

A Randomised Open Label Trial to Evaluate the Efficacy of TCA Peel with Oral Metformin vs TCA Peel with Oral Alpha Lipoic Acid in Acanthosis Nigricans

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ABSTRACT

Background: Acanthosis Nigricans (AN) is a condition acquired by keratinization. It presents as velvety skin and hyperpigmentation and can affect any area of the body, including the face. Several topical, systemic, and physical therapies, including laser therapy have been studied. For the most part, randomised controlled trials are lacking for therapy choices other than weight loss and lifestyle adjustments. Therefore, the present study was designed to compare the efficacy of 15% trichloroacetic acid (TCA) peel with oral metformin against 15% TCA peel with alpha lipoic acid in cases of AN with metabolic syndrome.

Methods: Fifty patients were included & divided into two groups. Each patient in Group A was given oral alpha lipoic acid 200 mg BID along with monthly 15% TCA for 03 months, while in Group B, patients were given monthly oral metformin 500 mg BID for three months along with monthly 15% TCA. The effectiveness of each peel was assessed by looking into the severity of neck lesions & texture.

Results: The generalized estimating equations method was used to compare the total change over time in the two groups. Over time, there was a substantial difference between the two groups ($p < 0.001$). When compared to a TCA peel with an oral lipoic acid group, the skin thickness and texture changed more in the metformin group.

Conclusion: In both groups, oral metformin with TCA peel was more effective than oral alpha lipoic acid in our study. As a safe and efficient treatment for AN, we advise using metformin in conjunction with a 15% TCA peel. For supporting data, however, more thorough randomized control studies are needed.

Key-words: Acanthosis Nigricans, Alpha lipoic acid, Metformin, Trichloroacetic acid, Randomised Open Label Trial

INTRODUCTION

Acanthosis nigricans is identified by velvety, brownish-black pigmentation in primarily flexural areas.

It is assumed to be a cutaneous indication of internal illnesses such insulin resistance, diabetes mellitus, hypothyroidism, polycystic ovarian syndrome, and, in rare cases, internal malignancies ^[1,2]. It is a common dermatological aberration associated with various endocrine diseases, characterized by thinly marginated, hyperkeratotic, verrucous plaques with a velvety texture and brownish-black hue ^[3]. Lesions appear symmetrically in flexural areas such as the axillae, nape, sides of the neck, groin, antecubital, and popliteal areas.

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In rare cases, the eruption may extend to the mucosa ^[4]. It can also arise as a side effect of some medications, and there have been numerous reports of syndromic correlations with familial instances.

Therapy for acanthosis nigricans presents a problem. Treatment techniques for acanthosis nigricans that have been proven effective include topical application of retinoids, α -hydroxy acids, or salicylic acid in conjunction with underlying disease management ^[5]. Oral retinoids like isotretinoin and acitretin, as well as insulin sensitizers like metformin, rosiglitazone, and sitagliptin, have been shown to have some effect in reducing cutaneous lesions in acanthosis nigricans ^[6–8]. Alpha-lipoic acid's efficacy in treating acanthosis nigricans hasn't yet been well investigated. The current study was carried out to assess the effectiveness of 15% trichloroacetic acid (TCA) peel with oral metformin against 15% TCA peel with alpha lipoic acid in cases of AN with metabolic syndrome.

MATERIALS AND METHODS

It was a randomised open-level prospective study & was conducted in the Department of Dermatology at Tertiary Care Hospital from March 2021 to September 2022.

Inclusion criteria- Patients above 18 years clinically diagnosed as Acanthosis nigricans visiting Skin & VD OPD and referred from Endocrinology department were included in the study.

Exclusion criteria- Pregnant and lactating females, patients not given consent for the study, patients with a history of renal diseases, cardiac diseases and severe systemic disorders, Type 2 diabetes mellitus patients undergoing treatment, patients with any underlying malignancy & other causes of acanthosis nigricans, patients with unrealistic expectations with the treatment and patients with any known irritation to trichloroacetic acid were excluded from the study.

