Dermatology Practical & Conceptual

Prebiotic- and Panthenol-Containing Multipurpose Healing Dermocosmetics Post-Cryotherapy for Actinic Keratoses: Results of a Randomized Controlled Trial

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ABSTRACT

Introduction: Actinic keratosis (AKs) is a precancerous skin lesion that can progress to keratinocyte carcinoma.

Objective: The objective of the study was to evaluate the efficacy of a dermocosmetic (DC) formulation containing prebiotic active ingredients (Aqua Posae Filiformis, a complex made of ferments, sugars, plant extracts, panthenol, madecassoside, and zinc) on healing time and local skin reactions (LSR) following cryotherapy of AKs and to compare the application of DC and boric acid 3% solution soaks (BA) vs. BA alone.

Methods: Seventy-five adult patients presenting with a maximum of five isolated AKs on the face and/or scalp and who underwent cryotherapy (T0) were enrolled. Post-treatment, patients initiated the application of BA only or BA followed by DC once daily for 30 days (unblinded 1:1 randomization). The evaluation of efficacy in healing time and cosmetic outcomes was assessed 30 days post-treatment (T2); LSR was evaluated three days post-treatment (T1).

Results: There was a gain of 4.5 days (40%) in healing time in the BA+DC group compared to the BA group, with a median time of seven days versus 11.5 days (P <0.0005). Additionally, 50% of lesions in complete response had an excellent cosmetic outcome with BA+DC vs. 20% with BA only. The majority of patients treated with BA+DC had mild LSR vs. moderate LSR with BA, with a median value of two vs three, respectively (P <0.0001).

Conclusion: The addition of a prebiotic DC significantly reduced healing time, improved cosmetic outcomes, and minimized LSR post-cryotherapy. No adverse event was reported with this treatment.

Introduction

Actinic keratosis (AKs) presents as a prevalent precancerous skin condition, with its prevalence escalating due to aging demographics and heightened ultraviolet exposure. Its onset is linked to the accumulation of genotoxic DNA damage, necessitating prompt removal to mitigate the risk of evolving into invasive squamous cell carcinoma [1]. Numerous treatment modalities exist for AKs, each with distinct merits and drawbacks. This variety poses a challenge for clinicians in determining the optimal, well-tolerated treatment for individual patients [2]. Treatment for AKs may target either individual lesions or the entire affected area, known as field-directed therapy. Among treatments for individual lesions, cryotherapy is one of the most widespread and commonly used. Liquid nitrogen cryotherapy is classified as a destructive procedure and is today considered a standard first-line approach in cases of single Aks [3]. The destructive impact of freezing encompasses two primary mechanisms: a direct mechanism entails the immediate destruction of cells through intense freezing, leading to cell rupture due to osmotic shock and the formation of intracellular ice crystals, while an indirect mechanism operates through vascular and immune-mediated processes [4]. Despite its benefits, cryotherapy procedures carry inherent risks, with infections being a notable complication in the short term post-treatment. Infections following cryotherapy can lead to delayed wound healing, prolonged recovery periods, and potentially more severe complications if left untreated [5].

Given the potential for infections, proper management of the treated site is paramount to minimize this risk. Several strategies are commonly employed in clinical practice to prevent infections following cryotherapy. Antiseptics such as chlorhexidine, povidone-iodine, hydrogen peroxide, or boric acid are commonly utilized to disinfect the treated area and reduce microbial colonization [6]. Cryotherapy is also accompanied by pain and burning during the procedure and by the subsequent appearance of blisters that result in erosions and crusts. Furthermore, as a consequence of melanocytes' susceptibility to freezing, dyspigmentation is the most common and unpleasant long-term complication of cryosurgery in patients with fair skin, while darker skinned individuals can develop hyperpigmentation [4]. At present, there are no post-treatment care standards aimed at reducing procedure-related pain, minimizing infection risk, or accelerating skin repair.

In recent times, various dermocosmetic (DC) formulations with repairing and anti-inflammatory properties have become available on the market. These formulations owe their efficacy to active ingredients with direct functions as well as to components that regulate the cutaneous microbiome. They represent a promising alternative and support antiseptic solutions and are often preferred by patients due to their superior cosmetic characteristics [7].

Aqua Posae Filiformis is a skincare complex comprising prebiotic ingredients like ferments, sugars, and plant extracts, alongside panthenol, madecassoside, and zinc. It nurtures the skin's microbiome, promoting a healthy barrier. Panthenol moisturizes and soothes, madecassoside reduces inflammation and aids in healing, while zinc offers antimicrobial and anti-inflammatory benefits, making it versatile for various skin concerns, from hydration to soothing and repair [8].

