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ORIGINAL CONTRIBUTION

Fractional carbon dioxide laser versus trichloroacetic acid peel in the treatment of pseudo-acanthosis nigricans

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Abstract

Background: Treatment of acanthosis nigricans (AN) is challenging, and new modalities are being explored continuously to increase the therapeutic efficacy.

Aim: To evaluate the efficacy and safety of fractional CO2 laser compared to trichloroacetic acid (TCA) peel in the treatment of pseudo-acanthosis nigricans (pseudo-AN).

Methods: The study included 40 patients with pseudo-AN on the neck and axilla allocated into two groups each containing 20 patients. Group (A) was treated with TCA 20% peel applied on the pigmented area while group (B) received fractional CO2 laser. Both treatments were performed till complete clearance or for a maximum of four treatment sessions. Patients with excellent response were further followed up for 6 months after the end of treatment.

Results: Both modalities were effective in the treatment of pseudo-AN; however, the therapeutic response was significantly higher in the fractional CO2 laser group compared to the TCA peel group ($p < 0.01$). Marked to excellent response (51%–100% clearance of AN lesions) was achieved in 85% of the patients in the fractional laser group versus 10% of the patients in the TCA group. Adverse effects, for example, persistent erythema, post-inflammatory hyperpigmentation, and burning sensation, were also statistically higher in the TCA group compared to the laser group ($p = 0.04$).

Conclusion: Fractional CO2 laser is a promising effective and well-tolerated treatment modality for pseudo-acanthosis nigricans.

KEYWORDS
acanthosis nigricans, CO2 laser, trichloroacetic acid

1 | INTRODUCTION

Acanthosis nigricans is a common pigmentary disorder characterized by hyperpigmented and hyperkeratotic velvety skin lesions that presents mainly on the flexural sites, for example, the neck, the axillae, and groin.[1] The pathogenesis is mostly attributed to increased insulin resistance and hyperinsulinemia that result in stimulation of insulin growth factor 1 (IGF-1) receptors on keratinocytes and fibroblasts, leading to cellular proliferation. The dark color of AN is mostly due to hyperkeratosis rather than an increase in melanocytes.[2]

It can be simply classified into four types: benign, malignant, drug-induced, and syndromic/pseudo-acanthosis nigricans. The term pseudo-acanthosis nigricans was referred to obese individuals who have AN with no underlying endocrinopathies. In these cases, the etiology was attributed to obesity, excessive local friction, and sweat.[3]

The goal of therapy in AN is to correct the underlying disorder and treatment of AN lesions through cosmetic correction of the pigmentation.[4] Several topical and systemic agents have been used in the treatment of AN, for example, tretinoin, salicylic acid,

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calcipotriol, and oral retinoids. Laser therapy and peeling agents have also been investigated.[5] However, the results are generally unsatisfactory and the therapy of choice is not established yet. Clinical trials are needed to evaluate the comparative safety and efficacy of these different modalities in AN. In this clinical study, we aim to compare the efficacy and adverse effects of fractional CO2 laser therapy versus TCA 20% peel in the treatment of pseudo-AN.

2 | METHODS

Forty patients with pseudo-AN of any severity were enrolled into the study after obtaining written informed consent. The diagnosis was confirmed clinically based on the presence of hyperpigmented and velvety plaques of AN on the neck or axilla with no underlying cause. Exclusion criteria: children <12 years old, active herpes infection, keloidal tendency, pregnancy, lactation, diabetes, history of drug intake or hormonal disorders that may be related to AN, underlying malignancy, and history of any procedures for the treatment of AN at least 1 month before enrollment.

The severity of AN lesions was graded on a (1–4 scale) described by Hoffmann et al.[6] (evident, mild, moderate and severe AN). The patients were randomly assigned into two treatment groups each containing 20 patients: Group (A) received TCA 20% peel while group (B) received fractional CO2 laser therapy on the pigmented areas. Detailed clinical history was taken regarding the duration of AN, family history, history of drug intake or associated systemic diseases, and previous therapy. A dermatologic examination was done to assess the skin phototype, the involved area, and severity of pigmentation.

2.1 | Treatment protocol

2.1.1 | Laser group

Preoperative topical anesthetic cream (pridocaine 5%) was applied for 60 min under occlusion on the treated site. Fractional CO2 laser (DEKA Smartxide DOT C60) was used. Each patient received a treatment session every 4–6 weeks until complete clearance or for a maximum of four sessions. The used laser parameters included power (10 w), density (31.8%), dwell time (200 μs), and spacing (200 μm) with a single pass on the affected areas without overlapping.