Methodology

Methods of data collection- The study sample consisted of fifty patients with clinically diagnosed acanthosis nigricans who visited the SKIN VD OPD. The patients were then randomly assigned to two groups: Group A and Group B. Randomization was accomplished by computerised random number allocation. Following written consent, a detailed history of each patient was

obtained, including demographic information, disease history, age of onset, duration, anthropometric measurements, progression, treatment, and drug history. A proper clinical examination was performed. According to gradations by Burke *et al.* and Sharquie *et al.*, over the neck and face, acral areas, respectively, acanthosis lesions were identified, graded, and had a well-defined texture. A two-day run-in period was granted to every patient.

Anthropometric measurements included weight, height, waist-hip ratio, and waist circumference. The routine studies for which blood was obtained were the fasting insulin level, fasting lipid profile, thyroid stimulating hormone, and fasting and postprandial blood sugar. Each patient in Group A received oral alpha lipoic acid 200 mg BID in addition to 15% trichloroacetic acid monthly for three months. In Group B, patients received oral metformin 500 mg BID for the same duration of three months in addition to monthly 15% trichloroacetic acid. Peeling was done using 15% concentration of trichloroacetic acid.

Before application of the peel, a skin patch test was done. A small amount of TCA peel was applied behind the pinna and observed for any burning sensation or other adverse reaction. The compliant patients who experienced no irritation or hypersensitivity reaction proceeded to the peel session. To ensure the peel penetrated evenly, the skin was cleaned or degreased with alcohol or acetone before application. Topical anesthesia was avoided because it typically produces local vasoconstriction, which reduces the concentration of the drug. TCA was administered sequentially using earbuds until the required icing was produced, then removed with a saline-soaked gauze. An emollient is then administered to alleviate any burning sensations. Post the TCA peel session. The patients were provided with a broad-spectrum sunscreen for photosensitivity and proper counselling for photoprotection. Follow-ups were carried out at 4 weekly intervals for three months. During follow-up periods, lesions' recurrence and changes in insulin resistance parameters using HOMA-IR values were evaluated. At the end of six months, blood investigations were performed.

Effectiveness parameter- Improvement in the texture and severity of neck lesions served as the main productive end measures. A 0–4 scale was used to rate

the severity of the neck lesions. Lesions can be classified as follows: "0: absent or not visible upon close inspection; 1: visible upon close observation; 2: mild lesions confined to the base of the skull but not extending to the lateral margins of the neck (less than 3 inches in breadth); 3: moderate lesions extending to the lateral margins of the neck (posterior border of the sternocleidomastoid), typically 3-6 inches; and 4: severe lesions located more than 6 inches anteriorly".

A 4-point grading system (0-3) was used to assess improvement in neck texture. Where: "0: smooth to touch with no distinction from normal skin on palpation; 1: rough to touch and distinguishable from normal skin; 2: coarseness observed visually with parts of skin raised above surrounding areas; and 3: exceedingly coarse with 'valleys and hills'". Insulin resistance results were evaluated using serum fasting insulin level, serum fasting glucose level, serum fasting lipid profile, and HOMA-IR. Insulin resistance can be measured simultaneously with fasting glucose and insulin using Homeostasis Model Assessment-Insulin Resistance, or HOMA-IR.

$$HOMA-IR = \frac{Fasting\ glucose(mmL) \times Fasting\ insulin\ (\frac{uU}{mL})}{22.5}$$

IR is diagnosed if HOMA-IR > 2.7

Glucose/insulin ratio- QUICKI (Quantitative insulin sensitivity check index): Consistent, precise, high positive predictive value.

$$QUICKI = \frac{1}{\log[\log\{Insulin\frac{uU}{mL}\}]} + \log[Glucose\frac{mg}{dL}]$$

QUICKI < 0.357 indicates insulin resistance

Safety parameter- At every follow-up, adverse events- both solicited and unsolicited- that patients reported and that doctors elicited were documented. Laboratory measurements of serum urea, creatinine, routine hemogram, and liver function test were shown to have changed.