Objective

The objective of the study was to evaluate the efficacy of a DC formulation containing prebiotic active ingredients (Aqua Posae Filiformis, a prebiotic complex made of ferments, sugars and plant extracts, panthenol, madecassoside, and zinc) on healing time, cosmetic outcome, and local skin reactions (LSR) following cryotherapy of actinic keratosis.

Methods

Adult patients able to understand the modalities of the study and provide informed consent to the study who presented with a maximum of five isolated actinic keratoses on the face and/or scalp and undergoing cryotherapy were enrolled in the study. The diagnosis of AKs was confirmed visually and through dermoscopy.

Exclusion criteria were as follows: subjects under 18 years of age, pregnancy or lactation, chemical dependency or alcoholism, likelihood of poor compliance, therapy with drugs known to possess anti-inflammatory, immunosuppressive, vasoactive, or phototoxic activities, presence of concomitant pathologies, metabolic dysfunctions, and clinical data that could reasonably raise doubts about the subject's eligibility for the study, pose a risk to the subject, or act as a confounding factor in data interpretation; concomitant systemic treatment that may impact skin repair (e.g., chemotherapy, corticosteroids, immunosuppressants); concomitant or previous local physical or chemical treatment at the site of

the evaluated skin (e.g., radiotherapy, 5-FU, imiquimod, tirbanibulin); systemic diseases that may influence skin repair (e.g., diabetes, immunodeficiencies, autoimmune diseases); smoking or dietary restrictions that may affect skin repair (e.g., vegan or vegetarian diet); other dermatological diseases apparent at the site of the evaluated skin.

For cryotherapy performed at baseline (T0), lesions were treated with a liquid nitrogen unit (CRY-AC; Brymill Cryogenic Systems) using a standard spray technique. Two freeze–thaw cycles were applied. The area was frozen for 15 to 30 seconds each time, with a thawing period of 2–4 minutes, depending on the size of the lesion. Cryotherapy was performed by the same clinician. Following a 6–8-hour interval post-treatment, patients initiated the application of BA or the application of BA followed by the application of DC, based on an unblinded 1:1 randomization. The products were applied once daily for 30 consecutive days.

The evaluation of local inflammation induced by cryotherapy through the LSR score resulting from erythema, desquamation, crust formation, edema, presence of vesicles/pustules, and/or erosions/ulcerations was assessed at three days post-treatment (T1). To each complication was given a score from 0 (absent) to 4 (severe), with a maximum achievable score of 24 [9,10].

The evaluation of efficacy in terms of healing time in days was reported by the patient, and the cosmetic outcomes were assessed at 30 days post-treatment (T2); at the same timepoint assessment of the overall cosmetic outcome by the investigators was graded into four categories: excellent (no or mild redness or pigmentation changes); good (moderate redness or pigmentation changes); fair (slight-to-moderate scarring, atrophy, and induration); poor (extensive scarring, atrophy, or induration). Clinical photographs were taken for a single target actinic keratosis lesion at baseline, T1, and T2.

In addition, as a pilot evaluation, basal architectural evaluation of treated skin with in vivo confocal microscopy (RCM) (Vivascope 3000, Lucid Inc.) and line-field optical confocal tomography (LC-OCT) (OCTAV V3, DAMAE Medical) was performed at baseline and at T2 for 30 out of the 75 patients (15 from each treatment group). The RCM and OCT images collected at T0 and T2 were evaluated and compared in terms of acanthosis, fibrosis, keratinocyte atypia, and inflammatory infiltrate.

The study was conducted in accordance with the Declaration of Helsinki, and it was evaluated by the Local Ethics Committee (Protocol Number 3718). All patients were given verbal and written information on the nature of the study, and they signed an informed consent form before enrolment.

Statistical Analysis

The study was a randomized single-center controlled clinical trial. The statistical analysis started with a database formatted in Excel© for use in importing versus IBM-SPSS© software ver. 26.1. The continuously expressed variables were subjected to the Kolmogorov-Smirnov test to assess their normality. Categorical variables were summarized by using percentages and continuous variables by calculating medians and range (minimum and maximum values). Medians and continuous variables were compared by using the Mann-Whitney test. Chi-square test was used for percentage comparisons. The comparison of the parameters analyzed in RCM and OCT was performed by general linear model with repeated measures and tests of within-subjects effects (arms; T0 vs T2). All tests were considered at an alpha significance level of 5%.

