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Evaluation of 30% Urea Pretreatment in Enhancing the Efficacy of Photodynamic Therapy for Actinic Keratoses of the Scalp

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ABSTRACT

Introduction: The use of curettage to reduce the hyperkeratotic component of actinic keratoses is a recommended step prior to photodynamic therapy (PDT); however, the procedure may not be well tolerated by the patient. Due to these drawbacks, alternative approaches aimed at reducing lesion hyperkeratosis and optimizing PDT effectiveness have been studied.

Objective: The aim of the present study was to assess whether a 14-day pretreatment with 30% urea cream enhanced the penetration of methyl aminolevulinate (MAL) and improved clinical outcomes of photodynamic therapy (PDT) in the treatment of scalp actinic keratoses (AKs).

Methods: A split-scalp design was used on adult patients with multiple AKs. One half received 30% urea emollient cream for 14 days before conventional MAL-PDT. Outcomes included PpIX fluorescence, AK reduction, pain scores, local skin reaction (LSR), cosmetic results, and patient satisfaction.

Results: PpIX fluorescence was significantly higher in the urea-treated area (P=0.0128), indicating enhanced MAL penetration. Urea pretreatment yielded significant reductions in AKs, particularly for OLSEN II grade lesions (P<0.0001). Pain scores were slightly higher in the urea group (P=0.029), while overall LSR, cosmetic outcomes, and patient satisfaction were comparable between the two sides.

Conclusion: Pretreatment with 30% urea cream significantly improves MAL uptake and clinical response in PDT for scalp AKs without compromising tolerability or patient satisfaction.

Introduction

Actinic keratoses (AKs) are considered premalignant cutaneous lesions resulting from the cumulative genotoxic effects of ultraviolet (UV) radiation on keratinocytes. Given the potential of each AK to evolve into squamous cell carcinoma (SCC), there is broad consensus [1] that both lesion treatment and long-term clinical surveillance are advisable, regardless of their clinical or histopathological grade [2].

Multiple therapeutic strategies are currently available [1]. In cases involving numerous lesions, it is widely accepted that adjacent photodamaged skin, referred to as the "field of cancerization", also harbors subclinical genetic damage. Consequently, therapeutic approaches that target the entire affected area are preferred.

Photodynamic therapy with methyl aminolevulinate (MAL-PDT) is a well-established, targeted modality used to treat both AKs and the surrounding field of cancerization [3]. This method involves the activation of a photosensitizing agent by visible light, leading to the generation of reactive oxygen species (ROS) within the target cells and inducing cytotoxic effects [4].

In conventional PDT protocols, mechanical removal of hyperkeratotic tissue, commonly referred to as curettage, is essential to enhancing MAL penetration. This procedure typically involves the use of a sharp curette to gently scrape off scales and crusts, thereby facilitating transcutaneous absorption of the photosensitizer.

Curettage is routinely employed in dermatological practice, especially in the treatment of superficial basal cell carcinoma (sBCC) and AKs, as it improves treatment efficacy by removing surface debris and enhancing drug uptake. Despite its clinical utility and cost-effectiveness, the technique is not always well tolerated due to its invasive nature, which may result in procedural pain, bleeding, and posttreatment discomfort.

Following curettage, MAL is applied to the treatment site. As a prodrug of the endogenous photosensitizer protoporphyrin IX (PpIX), a key intermediate in the heme biosynthesis pathway, MAL is metabolized within cells. Upon activation by light in the presence of oxygen, PpIX generates free radicals and ROS, culminating in targeted cellular necrosis.

This preparatory step is crucial to optimal MAL absorption and subsequent PpIX accumulation, directly influencing therapeutic outcomes. However, curettage-related pain and irritation, along with potential bleeding, particularly in high-grade lesions, can impede the uniform application and retention of MAL, ultimately reducing treatment efficacy. Furthermore, bleeding may physically displace the photosensitizer, obstruct light exposure, and compromise drug absorption. The implications of curettage for wound healing, especially on delicate areas such as the face and scalp, remain insufficiently characterized. Additionally, manual curettage is less practical in the setting of daylight PDT, where a topical alternative would enhance feasibility and patient adherence in home-based treatments.