Statistical Analysis- Descriptive statistics were used to analyse the acquired data, specifically the mean and standard deviation for quantitative variables. The data, produced using Microsoft Word and Excel spreadsheets, were presented as percentages with tables and graphs

where appropriate. The statistical analysis of the gathered data was conducted with SPSS 25.0. The significance level for categorical data was set at a probability value of 0.05, and the Chi-Square test (or Fischer exact test, if appropriate) was employed to identify significance.

Ethical Approval- The study was conducted after obtaining approval and clearance from the Tertiary care hospital's Institutional Ethical Committee (IEC) with IEC application number 797.

RESULTS

The total number of patients participating in the trial was fifty. Out of 50 patients, 25 are in either group. The study included 9 (52%) individuals in Group A and 19 (76%) patients in Group B between the ages of 15 and 30. The difference in age distribution between the two groups is not statistically significant, according to the Chi-Square test and p-value (0.127). In the study, male patients with acanthosis nigricans outweighed female patients in Group A, with a male-to-female ratio of 1.08:1. Still, male patients outnumbered females in Group B, with a male-to-female ratio of 3.166:1. The neck is the most usually affected region in both group A and B, accounting for 100% of patients in both groups. The axilla was the second most prevalent site, accounting for 48% of patients in Group A and 36% in Group B. The difference in the distribution of acanthosis nigricans lesions in the axilla was not clinically significant (p-value = 0.390). The mean waist-hip ratio in Group A was 0.91 with SD of 0.03, but in Group B the mean WHR was 0.92 with SD of 0.03 and a p-value of 0.458, which was clinically insignificant. In the study, the mean BMI in Group A is 26.34, whereas in Group B the mean BMI is 26.94 with an SD of 4.79 and a p-value of 0.682, which was clinically insignificant (Table 1).

The most commonly encountered associated dermatological condition in Group A was acrochordon in 36% of patients; in Group B, it was acne vulgaris in 20% (Table 2).

Table 1: Age, sex, body mass index and site of distribution of acanthosis nigricans.

Age group	Group		p-value
	A	B	
15 – 30 yrs	13 (52%)	19 (76%)	0.127
30 – 45 yrs	10 (40%)	6 (24%)	
45 – 60 yrs	2 (8%)	0	
Total	50	50	
Gender	Group		
	A	B	Total
Male p-value=0.077	13 (52%)	19 (76%)	32 (64%)
Female	12 (48%)	6 (24%)	18 (24%)
Site	Group		p-value
	A	B	
Neck	25 (100%)	25 (100%)	-
Axilla	12 (48%)	9 (36%)	0.390
Face	5 (20%)	5 (20%)	1.0
Acral	10 (40%)	14 (56%)	0.258
	Group		p-value
	A (Mean±SD)	B (Mean±SD)	
BMI	26.34±5.41	26.94±4.79	0.682
Waist Hip Ratio	0.91±0.03	0.92±0.03	0.458

Table 2: Associated dermatological conditions.

Associated dermatological condition	Group	
	Group A	Group B
Acrochordon	9 (36%)	2 (8%)
Acne vulgaris	6 (24%)	5 (20%)

T. versicolor	1 (4%)	0
Seborrheic dermatitis	0	1 (4%)
Polymorphic light eruption	1 (4%)	1 (4%)
Hirsutism	0	1 (4%)

In Study Group A, 3(12%) patients were found to be hypothyroid, while in Group B, 1 (4%) patient was found to be hyperthyroid and 3(4%) patients were found to be hypothyroid. The difference in deranged thyroid profile in both groups is clinically insignificant, with a p-value of 0.684. In the study, in Group A 8(32%) & Group B 7(28%) patients had abnormal serum fasting lipid profiles with dyslipidaemia with a difference in deranged fasting lipid

profile in both groups clinically insignificant p-value of 0.758. In study group A, incidentally, 2 female patients were diagnosed with polycystic ovarian disease. While in Group B, 1 female patient was found to have polycystic ovarian disease, and 2 patients were found to have fatty liver. The difference in USG abdomen in both the groups was clinically insignificant, with a p-value of 0.637 (Table 3).

Table 3: Thyroid function test, serum fasting lipid profile, USG abdomen in study group.