2.1.2 | TCA group

The pigmented area was cleaned with ethanol followed by application of TCA 20% peel in a single or double coat till the formation of a uniform white frosting on the treated sites. TCA was applied at a 4-week interval for a maximum of four treatment sessions.

2.1.3 | Post-treatment care

Topical mid-potent steroid and antibacterial ointment were prescribed twice daily for 3 days. The patients were instructed to avoid rubbing or picking the scabs, tight clothing, and exercise for 3 days. They were also advised to reduce body weight through diet and regular exercise.

2.2 | Evaluation of therapeutic response

The response to treatment was evaluated by clinical examination and photographic comparison at baseline and each treatment session. The response was assessed objectively by two blinded dermatologists using a percentage of improvement (0 = no improvement, mild = 1%–25% improvement, moderate = 26%–50% improvement, marked = 51%–75% improvement, and excellent = 76%–100% improvement).

Immediate and late adverse effects were documented after each treatment session. Patients who achieved excellent response were followed up clinically every month for 6 months after the end of treatment to detect any recurrence.

2.3 | Data management and statistical analysis

The statistical package SPSS version 23 was used for data analysis. Data were described in terms of mean ± standard deviation (SD), range, frequencies (number of cases), and percentages. Chi-square (χ^2), *t*-test, or Fisher's exact test were used when appropriate. Correlation between variables was done using the Spearman rank correlation equation. Level of significance: If: $p > 0.05$ = non significant (NS), $p < 0.05$ = Significant (S), $p < 0.01$ = highly significant (HS).

3 | RESULTS

The study included 40 patients with pseudo-AN (33 female 82.5%, seven male 17.5%) whose ages ranged from 20 to 45 years old. All the patients had skin phototypes (4–5). The duration of AN lesions in the studied cases varied from 1 to 3 years with a mean of 2 ± 0.8. The neck was involved in 13 patients (32.5%) while the axilla was involved in 27 patients (67.5%). According to the severity of the lesions, eight patients (20%) had mild AN, 22 patients (55%) had moderate AN, and 10 patients (25%) had severe AN. All the patients have previously attempted other modalities for the treatment of AN in the form of topical tretinoin, adapalene, keratolytics, and kligman formula. There was no significant difference between the study groups in both the demographic data and the clinical parameters ($p > 0.05$).

All enrolled patients completed the study. In the TCA group, three patients (15%) had no improvement of AN lesions, eight patients (35%) had mild improvement (1%–25% clearance of AN lesions), seven patients (40%) had moderate improvement (26%–50%

clearance), and two patients (10%) showed marked improvement (51%–75% clearance), Figure 1. No patients (0%) had excellent improvement (76%–100% clearance) after four sessions. The maximum peeling effect was noticed after 7–10 days on the neck and after 10–14 days in the axilla.

In the fractional CO2 laser group, three patients (15%) had moderate improvement (26%–50% clearance of AN lesions), eight patients (40%) showed marked improvement (51%–75% clearance), and nine patients (45%) had excellent improvement (76%–100% clearance), Figures 2 and 3. Among the nine patients who achieved an excellent response, five patients responded after two sessions, two patients responded after three sessions, and two patients responded after four sessions. Therefore, the median number of sessions needed to achieve excellent response in the fractional laser group was 2 sessions.

A high statistically significant difference was found between the clinical response to fractional CO2 laser and TCA chemical peel ($p < 0.01$). No statistically significant correlation was found between the therapeutic response and the different clinical variables, including age, sex, skin phototype, duration, and severity of AN.

The adverse effects were tolerable including burning sensation during the procedure in 70% of the studied cases in the TCA group. Post-treatment erythema persisting >2 weeks was noticed in two patients (10%) in the laser group and a single patient (5%) in the TCA group. Post-inflammatory hyperpigmentation was observed in one patient (5%) in the laser group and four patients (20%) in the TCA group. The adverse effects in the TCA group were statistically higher than the CO2 laser group ($p = 0.04$). Details of the baseline characteristics, clinical response, and adverse effects of the studied groups are demonstrated in Table 1. Out of the nine patients who achieved an excellent response in the laser group, two patients had a recurrence of pigmentation in the treated sites during the 6 months follow-up period which necessitated a fifth treatment session.

