Efficacy and Safety of 30% Urea Cream in Treatment of Acanthosis Nigricans

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ABSTRACT

Although various therapeutic approaches to this skin disease are available, a single unit of universal standard treatment is not yet established. The approach is to treat the underlying disease, weight management in obesity, avoidance of drug-induced skin lesions, application of topical agents, and cosmetic surgery. The potential of topical agents in the treatment with this skin disorder involves interfering with keratinocyte proliferation. The aim of this study is to assess the efficacy of 40% urea cream in the treatment of Acanthosis nigricans. The current investigation was meticulously structured as a single-arm, non-randomized trial aimed at assessing the therapeutic efficacy and safety profile of a 30% urea cream in the management of acanthosis nigricans. Participants received detailed instructions alongside jars containing the 30% urea topical cream, which bore an official label. At baseline, all patients had lesions of grade 1 or more. After 3 weeks of treatment, 3 (11.1 %) cases showed marked improvement and the lesions became of grade 0. There was also marked reduction in proportion of cases of grade 3 and 4 and marked increase in cases of grade 1. We obtained significant changes when comparing proportions of cases with lesions of grade 2 or less versus cases with grade 3 and 4 lesions between week 0 and week 3. After 6 weeks, most cases had less severe lesions of grades 0 and 1 and no case reported lesions 3 or 4 and the differences were significant ($p < 0.001$). The 30% urea cream is effective in reducing hyperpigmentation in acanthosis negricans without any significant adverse outcomes.

Keywords: urea cream, acanthosis nigricans

INTRODUCTION

Acanthosis nigricans constitutes a dermatological condition that is distinguished by the hyperpigmentation and thickening of the epidermis, predominantly observed in the intertriginous regions, notably within the cervical, axillary, and inguinal areas[1]. Despite the availability of multiple therapeutic modalities for this dermatological affliction, a singular, universally accepted standard treatment protocol has yet to be delineated. The therapeutic strategy encompasses the management of the underlying pathology, weight reduction in cases of obesity, prevention of drug-induced dermatoses, the utilization of topical pharmacological agents, and cosmetic surgical interventions[1,2].

Acanthosis nigricans exhibits a significant correlation with obesity, type II diabetes mellitus, and insulin resistance, and it is frequently observed in both pediatric and adult populations[3,4]. The pathogenesis of this dermatological condition is primarily associated with the activation of insulin and insulin-like growth factor in keratinocytes, resulting in augmented stimulation of epidermal keratinocytes[5,6]. The predominant concerns for patients are frequently of a cosmetic nature; however, the presence of hyperpigmentation may induce psychological distress as it could indicate other underlying pathologies; thus, the implementation of effective management strategies is imperative to mitigate skin hyperpigmentation[1]. In light of the increasing prevalence of diabetes, obesity, and other non-communicable diseases within the global populace, the occurrence of acanthosis nigricans is presently on the rise, exhibiting variability in relation to factors such as obesity severity, age, ethnicity, and other endocrine disorders[2].

The therapeutic potential of topical agents in addressing this dermatological disorder encompasses the modulation of keratinocyte proliferation. Urea cream, which contains carbamide, has been extensively researched, demonstrating its efficacy as a potent emollient and exhibiting both a proteolytic effect and keratolysis, thereby establishing its role as an effective treatment for ailments linked to xerosis[7,8]. Urea significantly enhances the appearance of skin hyperpigmentation, thus indicating promising outcomes as various formulations of urea creams possess beneficial attributes, including keratolysis and potential tissue softening effects for nails and/or skin[7].

The process of chemical exfoliation entails inflicting controlled injury to the dermal layers in order to promote skin rejuvenation, which subsequently results in enhanced skin texture and a reduction in surface irregularities[1]. At present, there exists a paucity of clinical trials conducted in Iraq that evaluate the therapeutic effectiveness and safety profile of topical urea cream. Consequently, the objective of this investigation is to evaluate the therapeutic efficacy of 40% urea cream in the management of Acanthosis nigricans.

PATIENTS AND METHODS

Study design: The current investigation was meticulously structured as a single-arm, non-randomized trial aimed at assessing the therapeutic efficacy and safety profile of a 30% urea cream in the management of acanthosis nigricans. This research was conducted within the dermatology department of Adiwaniyah Teaching Hospital, located in Adiwaniyah Province, Iraq, over a duration spanning from February 9, 2023, to April 18, 2024. A total of 27 individuals diagnosed with acanthosis nigricans were enrolled in the study. Participants received detailed instructions alongside jars containing the 30% urea topical cream, which bore an official label. A quantity of one gram of the cream was systematically applied to each side of the posterior neck bi-daily. Adherence to the treatment regimen was evaluated by quantifying the weight of the jars containing the cream at each visit, and these

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measurements were meticulously recorded.

