. Most KD occurred

in obese patients (14 out of 18). The mean BMI was 26.33 ± 4.03. The most common area of KD appears on the chest (9 out of 18), and the shoulder is the second most common (5 out of 18).

3.1 | Evaluation of efficacy

3.1.1 | Data on subjective assessment

Patient and observer scar assessment scale (POSAS)

In this study, interclass correlation coefficients (ICC) used to evaluate the reliability of the measurement scales were greater than 0.9 in all measurement scales, referring to excellent reliability. The PSAS total score rated by patients showed statistically significant improvement after two treatments, both within and between the treated and untreated groups. The total score of all parameters within the treated group compared between each session and follow-up period 30 days after finishing the last treatments was decrease from 35.39 ± 11.91 points at baseline to 30.56 ± 9.6 points (D30) ($p < 0.05$) further to 28.83 ± 8.83 points (D45), 27 ± 8.3 points (D60) and 24.94 ± 7.73 points at end visit (D90) ($p < 0.001$, respectively). Pain and stiffness are among the first symptoms which show the earliest improvement after a single treatment. In contrast, irregularity, color, itching, and thickness improvement are slowly appreciated by patients after the final treatment visit and continue to the last follow-up visit. OSAS score rated by observers showed statistically significant improvement after two treatments, both within and between treated at the untreated group, similar to PSAS. The total score of all parameters within the treated group compared between each session and end visit was decreased from 45.11 ± 10.39 points at baseline to 40.83 ± 9.98 (D30) further to 37.64 ± 10.41 points (D45), 33.97 ± 10.65 points (D60) and 31.64 ± 11.07 points at end visit (D90) ($p < 0.001$ in all visits). Pliability was the first sign of improvement after one treatment ($p < 0.001$*). A later improvement was vascularization, pigmentation, and thickness improvement after three treatments ($p < 0.001$*), both within the treated group and compared between the treated and untreated groups. (Figure 2) The color, determined by vascularization and pigmentation, was rated later improvement by patients than physician assessors at D90 and D45, respectively.

3.2 | Vancouver scar scale (VSS)

The operator assessed VSS score. VSS score showed improvement after two treatments from 9.94 ± 1.43 points at baseline to 8.44 ± 1.72 points (D30) further to 6.94 ± 2.51 (D60) and 6.83 ± 2.60 points at end visit (D90), ($p < 0.001$).

3.3 | The patients' satisfaction score

The satisfaction score was evaluated by all patients 30 days after the final treatment session. Most of the patients, 72.2%, valued this treatment as a moderate improvement. 11.1% rated as a great improvement and slight improvement. 5.6% (1 out 18) rated it as no change. All patients agreed that there was no extreme improvement with this modality. Great improvement was rated at 11.1%.

3.3.1 | Data on objective assessment

The color, pigmentation, redness, texture, and volume were compared before each treatment and a follow-up 30 days after the final treatment within the treated and untreated groups using Antera 3D® skin imaging system (Miravex, Dublin, Ireland) (Figure 3). All parameters were improved after the treatment. The first two signs were redness and texture improvement after two treatments compared with the treated and untreated groups ($p < 0.005$ *and $p \leq 0.001$*, respectively). The color and pigmentation were improved later after three treatments ($p < 0.001$*). The only parameter of volume reduction was not statistically significant, from 63.06 ± 174.5 points to 51.2 ± 143.52 points when compared both within and between the treated and untreated groups. 2D and 3D before and after treatment pictures exhibited visible improvement. (Figures 4 and 5).

3.4 | Evaluation of treatment safety

3.4.1 | Pain assessment

Visual Analog Scale (VAS) assessment was used immediately after each treatment for five sessions. The pain scale (numeric rating scale) is as follows: 0 = acceptable, 2–3 = annoy, 4 = a little pain but can endure, 5 = moderate pain, 6–7 = a lot of pain, 8–9 = painful until not wanting to do anything, 10 = severe pain. The average treatment pain ranges from a little pain but can endure to moderate pain. There was no statistically difference between each visit.