Objectives

This study aimed to investigate the efficacy, safety, and tolerability of photodynamic therapy performed on facial or scalp fields of cancerization in the absence of curettage, utilizing instead a 30% urea-based compound (UBC) to enhance skin permeability and photosensitizer uptake.

Materials and Methods

In this single-center prospective intra-patient controlled study, adult patients presenting with multiple nonpigmented, non-hyperkeratotic (Olsen grades I and II) AKs on the scalp were enrolled [5]. Exclusion criteria were concomitant clinically significant unstable medical conditions, active severe systemic infectious diseases, drug abuse or alcoholism, current participation in another clinical study, known allergies to any molecule in the study drugs, use of photosensitizing drugs, pregnancy or lactation, any other dermatological disease in the treatment area or a distance of 3 cm, prior topical or physical treatment for AKs within six months prior, and likelihood of poor compliance.

This study was conducted at the Dermatology Department of the University of Brescia between September 2024 and April 2025 and was approved 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.

At baseline (T0 V0), researchers collected demographic and medical data, including date of birth, sex, weight, ethnicity, Fitzpatrick skin type, general health status, and history of skin diseases, with a particular focus on actinic keratosis (AK) and any prior treatment undertaken in recent years.

Two contralateral and symmetrical target areas on the scalp harboring at least five AKs were selected. Randomization with a 1:1 allocation ratio to the treatment options was done with a computer-generated list using random permuted blocks of six to ensure the concealment of allocation. Patients and treating physicians were not blinded to group assignment.

For each side, the number of actinic keratoses and their thickness according to Olsen grading [5] were recorded.

Patients were instructed to apply approximately 0.5 mg/cm² of the urea cream once daily, in the evening, exclusively to the designated half of the scalp. This amount was standard for all patients and corresponded to a fingertip unit,

which is a commonly used standard quantity for the application of topical treatments [6]. The treatment area was then gently rinsed the following morning, and no additional cosmetic or therapeutic product was applied during the pretreatment period.

Following the two-week pretreatment phase (designated as T1), the total number of AKs and their clinical grade were recorded; all the patients then underwent a conventional indoor MAL-PDT session according to the protocol status of the European Medicines Agency [4]. Mechanical curettage was intentionally avoided. The light source used was a monochromatic red light (630 nm) generated by an Aktilite CL128 lamp (Photocure ASA, Oslo; Norway). After the 3-hour MAL incubation period, the intensity of PpIX fluorescence was measured using a Wood lamp with a peak wavelength of 365 nm (Sunlamp 70 Wood, JELOSIL SRL, Milan, Italy). Fluorescence intensity was graded using a standardized photographic protocol by a blinded evaluator using an arbitrary 10-point scale.

Both sides of the scalp were irradiated with a red LED light at a fluence of 7.5 J/cm² (peak wavelength: 652 nm). During the irradiation phase, patients reported perceived pain using the visual analog scale (VAS), ranging from 0 (no pain) to 10 (severe pain).

Three days posttreatment (T2), local skin reactions (LSRs) were assessed using a composite clinical scoring system. This system quantifies six common adverse effects of PDT (erythema, desquamation, crusting, oedema, vesicles/pustules, and erosions/ulcerations), each scored from 0 (absent) to 4 (severe), yielding a total maximum score of 24 [7].

At 28 days posttreatment (T3), the clinical efficacy of the therapy was assessed by counting the remaining AKs, if present, and their thickness. Cosmetic outcomes were evaluated by an investigator (A.C.) who was blinded to the initial treatment allocation, and classified the results into four categories: excellent, good, fair, or poor [8]. Patient-reported outcomes were assessed using a 5-point Likert scale (5PLS), which included five questions related to usability, healing time, cosmetic satisfaction, comparison with previous treatments, and overall satisfaction [9].

Each stage of the protocol (pretreatment phase, fluorescence intensity, local skin reaction, and 28 days posttreatment) was systematically documented through standardized image acquisition (Figure 2). This approach ensured reproducibility and allowed for consistent comparison across time points.

