Original Article

A Study Comparing 0.025% Topical Tretinoin Versus 4% Retinol Peel and 10% Retinol Peel in the Management of Acanthosis Nigricans

Abstract

Background: Acanthosis nigricans (AN) presents a significant challenge for dermatologists, as it is a common condition yet often proves resistant to treatment. **Aim and Objective:** To compare the effects of 0.025% topical tretinoin, 4% retinol peel, and 10% retinol peel, in the management of AN of neck using Acanthosis Nigricans Area Severity Index (ANASI) score. **Patients and Methods:** Patients with AN of neck were recruited to the study with due consideration to the inclusion criteria and were divided into 3 groups based on the treatment administered which was either 0.025% topical tretinoin, 4% retinol peel, or 10% retinol peel. The patients were followed-up every 2 weeks up to 8 weeks with ANASI score and Likert scale. **Results:** All the groups demonstrated statistically significant improvement but participants in the topical group achieved a slightly better reduction, with a mean ANASI score of 10 at final follow-up, followed by 10% retinol and 4% retinol peel with a mean ANASI score of 12 and 11, respectively. Overall, though 4% retinol peel group had the least reported side effects, patient satisfaction score was found to be higher among the participants in the topical group. **Limitations:** Small sample size and allocation of patients to different treatment groups was not randomized. **Conclusion:** Among the three groups, topical tretinoin group showed better response when compared to 4% and 10% retinol peels and, as such, can be a preferred mode of treatment since it is also cost effective over the more expensive chemical peels. Thus, in the era of chemical peels and lasers, topical treatment with retinoids still holds good.

Keywords: *Acanthosis nigricans, retinol peel, topical retinoids*

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Introduction

Acanthosis nigricans (AN) is a skin condition characterized by presence of dark, thickened, and coarse skin with a velvety texture. These skin changes typically occur symmetrically in areas such as the neck, axilla, antecubital and popliteal fossae, as well as the groin folds.[1] The exact underlying cause of this condition is not fully understood. It is often associated with insulin resistance, obesity, and hormonal disorders, signalling underlying health issues.[2] However, it is known that elevated insulin levels can directly and indirectly activate insulin growth factor-1 receptors on keratinocytes (skin cells) and fibroblasts, leading to cell proliferation.[3]

Despite the availability of various treatment options, AN remains a challenging dermatological condition to manage. Commonly used topical agents for the treatment of AN include tretinoin, salicylic acid, urea, calcipotriol and podophyllin. In recent developments, retinoic acid peel, which is a superficial chemical exfoliative agent, has demonstrated effectiveness in the treatment of AN. This study was initiated to assess the efficacy of retinoic acid peel in comparison with the standard treatment using topical tretinoin.[4]

Patients and Methods

Study design

This before and after study was conducted at the skin outpatient department of a tertiary care hospital, for a period of 18 months (23/9/2022 to 31/3/2024). All participants signed the informed consent form before the study enrolment. The study was approved by the Institutional Human Ethical Committee (Ref. No. 005/IHEC/2022/1782). All procedures in the study were in line with the Declaration of Helsinki.

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Participants

Patients clinically diagnosed with acanthosis nigricans of the neck, who met the following inclusion criteria, were recruited for the study.

Inclusion criteria

Patients above 18 years of age (both male and female) diagnosed with AN of the neck were included in the study.

Exclusion criteria

Patients not consenting for the study, patients who received treatment for AN of neck in the past 8 weeks, patients on treatment for insulin resistance, patients with known allergy to retinol, those with active infections as well as pregnant and lactating women were excluded from the study.

Treatment protocol

A total of 33 patients meeting the required criteria were recruited for the study. Patients were divided into 3 groups as group A, group B, and group C based on the type of treatment advised which included topical 0.025% tretinoin (Group A), 4% retinol peel (Group B) or 10% retinol peel (Group C). In the first visit, a detailed history was taken followed by clinical examination and laboratory tests, and baseline Acanthosis Nigricans Area and Severity Index (ANASI) score was calculated for all patients. Patients in 0.025% topical tretinoin group were advised to apply topical tretinoin as a thin film on the lesions of AN every night for a period of 8 weeks. For patients in 4% retinol peel group and 10% retinol peel group, peel was applied on the lesion and patient was observed for a period of 30 minutes for immediate side effects like itching and burning. Patients were asked to wash the area after a period of 6-8 hours. Similar procedure was repeated once every 2 weeks for a period of 6 weeks (4 sittings) with a final follow-up at week 8.