3.4.2 | Adverse events

Only one out of 18 patients had a scab post-treatment, which was not a significant adverse effect. (Figure 6) After using white petrolatum ointment application, the scab spontaneously fell off within 1 week with no sequelae. The patient can continue the treatment on the next visit.

4 | DISCUSSION

This study aims to investigate the efficacy of cold atmospheric pressure plasma technology (CAP) as an innovative and alternative treatment modality for abnormal healing process conditions such as KD. KD has various medical and surgical intervention treatments available, but no single therapeutic modality gives a persistent and reliable treatment. KD treatment remains one of the notoriously tricky dermatologic conditions to be treated.

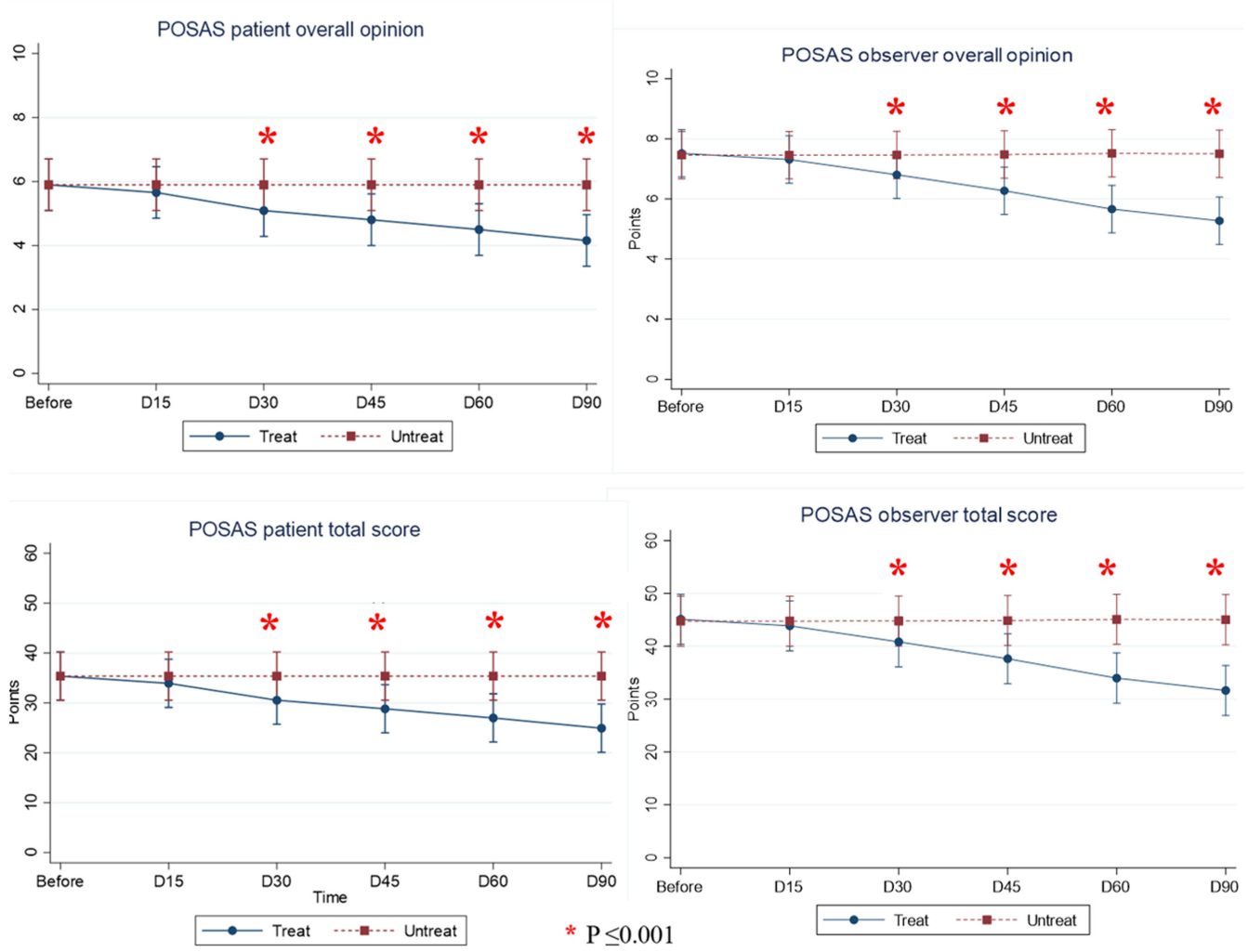

FIGURE 2 Development of POSAS patient and observer overall opinion score and patient and observer total score in the summary of all rated characteristics, comparing treated and untreated areas. Statistically significant improvement in all parameters after two treatments ($p < 0.001$) was shown, demonstrating how keloid improved over time through the patient and observer perspectives.

KD is a poorly regression cutaneous growth that is characterized by haphazard dermal fibrosis and excessive skin growth beyond the original boundaries.[25] This reflects abnormal pathology in wound healing.[27] Individuals with darker skin tones are more prone to KD than faired skin individuals.[28] Incidence is higher in African, Hispanic, and Asian populations, approximately 5%–16%.[29] KD can also cause pain, itching, stiffness, and erythema, affecting the quality of life and self-esteem.[30] There is currently unclear which modality gives the best result to reduce these symptoms. Available KD treatment modalities do not provide a satisfactory outcome.