Statistical analysis was performed starting from the formatting of the database in Excel© for import use versus IBM-SPSS© software ver. 26.1. Normal distribution of collected data was analyzed by the Kolmogorov-Smirnov test. Categorical variables were summarized by using percentages and continuous variables by calculating medians and ranges (minimum and maximum values). Medians and continuous variables were compared by using the Wilcoxon test and Mann-Whitney test. The chi-square test was used for percentage comparison. A significance threshold was set at $P<0.05$.

For the calculation of the sample size and formalization of the design, the following was assumed: based on former data looking at urea 10% in the pretreatment of facial AKs [2], a hypothesis was formulated that 14-day premedication with 30% urea would result in a 45% difference in fluorescence area (evaluated with Wood's lamp) between the premedicated and non-premedicated areas. A total of 48 half-scalps (from 24 subjects) were required to achieve a statistical power of 83%.

Results

Thirty-four patients were enrolled in the study. The median (range) age was 79 (60–89) years old, and all the patients were male (100%). Four (11.8%), 25 (73.5 %), and 5 (14.7%) had skin phototypes I, II, and III, respectively. All patients completed the study protocol.

Kolmogorov-Smirnov test showed that the population was not normally distributed ($P<0.05$). The total number of treated lesions was 798: 401 AKs were treated with 30% urea+PDT and 397 with PDT alone ($P=0.89$). At baseline, the two treatment areas had the same distribution of AKs in terms of Olsen's grade. The areas treated with 30% Urea+PDT had 283 Olsen grade I AKs and 273 Olsen grade II, while Olsen grades I and II AKs on skin areas treated with PDT alone were 118 and 124, respectively ($P=0.71$ and $P=0.54$).

After 14 days of 30% urea-based keratolytic compound(UBC), a reduction of 13% in total AKs was observed, along with a 14% and 13% decrease in Olsen grades I and II actinic keratoses, respectively ($P>0.05$).

The application of 30% UBC for 14 days prior to PDT was associated with a significant enhancement in MAL penetration, as evidenced by higher PpIX fluorescence. The median fluorescence intensity in the urea-pretreated side was 8 (range 6–9), compared to 5 (range 3–6) in the control side, with a statistically significant difference ($P<0.0001$).

Pain intensity during light irradiation was slightly higher on the 30% UBC side, with a median VAS score of 7 (range 6–9), compared to 7 (range 5–8) on the control side ($P=0.0128$). Despite this, both treatments were generally well tolerated.

Local skin reactions assessed at day 3 posttreatment (T2) showed higher scores in the areas pretreated with urea compared to those not treated with the topical agent (median 30% UBC: 5, range 2–12) vs control: 4 (range 2–9; $P=0.029$) (Figure 1).

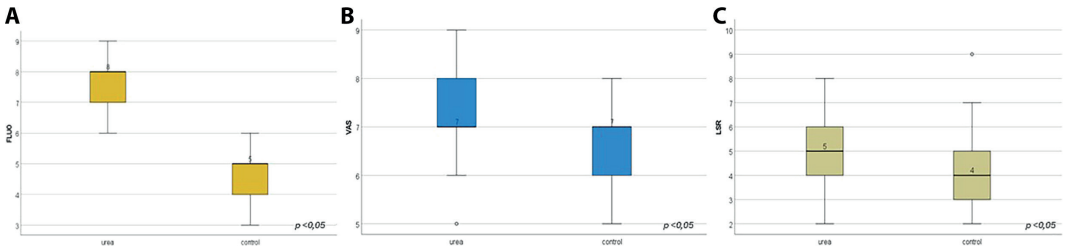

Figure 1. Comparison of fluorescence emitted after MAL incubation: (A) in 30% UBC-pretreated skin areas and control areas; B) evaluation of VAS pain scale during irradiation; C) LSR after treatment at T2.

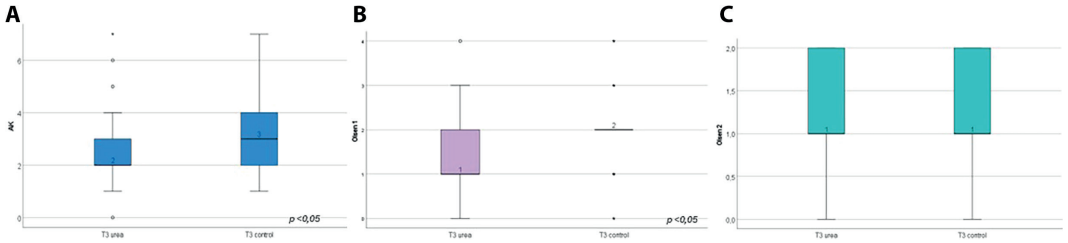

Figure 2. Comparison of the number and thickness of lesions 28 days after treatment (T3): A) all AKs; B) Olsen grade I; C) Olsen II.