For the calculation of sample size and formalization of the design, the following was assumed: from preliminarily data collected, the hypothesis was that DC product would reduce the LSR score by at least 45% compared with BA alone; the mean of the aforementioned post-treatment score was assumed to be 20 (DS 15.5) for BA treatment and 11 (DS 8.5) with the use of BA+DC. To achieve a statistical power of at least 80%, the sample size for each treatment arm turned out to be 32 subjects.

Results

Seventy-five patients were enrolled and completed the study. Thirty-six (48%) patients were treated with BA+DC and 39 (52%) patients with BA alone. Characteristics of the population are summarized in Table 1. All patients completed

Table 1. Characteristics of the Population.

	Total	BA group	BA+ DC group
Patients N (%)	75 (100)	39 (52)	36 (48)
Age [median (range)] (years)	78 (60-91)	79 (60-89)	77 (62-91)
Sex:			
Males N (%)	57 (76)	30 (52.6)	27 (47.4)
Females N (%)	18 (24)	9 (50)	9 (50)
Skin phototype: N (%)			
I	2 (2.7)	1 (2.6)	1 (2.8)
II	45 (60)	24 (61.5)	21 (58.3)
III	28 (37.3)	14 (35.9)	14 (38.9)
IV	0 (0)	0 (0)	0 (0)
Body site treated: N (%)			
• **Head**	23 (30.7)	11 (47.8)	12 (52.2)
• **Forehead**	24 (32)	13 (54.2)	11 (45.8)
• **Nose**	11 (14.7)	6 (54.5)	5 (45.5)
• **Cheek**	16 (21.3)	9 (56.2)	7 (43.8)
• **Chin**	1 (1.3)	0 (0)	1 (100)

Abbreviations: BA: boric acid 3% solution; DC: dermocosmetic.

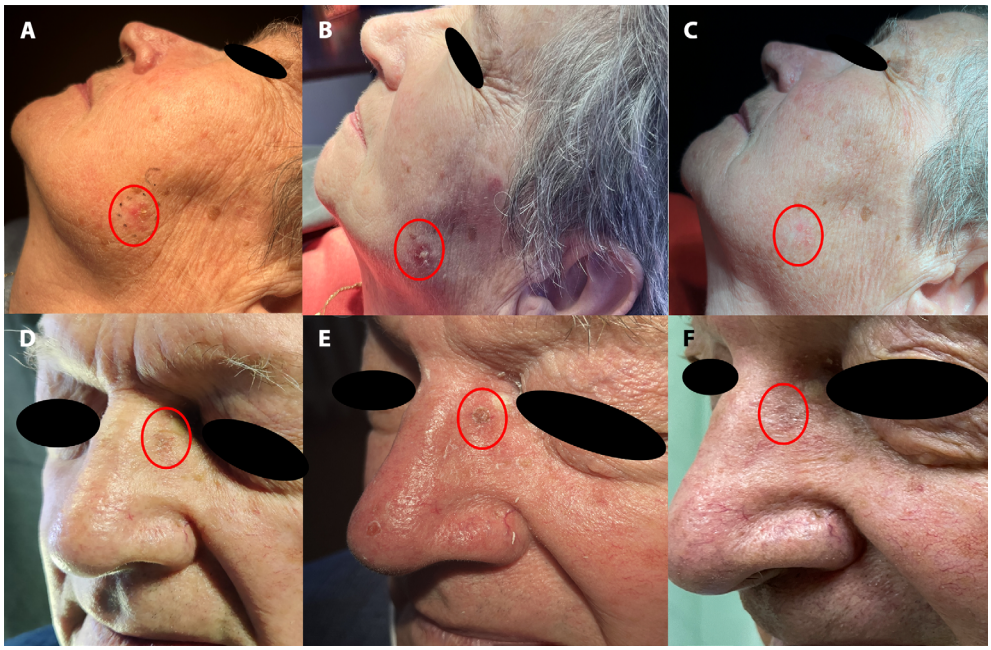

Figure 1. Clinical evaluation of AK of the face before cryotherapy (A) BA+DC; (D) BA; LSR assessment at T1 (B) BA+DC; (E) BA and final result at T2 (C) BA+DC; (F) BA. Abbreviations: AK: actinic keratosis; BA: boric acid 3% solution; DC: dermocosmetic.

the study; 100% of patients exhibited a complete response of actinic keratoses treated with cryotherapy without experiencing significant adverse events.