[31,32] New drugs, innovative treatment modalities, and combined strategies have been consistently introduced with various successes. There has been a substantial exploration to find the most effective treatment to cure KD. However, KD pathophysiology is still unclear, leading to unpredictable treatment outcomes. One of the reasons that could explain the previously unsatisfied KD treatment result is the lack of understanding of the involvement of several molecular mechanisms. Previous studies have shown that KD formation involves several molecular mechanisms and signaling during the healing process. These includes the signaling regulated by growth factors such as epidermal growth factor receptor (EGFR), transforming growth factor (TGF-β), and vascular endothelial growth factor (VEGF).[33–35]

CAP offers a new noninvasive, selective targeting therapy to biological tissue at the molecular level with various applications in dermatology.[36–39] It can potentially improve and normalize the wound healing process.[40,41] Short plasma treatment times/low plasma does have stimulating effects by increasing proliferation and migration and induction of DNA repair.[42] Mild plasma also inactivates microorganisms leading to wound healing improvement.[21,22,25] KD formation also occurs in response to the transforming growth factor (TGF-β) stimulation.[43,44] Type I collagen overexpression in KD induced by TGF-β was demonstrated in a previous study.[27] In addition, numerous studies, both in vitro and in vivo, showed that CAP plays a role in wound healing. In vitro, CAP induced the expression of IL-6, IL-8, MCP-1, TGF-ß1, and TGF-ß2, and promoted the production of collagen type I and alpha-SMA.[19] CAP also increased the production of the vascular endothelial growth factor and integrin expression, modulating the adhesion molecules, matrix metalloproteinase 9,