In terms of lesion reduction, at T3, the total number of AKs was significantly reduced compared to the control areas (median number of remaining AKs 30% UBC side: 2, range 0–7 vs control side: 3, range 1–7; p= 0.0328). This value corresponds to a 79% reduction compared to baseline. Importantly, when analyzing subtypes of lesions, a significant reduction was observed in Olsen grade I AKs on the 30% UBC treated side (-84%; *P*=0.007), whereas no significant difference between the two sides was noted for grade II lesions (-67%; *P*=0.87) (Figure 2).

Patient satisfaction, as assessed by the 5-point Likert scale (5PLS), was similarly high in both groups, with total scores of 394 for the urea-treated areas and 404 for the control areas, indicating comparable levels of acceptance and perceived benefit.

Likewise, cosmetic outcomes were favorable in both groups, with 20 patients rating the 30% UBC side as "excellent" and 14 as "good," while 19 and 15 gave the same respective ratings to the control side.

Discussion

During PDT, it is common practice to use physical methods that reduce the thickness of lesions to be treated, particularly in cases of hyperkeratotic actinic keratoses or nonmelanoma skin cancers (NMSC). Among the available physical debulking techniques, curettage is undoubtedly the most commonly employed [10]. The underlying principle of this combined approach is that curettage facilitates deeper penetration of the photosensitizing agent, thereby enhancing lesion clearance [11,12]. Several studies conducted on mice and ex vivo human skin have shown that disrupting the skin barrier through abrasion improves permeability to photosensitizers and other medications [9]. Notably, curettage has proven effective in increasing PDT efficacy on extremities, where PDT alone is generally less effective compared to areas like the face, scalp, and torso. While curettage offers therapeutic benefits, it is a physical intervention that thins the stratum corneum but can cause considerable bleeding and oozing, which may result in leakage of the photosensitizer [13]. Additionally, hemoglobin present in the blood can absorb the light used during PDT, potentially diminishing treatment effectiveness [11,14]. Pain is another common side effect of curettage, often making the procedure unpleasant for patients (Table 1).

Due to these drawbacks, alternative approaches aimed at reducing lesion hyperkeratosis and optimizing PDT effectiveness have been studied. The study by Caccavale et al. showed, for example, that the use of a topical formulation containing 30% urea applied for seven days prior to daylight PDT resulted in an AK clearance rate on the face and scalp comparable to that observed in patients treated with curettage [9]. The current research evaluated and compared the efficacy (via clinical evaluations), safety, and patient satisfaction of conventional indoor PDT for multiple AKs of the scalp-associated field cancerization in patients pretreated with a keratolytic agent (30% urea) versus an untreated control group (Table 2). Results showed that urea pretreatment

enhanced the fluorescence intensity of protoporphyrin IX (PpIX), indicating better penetration and activation of methyl aminolevulinate (MAL). Clinically, the group receiving urea pretreatment experienced a greater median reduction in AK lesions, particularly in grade I lesions, highlighting the role of keratolytics in improving MAL absorption.

An interesting finding from our analysis is that after just two weeks of application, the product containing 30% urea was able to reduce the number of actinic keratoses by more than 10%, affecting both thinner and more hyperkeratotic lesions. Regarding treatment tolerability, we observed that 30% UBC application induced increased pain symptoms and was associated with a more pronounced local inflammatory reaction compared to controls. This is likely related to an enhanced penetration of the photosensitizer at the topical application site. Nonetheless, both groups reported high levels of aesthetic satisfaction and adherence, with no significant difference between them.