Assessment of treatment

The patients in Groups A, B, C were asked to follow-up every 2 weeks from baseline to 6th week with a final follow-up at 8th week (Baseline—week 0, 1st follow-up—week 2, 2nd follow-up—week 4, 3rd follow-up—week 6, 4th follow-up—week 8). During each visit, the investigator observed and recorded the findings related to response to the treatment. Clinical improvement was assessed using ANASI score.[5] The total length of one-half of the neck (measured from the junction between the chin and upper neck with the neck in flexion, to a point at the inter-clavicular space) and the total width of one-half of the neck (measured from the junction between the chin and upper neck to a point just below the nape hairline) were measured. The length and width obtained were multiplied giving the area of one side of the neck. This value was multiplied by 2 to get the total area of the neck. The affected area was obtained by multiplying the longest area (length) of AN and the widest area (width) of AN. Percentage of involvement was calculated by dividing the affected area with the total area of the neck. Area index was obtained based on the percentage of involvement. Similarly, severity index was obtained based on the severity of pigmentation and thickness of the involved site as shown in Figure 1. Both the values of severity score were summed up and multiplied with the area index to obtain the final ANASI score.

AREA (A) INDEX

0	1	2	3	4	5
NO INVOLVEMENT	<10%	10-29%	30-49%	50-69%	70-100%

SEVERITY INDEX

- Pigmentation (p)

0	1	2	3	4
absent	Mild	Moderate	Marked	Severe

- Thickness (T)

0	1	2	3	4
none	Mild	Moderate	Marked	Severe

P + T = x A =ANASI SCORE

According to the assessment by ANASI score system, patients were classified into3 subgroups corresponding to severity, that is, (ANASI score <10) =mild case, (ANASI score >10 <20) = moderate case, and (ANASI score>20) = severe case

Figure 1: Acanthosis nigricans Area and Severity Index (ANASI) score[5]

The patients were scored based on Likert scale[6] of patient satisfaction and categorised as:

Score of 5—very much satisfied, score of 4—somewhat satisfied, score of 3—undecided, score of 2—not really satisfied, score of 1—not at all satisfied.

In addition, any complications like mild erythema, edema, and peeling were noted. Clinical photographs were taken with patients' consent in identical settings and lighting at every follow-up before successive session.

Statistical analysis

Data entry was done on Microsoft Excel and data analysis was done in SPSS 22 version. The Chi-square test was applied to check the association between categorical variables. Repeated measures ANOVA was applied to check the intra- and inter-comparison. P value < 0.05 was considered to be significant throughout the study.

Sample size

Randomisation was not done. Purposive sampling was done where an independent consultant not related to the study selected the patients for each group and another consultant assessed the patients during follow-up. Sample size calculation was done as follows:

$N = (Z^2_{(1-\alpha/2)} \times SD^2)/E^2$

$N = \frac{1.96 \times 1.96 \times 8.3 \times 8.3}{25}$

$Z^2_{1-\alpha/2}$ = Level of confidence = 1.96 × 1.96 = 3.84

SD = 8.3[2]

E = precision = 5%

Sample size = 33(11 in each group)

Results

A total of 33 patients were included in this study, who were distributed equally among the three groups. Age of the patients ranged from 19 years to 50 years. The majority of participants in each treatment group were females, with varying percentages across the different interventions. Notably, the highest proportion of female participants was observed in the 4% retinol peel group, while the highest proportion of male participants was in the 10% retinol peel group. Duration of AN was divided into < 6 months (12 patients), 6 months – 1 year (9 patients) and >1 year (12 patients), and each treatment group was comprised of approximately one-third of the total participants, suggesting a balanced distribution of participants based on the duration of AN. While polycystic ovarian syndrome and acrochordon were observed in a notable number of participants, significant proportion of participants reported no associated conditions. A substantial proportion of participants (23, 69.7%) exhibited insulin resistance, 15 participants (45.5%) were categorised under normal body mass index (18.5-24.9), and 18 participants (54.5%) were categorised under overweight (25-29.9).