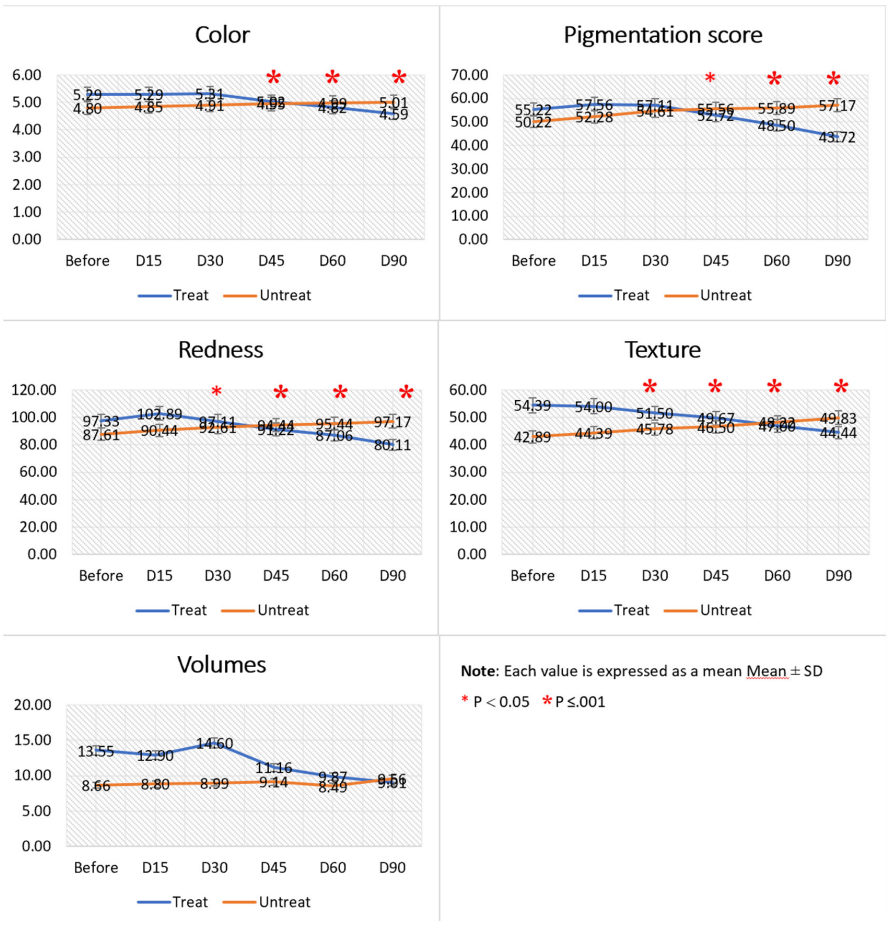

FIGURE 3 Objective assessment using Antera 3D® skin imaging system (Miravex, Dublin, Ireland) demonstrated the comparison of color, pigmentation, redness, texture, and volume comparing between the treated and untreated side (control). The statistically significant improvement in redness and texture was shown after two treatments when compared between the treated and untreated groups ($p = 0.044$* and $p < 0.001$*, respectively). The color and pigmentation improvement were shown later after three treatments ($p < 0.001$*). Volume reduction was not statistically significant.