Thyroid abnormality	Group	
	A	B
Hypo	3 (12%)	3 (12%)
Hyper	0	1 (4%)
Lipid abnormality		
	A	B
Present	8 (32%)	7 (28%)
Absent	17 (68%)	18 (72%)
USG		
	A	B
PCOS	2 (8%)	1 (4%)
Fatty liver	0	2 (8%)

The mean HOMA-IR for group A was 2.66 ± 1.52 , whereas the mean HOMA-IR for group B was 2.94 ± 1.03 . The p-value of 0.617 indicates that the difference in HOMA-IR between the two groups is clinically insignificant. Group

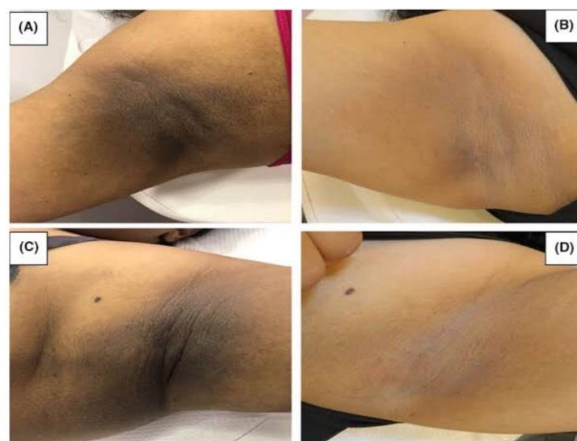
A had a mean fasting blood sugar level of 107 ± 14.67 , while Group B had a mean FBS of 105 ± 13.55 . At a p-value of 0.788, the difference in the two groups' fasting blood sugar levels was clinically insignificant (Table 4).

Table 4: Measures of insulin resistance.

	Group		p-value
	A (Mean±SD)	B (Mean±SD)	
HOMA-IR	2.66±1.52	2.94±1.03	0.617
INSULIN	23.94±5.46	24.00±6.39	0.973
FBS	107.0±14.67	105.92±13.55	0.788
PPBS	146.76±44.46	140.92±29.83	0.588

In the study group A receiving metformin with monthly trichloroacetic acid peel, at the treatment median grading in the third sitting was 1.0 as compared to baseline median IQR grade of 4.0 on pre-treatment scaling with a difference in the grading of lesions was clinically significant with a p-value of 0.001 as calculated by intragroup test by Friedmann Annova. Meanwhile, in study group B, receiving alpha lipoic acid with monthly trichloroacetic acid peel, the end-of-treatment median grading was 2.0 compared to baseline median grading 3.0. The difference in lesion grading in group B pre and post-treatment was clinically significant as calculated by Friedmann Annova technique with a p-value of 0.001. The difference in grading of lesions post-treatment

between groups Group A and Group B was calculated by the Intergroup test by Mann Whitney U, which was clinically significant with a p-value of 0.034. At the end of the study period, 100% of the patients of Group A responded to the treatment, while 96% of patients of Group B responded. The difference in response to treatment was clinically insignificant, with p-value of 1.0. In this study, group A's maximum patients (56%) showed excellent response. In comparison, 20% of patients showed mild and 24% showed moderate response (Fig. 1). In group B, 32% showed excellent response, while a maximum (52%) showed mild response. 4% of the patients showed no response to the treatment at the end of the study (Fig. 2).

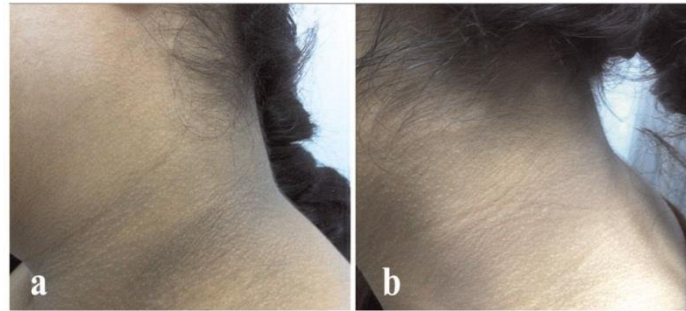


A,C- Baseline acanthosis lesion over bilateral axilla
C,D- Post-treatment resolving acanthosis lesion after 8 weeks interval showing excellent response in Group A



PRE-TREATMENT

POST TREATMENT- EXCELLENT RESPONSE in facial acanthosis nigricans
In Group A patient



a- Baseline skin lesion
b- POST TREATMENT- Mild response

Fig. 1: Excellent and mild responses in Group A patients.