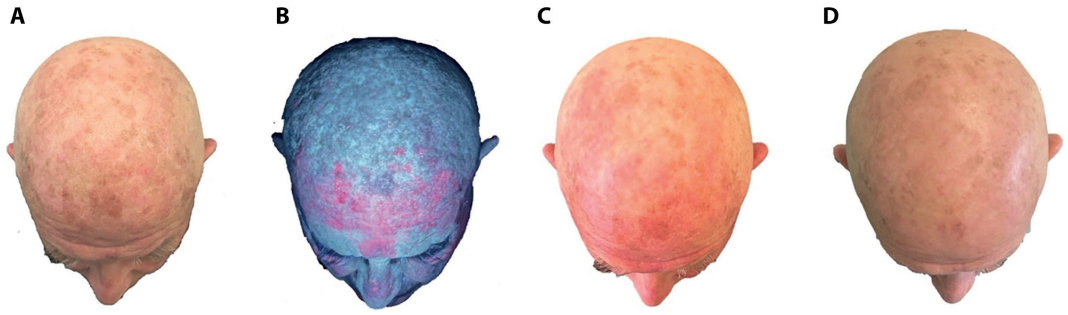

Figure 3. Clinical evaluations at different timepoints in a patient treated with 30% UBC on the anterior scalp: A) baseline at T0; B) wood lamp's fluorescence; C) local skin reaction; D) post-treatment at T3.

Table 1. Comparison of PDT pretreatment approaches.

Pretreatment method	Mechanism	Advantages	Drawbacks
Curettage (Heusinkveld et al.) [11]	Physical removal of hyperkeratosis	Enhances penetration of photosensitizer; improves PDT efficacy, especially on extremities	Bleeding, oozing, risk of photosensitizer leakage; hemoglobin absorbs light, reducing PDT effectiveness; pain
Topical 30% Urea (Caccavale et al.) [9]	Keratolytic effect, thinning of stratum corneum	Noninvasive; improves MAL penetration; comparable clearance to curettage on face/scalp; reduces AKs (>10% after two weeks)	Increased pain and stronger inflammatory reaction; not as immediate as curettage

Table 2. Clinical outcomes: urea pretreatment vs. control.

Outcome	Urea pretreatment group	Control group	Notes
PpIX fluorescence	Higher	Lower	Indicates better MAL penetration
Median reduction in AK lesions	Greater reduction, esp. grade I lesions	Lower reduction	Clear benefit of keratolytic pretreatment
Pain during PDT	More intense	Less intense	Likely due to enhanced photosensitizer uptake
Local inflammatory reaction	Stronger	Milder	Related to increased penetration
Aesthetic satisfaction	High	High	No significant difference
Treatment adherence	High	High	No significant difference

Conclusions

These findings suggest that mild keratolytic pretreatment may be an effective, less invasive alternative to curettage to enhance PDT outcomes for scalp AKs, providing advantage in preparing the field of cancerization, and allowing patient comfort with no compromise of efficacy.

From a practical perspective, keratolytic pretreatment could be particularly advantageous in patients with multiple, thin-to-moderate (Olsen I–II) AKs, where the goal is to optimize field treatment while minimizing procedural discomfort and bleeding. In contrast, curettage may still be preferred in the presence of thick, hyperkeratotic lesions or when rapid mechanical debulking is required as it ensures immediate removal of obstructive keratin [15]. Thus, the two approaches should be considered complementary rather than mutually exclusive, with the choice guided by lesion grade, patient comorbidities, tolerance, and treatment setting.

Moreover, the existing literature indicates that some patients prefer home-based topical skin preparation methods before AK treatment [9]. In this regard, urea pretreatment may expand the feasibility of daylight PDT protocols, offering patients a simpler, more tolerable, and potentially home-manageable option, especially in older populations with extensive scalp involvement. Importantly, allowing patients to apply keratolytics at home before PDT would also streamline in-office procedures, reducing preparation time prior to photosensitizer application and enabling dermatology units to treat a greater number of patients within the same clinical time slots. Considering the progressive increase in life expectancy and the consequent rise in the number of patients requiring dermatological care, such time savings represent a significant advantage for healthcare systems.

Future investigations could explore keratolytic pretreatment prior to PDT more extensively, potentially broadening access to effective AK management and reducing the discomfort associated with curettage. Further comparative trials are warranted to better define clinical scenarios in which each approach—keratolysis or curettage—should be prioritized, thereby optimizing personalized treatment strategies for actinic keratoses.

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