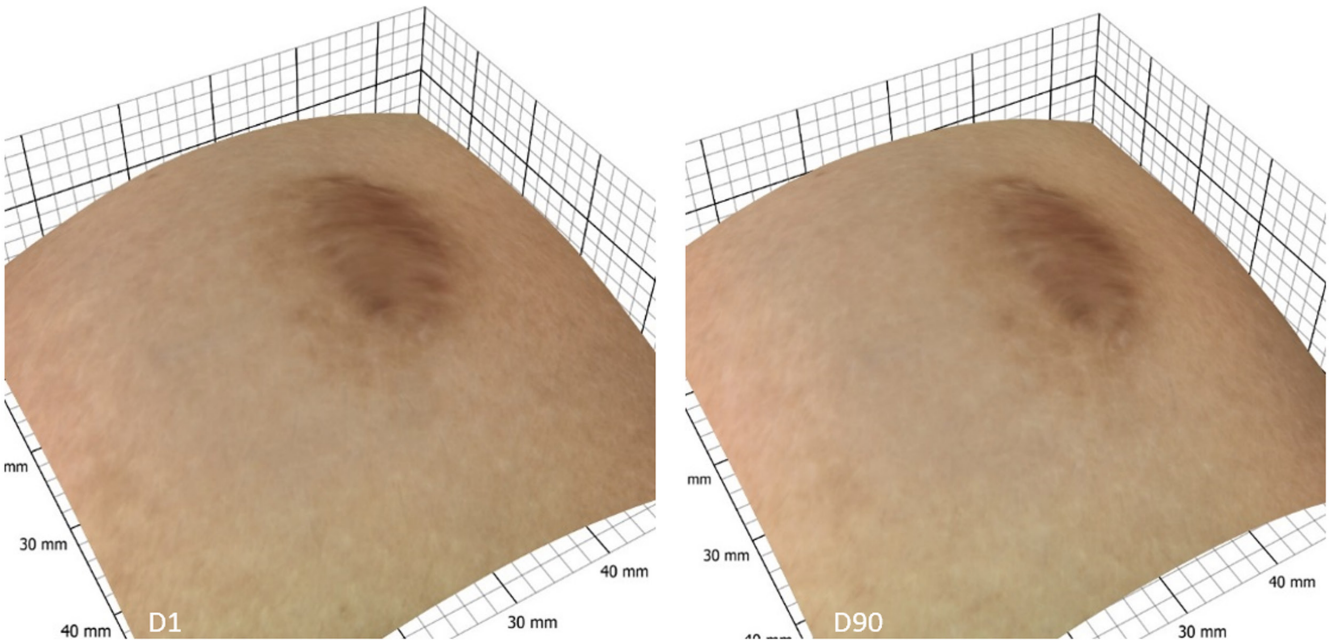

FIGURE 4 3D Pictures of the keloid at the shoulder taken by Antera 3D® skin imaging system (Miravex, Dublin, Ireland). In these pictures, the lower half was treated. The right image showed before treatment. The 30 days after finishing five biweekly treatments (D90) image on the left exhibited visible improvement in volume, redness, texture, color, and pigmentation. All parameters were statistically significant except for volume reduction.