There was a gain of 4.5 days (40%) in healing time in the group treated with BA+DC compared to the group treated with BA alone, with a median time of seven days (range 2–14) versus 11.5 days (range 5–20), respectively (P <0.0005). Moreover, a trend of improved cosmetic outcome was observed in the group treated with BA+DC compared to the group treated with BA alone. Among lesions in complete response, 50% of them had an excellent cosmetic outcome with BA+DC treatment compared to 20% of excellent cosmetic outcome among lesions in complete response in patients treated with BA only. The majority of patients treated with BA+DC had mild LSR compared to moderate with BA, median value 2 vs 3, respectively (P <0.0001; Figure 1). The comparison of images acquired in RCM and OCT at T0 and T2 revealed a trend of greater reduction in fibrosis at T2 in the BA+DC-treated group compared to the BA-only treated group. Additionally, a trend of correlation was observed between the reduction in keratinocyte atypia and acanthosis components and the efficacy of cryotherapy treatment in both groups (P <0.0001; Figures 2 and 3).

Discussion

Cryotherapy is the most widespread and utilized treatment for single AK due to its speed and simplicity of use. While there is substantial consensus in the literature regarding its indication for treating actinic keratosis [3], there is no agreement or standardization regarding the application methods. Various treatment regimens have been proposed [4], and there is also variability in the management of the treated site in the post-procedural period. It is well-known that the procedure is generally accompanied by inflammation and edema along with the appearance of blisters, leading to erosions and crust formation. Furthermore, there are a number of expected outcomes following cryosurgery such as scar formation and hypopigmentation or hyperpigmentation results that can impact the cosmetic outcome of the procedure. All these factors can be mitigated by proper management of the treatment site during the post-procedure period.

The majority of the available literature asserts that no special care is required during the healing phase. The use of specific topical formulations aimed at proper tissue repair represents an additional strategy in the management of outcomes following cryotherapy procedure [11]. The wound microbiota can affect various phases of healing, including hemostasis, inflammation, and cell proliferation. Specifically microbiota points out the role of commensal bacteria in influencing immune responses, keratinocyte growth, and blood vessel development [12]. From the results obtained in our study, the addition of Aqua Posae Filiformis with a prebiotic complex helps to restore the healthy skin microbiota [13] promoting tissue repair, thus reducing the average healing time and decreasing LSR.

The use of products containing panthenol or its stabilized derivatives is a widely employed strategy to promote tissue repair and reduce potential aesthetic outcomes [14]