Participants in the topical group exhibited a mean baseline ANASI score of 15 (SD = 4), while those in the 4% and 10% retinol peel groups had mean scores of 14 (SD = 5) and 16 (SD = 5), respectively. Throughout subsequent follow-ups, all treatment groups demonstrated reductions in mean ANASI scores, indicating improved AN severity over time.

By the final follow-up, participants in the topical group achieved the most significant reduction, with a mean score of 10 (SD = 3), compared to 11 (SD = 4) and 12 (SD = 4) in the 4% and 10% retinol peel groups, respectively. The *P* values associated with inter-group comparisons at each follow-up interval indicated statistically significant differences in treatment outcomes among the three groups as shown in Table 1. The clinical response obtained by the three modalities is evident in Figures 2-4.

By the end of final follow-up, the distribution of participants among mild and moderate severity categories differed among the treatment groups. The topical group had 6 participants (54.5%) with mild severity and 5 participants (45.5%) with moderate severity. In contrast, the 4% retinol peel group had 4 participants (36.4%) with mild severity and 7 participants (63.6%) with moderate severity, while the 10% retinol peel group had 3 participants (27.3%) with mild severity and 8 participants (72.7%) with moderate severity. Statistically significant differences in outcome improvement among the treatment groups were indicated by the associated *P* values. A *P* value of 0.003 was observed for the comparison between mild severity outcomes, while *P* value of 0.002 was noted for comparison between moderate severity outcomes.

In the topical 0.025% tretinoin cream group, participants with a duration of ≤6 months had a mean baseline ANASI score of 15, decreasing to 10 at the 4th follow-up. Those with durations of 6 months-1 year and ≥1 year had mean baseline ANASI scores of 14 and 16, respectively, decreasing to 9 and 11 at the 4th follow-up. The *P* value for the comparison was 0.009, indicating a statistically significant difference. In the 4% retinol peel group, participants with durations of ≤6 months, 6 months - 1 year, and ≥1 year had mean baseline ANASI scores of 13, 15, and 14, respectively, decreasing to 10, 12, and 12,

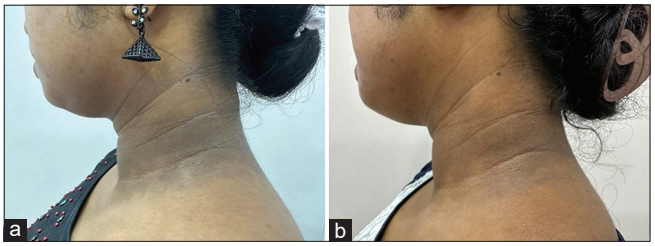

Figure 2: Clinical image of patient using topical 0.025% tretinoin cream. (a) Baseline presentation (1st visit). (b) Response at the end of study (8th week)

Table 1: Assessment of 0.025% topical tretinoin versus 4% retinol peel and 10% retinol peel in study participants with acanthosis nigricans using Acanthosis Nigricans Area and Severity Index (ANASI) Score

Group	Baseline		1st follow-up		2nd follow-up		3rd follow-up		4th follow-up		*P*
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Topical 0.025% tretinoin cream	15	4	15	4	14	4	12	4	10	3	0.03
4% retinol peel	14	5	14	5	14	5	13	5	11	4	0.04
10% retinol peel	16	5	16	5	15	5	13	4	12	4	0.01
P	0.02		0.02		0.01		0.01		0.009		

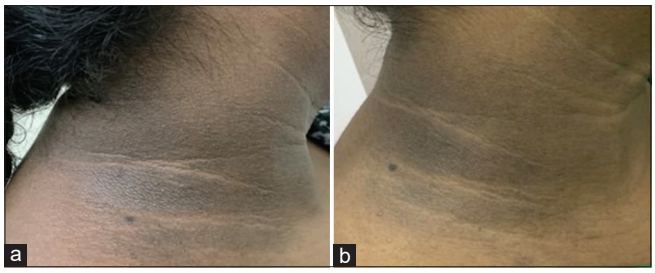

Figure 3: Clinical image of patient receiving 4% retinol peel. (a) Baseline presentation (1st visit). (b) Response at the end of study (8th week)

respectively, at the 4th follow-up. The *P* value for the comparison was 0.01, suggesting a significant difference. Similarly, in the 10% retinol peel group, participants with different durations had mean baseline ANASI scores of 13, 16, and 19, respectively, decreasing to 10, 12, and 13, respectively, at the 4th follow-up. The *P* value for the comparison was 0.009, indicating a significant difference.