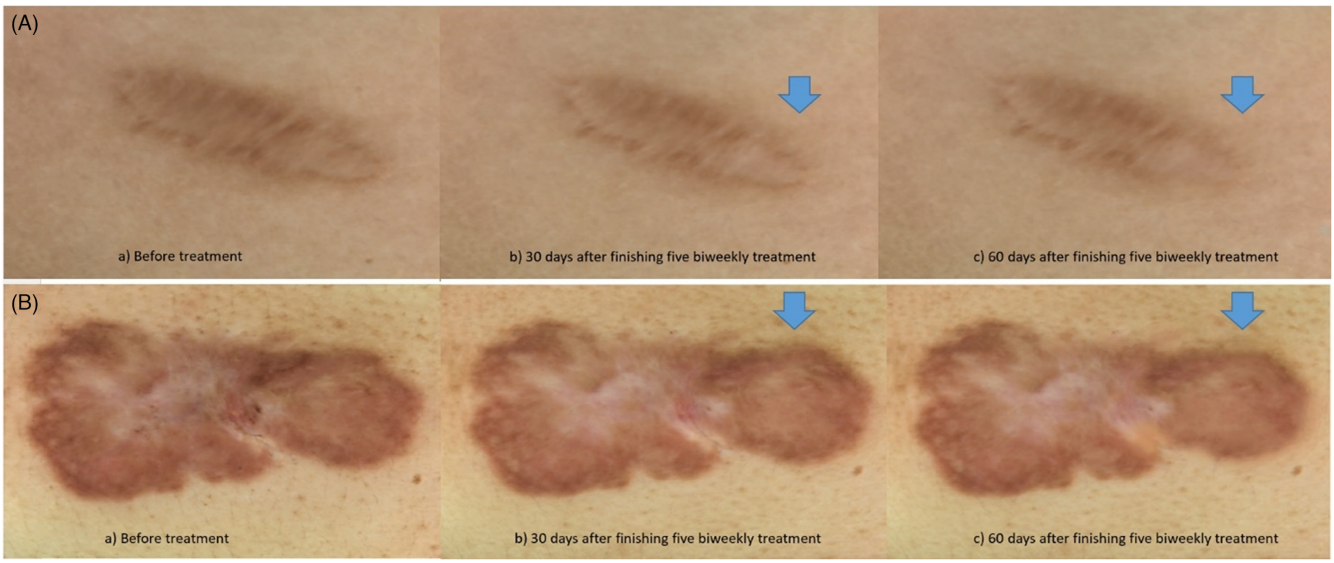

FIGURE 5 Series of matched images before treatment, 30 days (D90), and 60 days after finishing five biweekly treatments (D120) taken by Antera 3D® skin imaging system (Miravex, Dublin, Ireland). (A) keloid at the shoulder (B) keloid at upper chest. Only the left half of the keloids were treated (Blue arrow). The continued reduction in volume, redness, texture, color, and pigmentation was demonstrated 30 and 60 days after finishing five biweekly treatments.

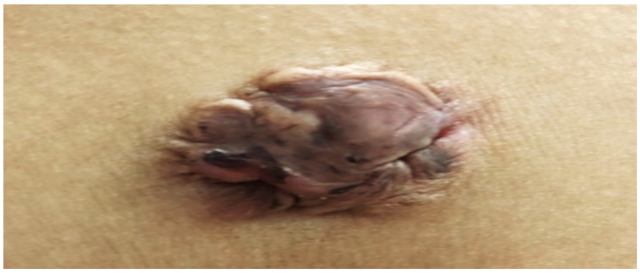

FIGURE 6 Treatment complications showed minimal scab formation in one patient (1 out of 18). No special treatment was required. It healed without permanent sequelae. The uneven texture and curved.

and CXCL 1, which induced angiogenesis.[20] Angiogenesis and tissue macrophage activation induced by CAP possibly improve wound healing.[21,22,25] Recent studies demonstrated that CAP induced proangiogenic and angiogenesis-related molecules in skin keratinocytes, fibroblasts, and endothelial cells. These lead to improvement in wound angiogenesis in an autocrine and paracrine mode.[18] Another recent study on human keratinocytes culture and in vivo mouse model revealed the induction of epidermal cell proliferation and increase skin remodeling with CAP treatment.[45] CAP-induced stem cell differentiation and cell proliferation aided in improve wound healing process.[9] These findings lead to the idea of any treatment modalities that can regulate the molecular mechanism or signaling such as inhibiting TGF-β could possibly pause KD abnormal growth leading to a success in KD treatment.

Interesting findings from a recent in vitro study on the inhibitory mechanism of CAP on cell migration and collagen production in KFs. While CAP showed the opposite effects in NFs, enhancing cell migration and collagen production in NFs.[25] The therapeutics effect of mild CAP on KD cells showed the suppression of KD fibroblasts (KFs) migration via down-regulation of EGFR and STAT3 and reducing Type I collagen production via suppressing transforming growth factor-β.[25] While in NFs, there are oppositely increased levels. This discovery leads to an innovative idea that CAP may be a missing therapeutic strategy for KD.

Another postulation of the mechanism of action is the inhibitory mechanism of CAP on cell growth and migration. The abnormal healing process in KD leads to aberrant collagen production producing 20 times more collagen by fibroblast (KFs) than normal fibroblast (NFs), making KD in hypercellular condition. CAP itself has tumor suppressive ability and has been recently used in cancer indications. A previous study showed that CAP suppresses cell migration, induces cell growth arrest, and delays tumor invasion in cancer models.[23,24] From this finding, CAP assumingly could reduce hypercellular conditions in KD. These experimental findings demonstrate the positive effects of CAP on KD. They could possibly lead to the idea of using CAP for wound healing and assisting tissue engineering[18–20] as a new treatment for various types of scars. It also may offer a favorable armamentarium for abnormal wound healing conditions such as KD. This study would also be the first to demonstrate CAP's effectiveness on KD treatment in humans.