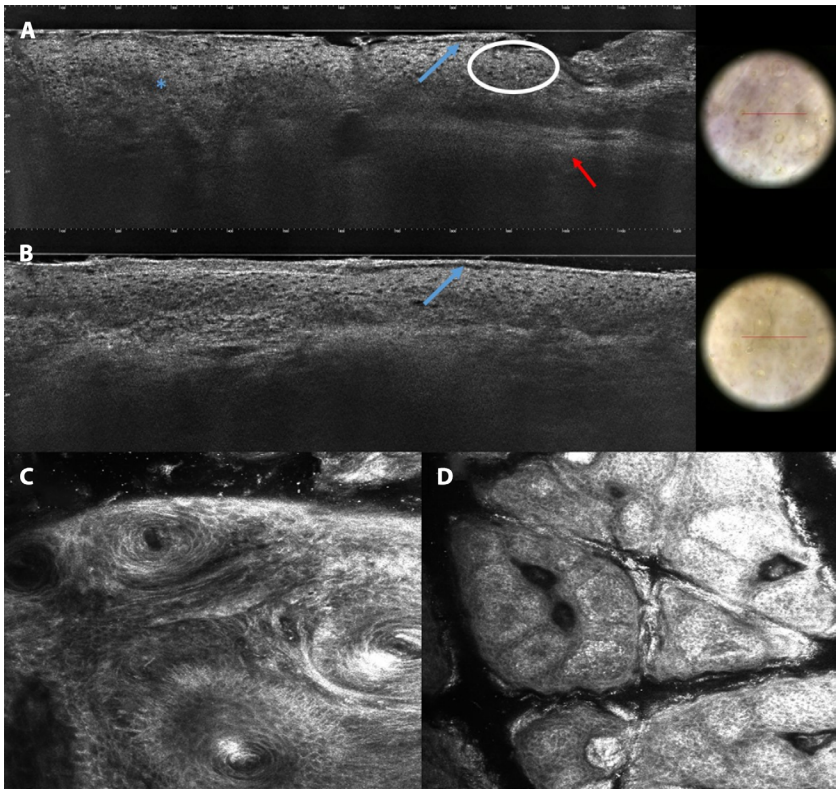

Figure 2. Noninvasive evaluation of AK before cryotherapy by (A) OCTand RCM (C) and at T2 by OCT (B) and RCM (D) in a patient treated with BA+DC: hyperkeratosis (blue arrow); keratinocytes with pleomorphic nuclei (white circle); fibrosis (red arrow); and acanthosis (blue arrows). Abbreviations: AK: actinic keratosis; BA: boric acid 3% solution; DC: dermocosmetic; LC-OCT: line-field confocal optical coherence tomography.

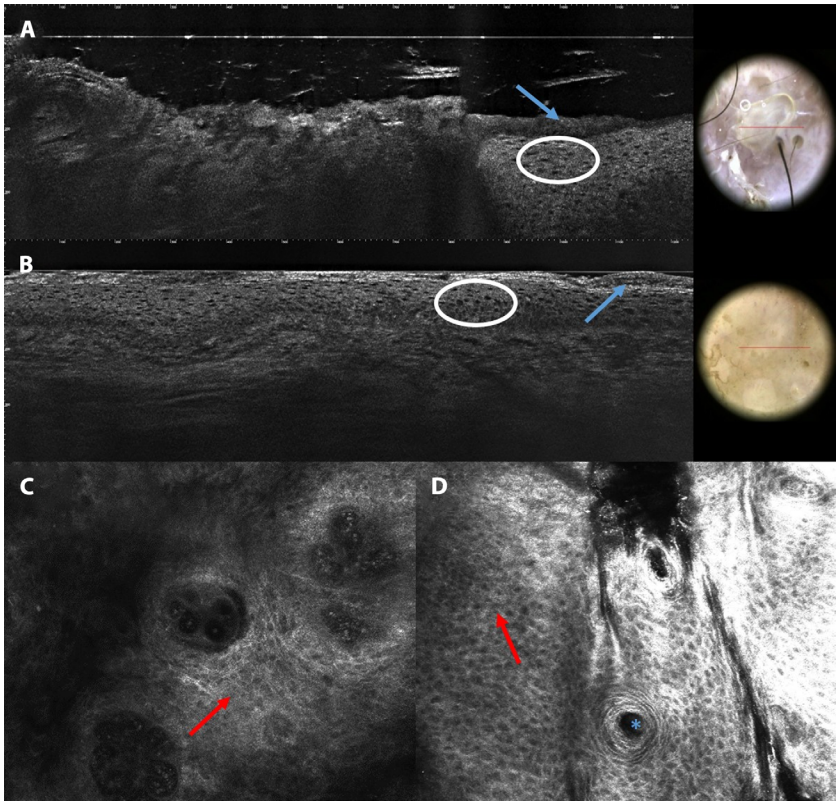

Figure 3. Noninvasive evaluation of AK before cryotherapy by OCT (A) and RCM (C) and at T2 by OCT (B) and RCM (D) in a patient treated with BA only: hyperkeratosis (blue arrow); keratinocytes with pleomorphic nuclei (white circles); atypical honeycomb pattern (red arrows); mid follicular dilatation (blue arrows). Abbreviations: AK: actinic keratosis; BA: boric acid 3% solution; DC: dermocosmetic; LC-OCT: line-field confocal optical coherence tomography.

after medical and cosmetic interventions in post-procedure wound healing. Panthenol and derivatives of vitamin B5 in general exhibit antioxidant, antibacterial, anti-inflammatory, and pro-angiogenic properties and promote keratinocyte and dermal fibroblast migration and proliferation [15], resulting in effectiveness in reducing healing time and improving cosmetic outcomes following cryotherapy treatment.

Conclusions

The addition of a prebiotic and panthenol-containing multipurpose healing DC is able to significantly reduce healing time, with a better cosmetic outcome, and local skin reactions post-cryotherapy for AK. Such capability was appreciated both clinically and in terms of reduction in fibrosis as observed on RCM and OCT. The limitation of the study is that the DC formulation contains many active ingredients, and we did not consider a third arm of patients treated with main active ingredient alone (the prebiotic Aqua Posae Filiformis). Further studies will be necessary to identify the optimal standard of care to be applied in the treatment of patients undergoing cryotherapy.

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