In the topical 0.025% tretinoin cream group, participants without insulin resistance exhibited a mean baseline ANASI score of 13, while those with insulin resistance had a higher mean score of 16. At the 4th follow-up, participants without insulin resistance had a mean ANASI score of 10, while those with insulin resistance had a mean score of 10 (*P* value = 0.003). In the 4% retinol peel group, participants without insulin resistance had a mean baseline ANASI score of 9, whereas those with insulin resistance had a higher mean score of 16. At the 4th follow-up, participants without insulin resistance had a mean ANASI score of 7, while those with insulin resistance had a mean score of 13 (*P* value = 0.001) and in the 10% retinol peel group, participants without insulin resistance had a mean baseline ANASI score of 12, while those with insulin resistance had a higher mean score of 17. At the 4th follow-up, participants without insulin resistance had a mean ANASI score of 9, while those with insulin resistance had a mean score of 13 (*P* value = 0.02).

In the topical treatment group, participants with a normal body mass index (BMI) had a mean baseline ANASI score of 14, while those who were overweight had a higher mean score of 16. At the 4th follow-up, participants with a normal BMI had a mean ANASI score of 9, while overweight participants had a mean score of 10 (*P* value = 0.02). In the 4% retinol peel group, participants with a normal BMI had a mean baseline ANASI score of 12, whereas overweight participants had a higher mean score of 15. At the 4th follow-up, participants with a normal BMI had a mean ANASI score of 9, while overweight participants had a mean score of 12 (*P* value = 0.01). In the 10% retinol peel group, participants with a normal BMI had a mean baseline ANASI score of 12, while overweight participants had a significantly higher mean score of 20. At the 4th follow-up, participants with a normal BMI had a mean ANASI score of 9, while overweight participants had a mean score of 15 (*P* value = 0.04).

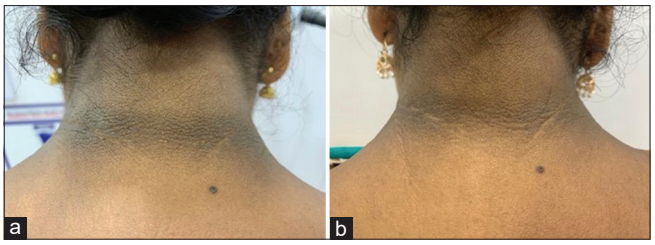

Figure 4: Clinical image of patient receiving 10% retinol peel. (a) Baseline presentation (1st visit). (b) Response at the end of study (8th week)

In the topical 0.025% tretinoin cream group, 1 participant (9.1%) reported burning, 4 participants (36.4%) reported erythema, 2 participants (18.2%) reported itching, and 4 participants (36.4%) reported no side effects. For the 4% retinol peel group, burning was reported by 2 participants (18.2%), erythema by 2 participants (18.2%), itching by 1 participant (9.1%), and the majority, 6 participants (54.5%), reported no side effects. Similarly, in the 10% retinol peel group, 2 participants (18.2%) reported burning, 2 participants (18.2%) reported erythema and 2 participants (18.2%) reporting itching. The majority, 5 participants (45.5%), reported no side effects. The provided *P* value of 0.01 indicated a statistically significant difference in side effect occurrence among the treatment groups.

Patient satisfaction scores based on Likert's scale were compared among the three treatment groups. The study found that participants in the topical group consistently reported higher satisfaction scores compared to those in the retinol peel groups, particularly at the 4th follow-up interval where the topical group had the highest mean score of 4. The significance of these differences was supported by the provided *P* values, with a significant difference observed at the 4th follow-up (*P* = 0.02) as shown in Figure 5.