Fig. 2: Excellent (A) and mild (B) responses in Group B patients.

In the study, one patient (4%) of Group A noticed hyperpigmentation in the end of the study period, while 2 patients (8%) of Group B had hyperpigmentation (Fig. 3).



Fig. 3: Post-peeling hyperpigmentation over naso-labial fold.

In study group A, most males (40.8%) showed excellent response to skin lesions at the end of treatment, while in group B, most male patients (50%) showed mild response to skin lesions at the end of treatment. Among females, in Group A, most female patients (66.7%) showed excellent response, while in Group B, the maximum number of female patients (66.7%) showed mild response in skin lesions. Most patients in the age

group of 32.4 ± 10.3 showed excellent response to the treatment in study group A, while in group B, the mean age of 27.0 ± 6.4 showed excellent response to the treatment modality. The mean BMI of the patient showing excellent response to the treatment was 24.2 ± 4.8 in group A, while in group B, the mean BMI of the patient showing excellent response was 29.4 ± 3 (Table 5).

Table 5: Response grading in both study groups based on sex, age, and BMI.

Sex (Mean \pm SD)		Grading response			p-value*
		Mild	Moderate	Excellent	
Group A	Male	3 (23.1%)	4 (40.8%)	6 (46.2%)	0.573
	Female	2 (16.7%)	2 (16.7%)	8 (66.7%)	
Group B	Male	9 (50%)	3 (16.7%)	6 (33.3%)	0.540
	Female	4 (66.7%)	0	2 (33.3%)	
Age (Mean \pm SD)		Grading response			p-value*
		Mild	Moderate	Excellent	
Group A		32.8 \pm 7.8	30.1 \pm 12.0	32.4 \pm 10.3	0.697
Group B		23.62 \pm 9.1	26.0 \pm 5.5	27.0 \pm 6.4	0.359
BMI (Mean \pm SD)		Grading response			p-value*
		Mild	Moderate	Excellent	
Group A		29.9 \pm 4.8	28.2 \pm 5.5	24.2 \pm 4.8	0.067
Group B		25.7 \pm 5.1	27.1 \pm 3.7	29.4 \pm 3.8	0.271

By the time the treatment ended, the mean fasting blood sugar level in both study arms had significantly decreased, from 107.0 ± 14.67 in group A to 98.61 ± 31.6 in group B. In contrast, Group B's mean post-treatment fasting blood sugar was 97.16 ± 18 , compared to a baseline mean of 105.92 ± 13.55 . The serum fasting insulin level decreased slightly in both research groups,

with group A exhibiting a statistically significant difference in serum fasting insulin level between the baseline and end-of-treatment values (p-value = 0.037). Both research arms had a decrease in insulin resistance as measured by HOMA-IR; however, group A showed a significant difference ($p < 0.001$) (Table 6).

Table 6: Comparison of fasting blood sugar levels, fasting insulin level and HOMA-IR in pre-treatment and post-treatment study groups.

Fasting blood sugar	Group A	Group B	p-value
Baseline	107.0±14.67	105.92±13.55	0.788
End of study period	98.61±31.6	97.16±18	0.233
p-value within the group	<0.001	0.527	
Serum fasting insulin level			
Baseline	23.94±5.46	24.00±6.39	0.973
End of study period	22.87±6.78	23.78±7.39	0.874
p-value within the groups	0.037	0.075	
HOMA-IR value			
Baseline	2.94±1.03	2.66±1.52	0.617
End of study period	1.64±0.93	2.31±1.74	0.272
p-value within groups	<0.001	0.537	