To comprehensively evaluate the ramifications of the topical creams, no additional agents were administered, and the subjects were instructed to refrain from utilizing alternative topical applications on the posterior neck or from prolonged exposure to sunlight. Participants were authorized to reach out to the investigators in the event that significant adverse effects were to manifest. Intermittent follow-up consultations were arranged for the third and sixth weeks. During the initial appointment, participants underwent an extensive physical assessment, encompassing body weight (kg), height (cm), body mass index (BMI), skin pigmentation, and the Fitzpatrick skin phototypes. The research employed the Body Mass Index (BMI) criteria for age as delineated by the Centers for Disease Control and Prevention (CDC), leading to the classification of participants into categories of healthy weight (5th to <85th percentile), overweight (85th to <95th percentile), and obesity (95th percentile or above).

Ethical considerations: This research investigation received endorsement from the ethics review committee at the College of Medicine, University of Al-Qadisiyah. All subjects were provided with an extensive elucidation of the aims and methodologies of the research, and written consent was duly acquired from each participant.

The inclusion criteria: The selection criteria for participants in the investigation encompassed individuals of all ages who had received a clinical diagnosis of acanthosis nigricans localized at the posterior aspect of the neck.

The exclusion criteria: The criteria for exclusion encompassed individuals presenting with significant comorbid conditions (including hepatic disease, renal disease, neoplasia, and coagulopathy), those actively engaged in breastfeeding, individuals with tattoos, cases of infection, immunocompromised individuals, a documented history of photoallergy, the current administration of oral retinoids, and those with a prior application of topical agents such as trichloroacetic acid, vitamin D, or corticosteroids on the designated area within the preceding four weeks.

Outcome variable: Lesions were systematically categorized in accordance with the severity grading established by Burke et al. (9) with the grading for the neck employed in the present investigation utilizing a scale ranging from 0 to 4, delineated as follows:

Grade 0: Absent; no lesions were detectable on close distance.
Grade 1: The lesions were detected at a close distance, but the margins could not be measured.
Grade 2: Lesions were restricted to the base of the neck (<3 inches in width).
Grade 3: The lesions were expanded from the base of the neck to the lateral sides (posterior border of the sternocleidomastoid, 3–6 inches), but were not visible from the front view.
Grade 4: Lesions were extended to the anterior sides of the neck (>6 inches) and were seen from the front view.

Statistical analysis: The SPSS software was used in this study (version 16, IBM, USA). The qualitative data were presented in form of number and percentage. Quantitative data were presented in form of standard deviation, minimum, maximum and mean. Comparison of changes in proportion of cases according to severity of lesions across week 0, week 3 and week 6 of study was carried out using McNemar test. The level of significance was considered at $p \leq 0.05$.

RESULTS

The general characteristics of study participants are shown in table 1. The age of enrolled patients with acanthosis negricans was ranging between 17 and 45 years and the mean age (± standard deviation) was 29.70 ±6.72 years. There were 7 (25.9 %) male patients and 20 (74.1 %) female patients. The mean body mass index of enrolled patients was 29.56 ±2.77 kg/m^2 and it ranged from 25.2 kg/m^2 to 34.3 kg/m^2. According to BMI, patients were categorized into 16 (59.3 %) overweight patients and 11 (40.7 %) obese patients. History taking form patients revealed 15 (55.6 %) cases of polycystic ovarian syndrome (PCOS), 3 (11.1 %) cases with type 2 diabetes mellitus (DM), and a single patient (3.7 %) with family history of acanthosis negricans.

Comparison of severity of skin lesions at week 0, week 3 and week 6 is shown in table 2. At baseline, all patients had lesions of grade 1 or more. After 3 weeks of treatment, 3 (11.1 %) cases showed marked improvement and the lesions became of grade 0. There was also marked reduction in proportion of cases of grade 3 and 4 and marked increase in cases of grade 1. We obtained significant changes when comparing proportions of cases with lesions of grade 2 or less versus cases with grade 3 and 4 lesions between week 0 and week 3. After 6 weeks, most cases had less severe lesions of grades 0 and 1 and no case reported lesions 3 or 4 and the differences were significant ($p < 0.001$).