4 | DISCUSSION

The prevalence of acanthosis nigricans has recently increased due to the concomitant increase in the prevalence of obesity and diabetes. It is most common in Native Americans and African Americans, Hispanics, and Caucasians.[7] As the pathogenesis of AN is greatly associated with obesity and hyperinsulinemia, weight reduction through diet and exercise can lead to the improvement of the lesions. Despite several therapeutic modalities, AN remains a difficult dermatosis to treat and identification of new treatment modalities is necessary.[4,5]

Topical retinoids, for example, tretinoin and adapalene, are considered to be the first-line treatment of AN as they can normalize epidermal turnover and correct the associated hyperkeratosis.[5] Topical vitamin D analogues, keratolytics, for example, ammonium lactate, salicylic, urea, and kligman formula, have been tried as alternatives to retinoids in AN with variable results. Topical treatment requires a long-term application to maintain adequate response and decrease the recurrence after cessation of treatment.[8]

The use of oral retinoids was associated with resolution of AN lesions in isolated case reports,[9,10] but the treatment requires large doses for a prolonged period and relapse is expected with lowering the dose.[8] In addition, oral retinoids are not a preferred option for the treatment of AN in young girls who seek pregnancy, due to their teratogenic effects.

The use of chemical peels as TCA can be effective in the treatment of AN through sloughing of the epidermis and removal of excess keratin and melanin. The depth of coagulative necrosis of the epidermis depends on TCA concentration.[11] Concentrations of 10%–30% induce necrosis of the entire epidermis up to the basal layer while in higher concentrations 35%–50%, necrosis reaches down to upper reticular dermis.[12]

In our study, TCA 20% single or double coat has been used on the treated sites every 4 weeks. After four sessions, 15% of the patients had no improvement, 35% had mild improvement, 40% had moderate improvement, 10% showed marked improvement, while no patients had excellent improvement (76%–100% clearance). These results were similar to those reported by Rajegowda et al.[5] who investigated TCA 15% peels (four sessions) compared to topical retinoids in 21 patients with AN. They noticed a mild improvement in 10% of patients, moderate improvement in 85%, marked improvement in 5% of patients, while none had achieved an excellent response. They also reported better response with



FIGURE 1 Pseudo-acanthosis nigricans on the neck. (A) Before treatment with TCA 20% peel. (B) Marked response (51%–75% improvement of AN lesions) after four sessions of TCA 20% peel

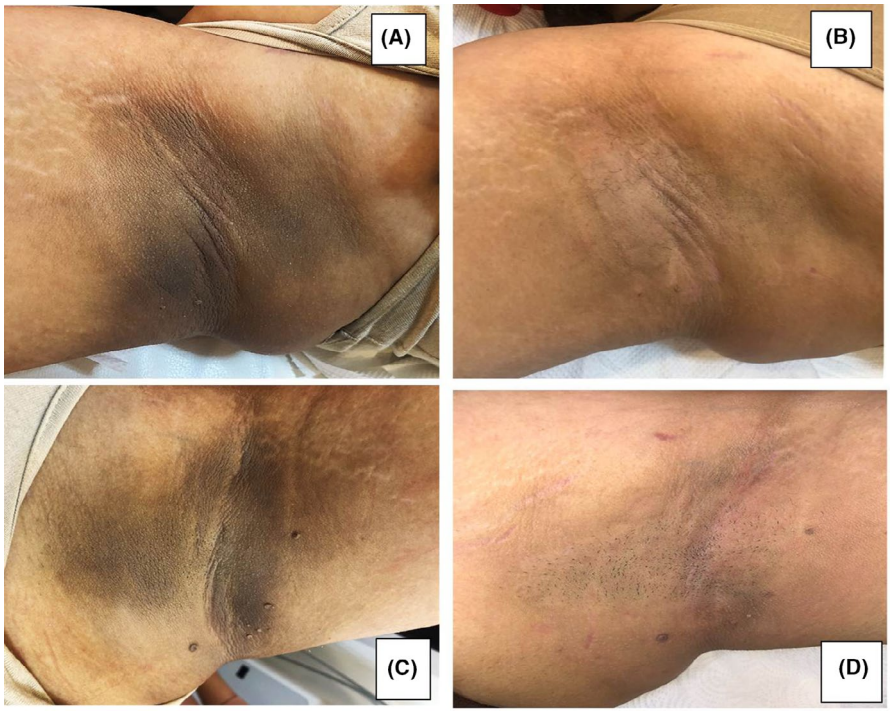


FIGURE 2 Pseudo-acanthosis nigricans in the axilla. (A) Pseudo-acanthosis nigricans in the right axilla before treatment. (B) Excellent response (76%–100% improvement of AN lesions) after two sessions of fractional CO2 laser. (C) Pseudo-acanthosis nigricans in the left axilla before treatment. (D) Excellent response (76%–100% improvement of AN lesions) after two sessions of fractional CO2 laser