DISCUSSION

The male-to-female ratio in our study was 1.77:1, whereas, in Puri and Varthakavi *et al.* investigations, it was 3:2 and 3.5:1, respectively ^[9,10]. The female-to-male ratio was 2.22:1 in a study conducted by Balasubramaniam *et al.* ^[11]. The study's most prevalent age group, including around 64% of the sample, was between 15 and 30. Additionally, there weren't many patients in the extreme age group—only 8% were older than 45. This was consistent with earlier research by Puri ^[9], which found that the age range of 11 to 20 accounted for the largest percentage of patients (33.3%). Additionally, 3.3% of patients were under the age of ten, while 10% were beyond the age of fifty. The average age in both research groups was 26.7 years, slightly lower than in a prior study by Varthakavi *et al.* ^[10], which was 26.3 years. The neck was the most usually involved site in both study groups, with the axilla coming in second, similar to Varthakavi *et al.* ^[10].

In group A patients, acrochordon was the most prevalent concomitant dermatological disorder, present in 36% of patients; however, in studies by Puri ^[9] and Balasubramaniam *et al.* ^[11], it was found in 26.6% and

38% of patients, respectively. For 24% and 17% of patients in groups A and B, respectively, incidental diabetes was the most prevalent endocrine condition accompanied by dysregulated fasting blood sugar. It was observed in 44.4% and 13.3% of patients, respectively, in studies by Varthakavi *et al.* ^[10] and Puri ^[9]. Compared to the Puri's study (13.3%), hypothyroidism was found in 24% of the patients. In Group A and B of our investigation, PCOD was found in 8% and 4% of female patients with acanthosis nigricans. The observation was close to Puri's study's (20%).

In this study, 15% trichloroacetic acid peeling with oral metformin resulted in the highest response grading in study group A; at the end of treatment, the median grading in the third sitting was 1.0, compared to the baseline median IQR grade of 4.0 on pre-treatment scaling, with a clinically significant difference in lesion grading (p-value = 0.001). Akter *et al.* found a substantial clinical improvement in acanthosis nigricans after metformin medication, with a baseline neck texture score of 1.87±0.08 and a post-treatment score of 1.25±0.86 (t-test) ^[12]. An open-label experiment from Mexico on obese acanthosis nigricans patients

demonstrated modest improvement in skin texture after 12 weeks of metformin, administered 500 mg thrice daily and rosiglitazone 4 mg once daily, with significant reduction in insulin levels evidenced only with rosiglitazone ^[13]. Our research showed that using metformin in addition to alpha lipoic acid and monthly chemical peeling improved the severity of the acanthosis nigricans lesion and the skin's texture. Therefore, the clinical efficacy of both medications is demonstrated. Jensterle *et al.* conducted a randomized controlled trial to compare the effects of liraglutide alone and in combination with metformin. They found that both treatments significantly reduced weight loss, but liraglutide alone had greater effects on waist circumference and BMI ^[14].

A 6-month randomized controlled trial on PCOS women found that metformin significantly reduced body weight, waist circumference, BMI, total body fat, and serum glucose levels ^[15]. Our study found that both metformin and alpha lipoic acid resulted in a substantial drop in body weight, BMI, and waist circumference in study individuals, as well as an improvement in physical appearance with chemical peeling. Okanović *et al.* found that administering alpha-lipoic acid reduced body weight and triglyceride levels but did not affect total cholesterol or serum glucose ^[16]. Cappelli evaluated the connection between insulin sensitizers and alpha-lipoic acid in obese PCOS patients, and alpha-lipoic acid in conjunction with myoinositol and metformin resulted in a considerable reduction in BMI ^[17]. Our study failed to show any significant change in BMI with alpha-lipoic acid alone, though it was well appreciated in the metformin group.

CONCLUSIONS

The advantages of this procedure are good patient acceptance and compliance, minimal side effects, early results and cost-effectiveness. Hence, alpha lipoic acid can be considered a new systemic armamentarium to combat the challenge of acanthosis nigricans or patients who cannot tolerate metformin. Limitations of the study were a small sample size and an inadequate follow-up period. So, in the future, a greater number of studies with more patients will be required to see the efficacy.

CONTRIBUTION OF AUTHORS

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Supervision- Jayashree Mohanty, Manjulata Dash

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