Table 1. General characteristics of study participants

Characteristic	Results
Age (years)	
Minimum-maximum	17 -45
Mean ±SD	29.70 ±6.72
Sex	
Male, *n* (%)	7 (25.9 %)
Female, *n* (%)	20 (74.1 %)
BMI (kg/m^2)	
Minimum-maximum	25.2 -34.3
Mean ±SD	29.56 ±2.77
Overweight, *n* (%)	16 (59.3 %)
Obese, *n* (%)	11 (40.7 %)
History of PCOS, *n* (%)	15 (55.6 %)
History of type 2 DM, *n* (%)	3 (11.1 %)
History of familial AN, *n* (%)	1 (3.7 %)

n: number of cases; **SD**: standard deviation; **BMI**: body mass index; **PCOS**: polycystic ovarian syndrome; **DM**: diabetes mellitus; **AN**: acanthosis nigricans

DISCUSSION

The rectification of the fundamental etiology represents the optimal therapeutic approach for acanthosis negricans[10]. Nonetheless, the objectives in managing hyperpigmentation linked to acanthosis negricans encompass the attenuation of skin pigmentation, enhancement of skin texture, and amelioration of the patient's overall quality of life. In addition to urea, a variety of therapeutic modalities have been suggested, particularly in instances where addressing the underlying pathologies is unfeasible. These modalities comprise alternative topical agents, including calcipotriol and trichloroacetic acid peels[11,14]. Furthermore, there are oral therapeutic alternatives available for acanthosis negricans. Both metformin and rosiglitazone have demonstrated a marginal improvement in acanthosis negricans related to insulin resistance[15]. Additional treatments, such as the Alexandrite laser, have been documented as applicable in the

Table 2. Comparison of severity of skin lesions at week 0, week 3 and week 6

Grades	Week 0	Week 3	Week 6	*p*1	*p*2	Interpretation
Grade 0	0 (0.0 %)	3 (11.1 %)	12 (44.4 %)	0.250 NS	<0.001 ***	Grade 0 vs other grades
Grade 1	5 (18.5 %)	7 (25.9 %)	13 (48.1 %)	0.062 NS	<0.001 ***	Grade 0 & 1 vs other grades
Grade 2	7 (25.9 %)	11 (40.7 %)	2 (7.4 %)	0.004 **	<0.001 ***	Grade 0, 1 & 2 vs other grades
Grade 3	11 (40.7 %)	5 (18.5 %)	0 (0.0 %)	0.250 NS	<0.001 ***	Grade 0, 1 , 2 & 3 vs grade 4
Grade 4	4 (14.8 %)	1 (3.7 %)	0 (0.0 %)			

***p*1:** Comparison between week 0 and week 3**; *p*2:** Comparison between week 0 and week 3; **NS**: not significant; **: significant at $p \leq 0.01$; ***: significant at $p \leq 0.001$

management of patients presenting with acanthosis negricans[16,17]. Oral retinoids have emerged as a viable therapeutic option for acanthosis negricans. However, the potential adverse effects associated with systemic treatment must be duly considered[18-20].

This singular group one-arm therapeutic investigation demonstrated significant advantages in treatment alternatives, whereby the application of 30% urea creams resulted in marked enhancement of the hyperpigmented lesions of the cervical region from baseline to the sixth week. The findings regarding the efficacy of 30% urea cream on the amelioration of neck hyperpigmentation were also corroborated by antecedent studies[1,7,21]; however, it is noteworthy that the concentration of urea cream utilized in previously published research was inferior to that employed in the current study. Regarding localized adverse reactions, 10% urea creams typically present with very minimal side effects, including slight desiccation and exfoliation[2,3], yet participants in the present study reported an absence of such adverse reactions.
Topical urea has been associated with proteolytic and keratolytic mechanisms[22]. Varying concentrations of topical urea exhibit distinct keratolytic effects. The application of a higher concentration of topical urea may confer advantages in the management of hyperpigmentation linked to acanthosis nigricans[23].

In relation to the limitations of the present investigation, long-term sequelae including the rate of recurrence, enduring compliance, or sustained enhancements in treatment efficacy have not been examined. Within the framework of our research, there is an absence of a placebo control group. Subsequent investigations may concentrate on varying concentrations or amalgamations of alternative topical agents to enhance efficacy in mitigating skin hyperpigmentation.

CONCLUSION

The 30% urea creams is effective in reducing hyperpigmentation in acanthosis negricans without any significant adverse outcomes.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 21 November 2024

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