Eighteen-KD patients were included in this study of CAP treatment aiming at the efficacy and safety of KD treatment. CAP was applied on the randomly selected, half-treated side and biweekly treated for five sessions in the same area. This study uses the POSAS and VSS scale to evaluate clinical efficacy by the patients and two-blinded assessors and an operator, respectively. The total PSAS score of all symptoms rated by patients showed statistically significant improvement after two treatments, both within the treated and untreated groups ($p < 0.05$). Pain and stiffness are among the first

symptoms which show the earliest improvement after a single treatment. OSAS score rated by observers showed statistically significant improvement after two treatments within and between treated and untreated groups, comparing each visit to PSAS ($p < 0.001$ in all visits). Pliability was the first sign of improvement after one treatment ($p < 0.001^*$). Early appreciation in pain and stiffness reduction, including pliability improvement after only one treatment, as evaluated by both the patients and two-blinded assessors, could indicate the advantage of the CAP technology in relieving this symptom in KD treatment. Surface area and thickness improved after two and three treatment sessions, respectively. KD reduction in size would take longer with more treatments to be improved. Even though CAP significantly alleviated KD symptoms. Most patients rated the patient satisfaction score mainly as a moderate improvement at 72.2%. 11.1% rated equally for a slight and great improvement, while no one rated extreme improvement. The possible explanation is inadequate treatment sessions in this study. Extensive treatment sessions may increase outcome success and patient satisfaction in clinical practice.

VSS score rated by an operator showed statistically significant improvement after two treatment sessions and continued to improve even after the final treatment. This finding indicates the CAP efficacy in vascularity, pigmentation, pliability, and scar height improvement.

The objective measurement of the CAP treatment efficacy on KD was quantified by the intelligent Antera 3D® Skin imaging system (Miravex, Dublin, Ireland) to assess the improvement of the surface texture, color, pigmentation, redness, and volume. All parameters were decreased after treatment. The improvement of redness and texture was demonstrated after two treatments compared with the treated and untreated groups ($p = 0.005^*$ and $p < 0.001^*$, respectively). The color and pigmentation improvement were shown later after three treatments ($p < 0.001^*$). The volume reduction, which is the main change in KD clinical features, was gradually exhibited. Even though it showed improvement, the reduction was not high enough to be significant in statistics in this study. It could be explained by inadequate treatment sessions proportional to KD size, non-customized treatment parameters, lesser interval, and greater frequency.

Regarding the treatment safety, the average treatment pain ranges from a little pain but can endure to moderate pain according to VAS scale. The treatment itself was very safe. Only 1 out of 18 patients had mild scab formation, spontaneously healing without special treatment. All these findings conclude that CAP is possibly one of the alternative treatment modalities for KD, offering mild-to-moderate improvement with high safety.

Limitations of this study include the small sample size, treatment sessions, and short-term follow-up. This study was done during the COVID-19 pandemic and influenced the participant's recruitment and compliance. The restricted number of treatment sessions might affect the treatment's success. Longer follow-ups have shown continued improvement. The additional improvement could be accomplished by increasing the number of treatments, shorter treatment intervals, and customizing individual parameter settings. Advancements from this study design could include a synergistic effect in combination with previous therapy. The RCT studies compared with existing treatment would gain interest for KD treatment. The skin biopsy demonstrates histopathology, and molecular analysis would gain higher benefits.

5 | CONCLUSION

This study showed CAP technology's efficacy and safety in KD treatment. It could be considered as one of the alternative treatment options for abnormal healing processes such as KD. There was an improvement after CAP treatment in all parameters demonstrating both subjectively and objectively with minimal adverse effect profile. CAP treatment is postulated to regulate the molecular mechanism or signaling and support the inhibitory mechanism on cell growth and migration in hypercellular conditions. These could modulate the abnormal healing process leading to a successful KD treatment. An additional number of treatments, higher frequency, adjustable treatment parameters, and longer follow-up may show a more significant outcome.

CONFLICT OF INTEREST

No conflict of interest relevant to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was obtained from Institutional Review Board committee of Human Rights Related to Research Involving Human Subjects, Mae Fah Luang university (Protocol Number EC 20140–20).

CONSENT STATEMENT

Written consents were obtained from all patients before treatment after explaining the nature, risk, and purpose of the study. All collected data were kept confidential.

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