Discussion

In AN, the etiopathogenesis is multifactorial and involves both endocrine and metabolic factors. Retinol, owing to its lipophilic nature, possesses the capability to efficiently traverse the stratum corneum and hence helps in the treatment of AN.

The findings underscore the efficacy of topical 0.025% tretinoin cream in reducing AN severity compared to retinol peel treatments, with the 0.025% concentration being the most effective, followed by 10%, and then 4% retinol peel. The use of topical retinoids as well as retinol peels align with articles by Davis and Callender[7] and Gold *et al*.,[8] emphasizing the importance of topical 0.025% tretinoin cream as an effective treatment option for a pigmented conditions like AN.

The data suggest that topical 0.025% tretinoin cream may be associated with a higher proportion of participants exhibiting mild severity, whereas 10% retinol peel showed the highest proportion with moderate severity. These findings align with comparative efficacy study by

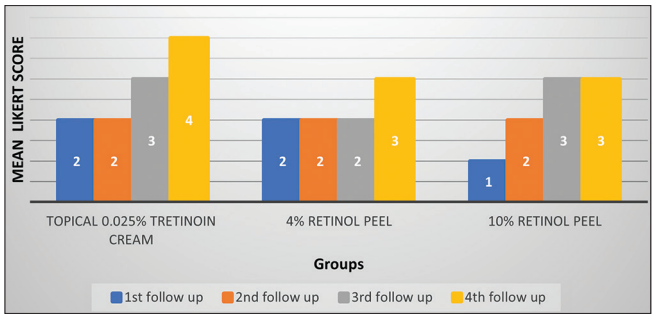

Figure 5: Patient's satisfaction score based on Likert's scale[3]

Rajegowda *et al*.[9] highlighting the importance of treatment selection in achieving optimal outcomes for AN patients.

Among all the three groups, participants with a duration of 6 months-1 year and more than 1 year exhibited the most improvement in ANASI scores. This is in contrast with findings by Milosheska and Roškar,[4] and Salati *et al*.,[10] supporting the influence of AN duration on treatment response.

Overall, participants with insulin resistance consistently showed better outcomes in terms of ANASI score improvement compared to those without insulin resistance. While Kutlubay *et al*.,[11] mentioned the impact of insulin resistance on acanthosis nigricans, not many studies have highlighted the association of insulin resistance with the treatment outcome. In the current study, the presence of insulin resistance did not influence the ANASI scores and treatment response.

Overall, the results suggest that while BMI influences ANASI scores at baseline and during treatment follow-ups across all treatment groups, participants who were overweight tended to exhibit slightly better improvement in ANASI scores compared to participants with normal BMI. This is in contrast with the findings from studies by Huang *et al*.,[12] Patel *et al*.,[13] and Carnevale Schianca *et al*.,[14] highlighting the influence of BMI on ANASI scores.

Overall, though 4% retinol peel group had the least reported side effects, topical 0.025% tretinoin cream group had better patient satisfaction as burning was less compared to the other treatment groups. These findings are consistent with previous studies by Milosheska *et al*.,[4] which highlighted differences in side effect profiles between topical tretinoin cream and retinol peel treatments.

The topical group exhibited better outcomes in terms of patient satisfaction compared to the retinol peel groups. These findings align with previous research by Venkatswami and Anandan,[15] who also reported higher patient satisfaction with topical tretinoin cream compared to retinol peel treatments.

Limitations

One of the limitations of the current study was the small sample size. Another limitation is that the allocation of patients to different treatment groups was not randomised. Future studies with large sample size and randomisation can help in validating the findings of the current study.

Conclusion

The study evaluated the effectiveness of three modalities of treatment for AN across various parameters. While all groups demonstrated statistically significant improvement, the analysis revealed that topical 0.025% tretinoin cream consistently exhibited favourable outcomes compared to 4% and 10% retinol peel treatments, showcasing significant improvements in ANASI scores across all follow-up intervals. Moreover, topical tretinoin treatment exhibited better patient tolerance, suggesting its potential as a preferred treatment option.[16] Though all the three groups showed statistically significant improvement, considering the cost and ease of application for the patient, topical tretinoin can still be considered over the other newer modalities.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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