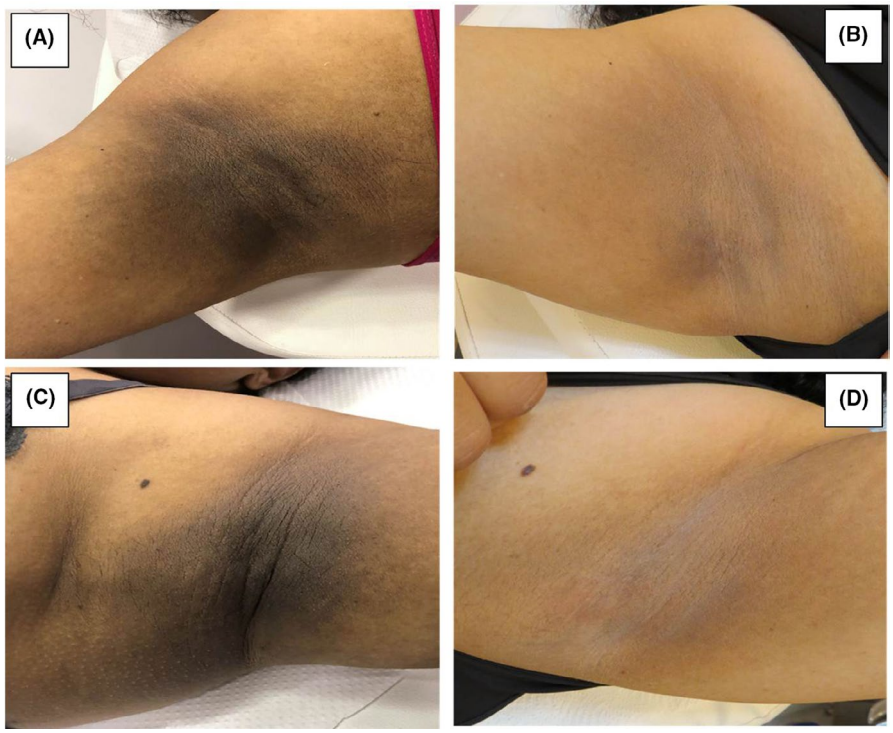


FIGURE 3 Pseudo-acanthosis nigricans in the axilla. (A) Pseudo-acanthosis nigricans in the right axilla before treatment. (B) Complete clearance of pseudo-AN lesions after three sessions of fractional CO2 laser. (C) Pseudo-acanthosis nigricans in the left axilla before treatment. (D) Complete clearance of pseudo-AN lesions after three sessions of fractional CO2 laser

topical retinoids compared to TCA peels; however, TCA was more tolerated with less erythema and burning sensation. Our results were slightly lower than the pilot study of Zayed et al.[13] who investigated TCA 15% weekly peeling for four sessions in dark-skinned AN patients. The clinical response was excellent in 30% of lesions, moderate in 50%, and was mild in 20% of the treated lesions. Their study was limited by the small sample size (six patients). Apart from burning sensation, they did not report any side effects with TCA peels.

Care should be taken with the use of TCA peel in darker skin phototypes (IV–VI), as it may induce post-inflammatory hyperpigmentation (PIH). This is most important when TCA is applied in intertriginous areas which are commonly the predilection sites of AN. In our study, PIH was noticed in 20% of the studied patients after TCA application on the neck. This can be explained by the inevitable friction at this particular site and the lack of adherence to post-operative care. In cases of PIH, we resumed TCA peeling sessions till complete recovery of hyperpigmentation.

TABLE 1 Baseline characteristics, clinical response, and adverse effects of the studied groups

	TCA group (*N* = 20)		Laser group (*N* = 20)		*T*	*p*
Age (years)						
Range	20–37		21–45		0.77	0.44
Mean ± SD	28.9 ± 6		30.6 ± 7.8			
Duration (years)						
Range	1–2		1–3		2.1	0.40
Mean ± SD	1.6 ± 0.5		2 ± 0.8			
	No	**%**	**No**	**%**	χ^2	*p*
Gender						
Female	15	75	18	90	1.5	0.2
Male	5	25	2	10		
Previous therapy						
Yes	20	100	20	100	0	1
No	0	0	0	0		
Severity of lesions						
Mild	5	25	3	15	0.68	0.7
Moderate	10	50	12	60		
Severe	5	25	5	25		
Involved sites						
Neck	6	30	7	35	0.11	0.7
Axilla	14	70	13	65		
Skin phototype						
4	18	90	17	85	0.53	0.7
5	2	10	3	15		
Therapeutic response						
0 = no improvement	3	15	0	0	25.2	<0.01 (HS)
Mild = 1%–25%	8	35	0	0		
Moderate = 26%–50%	7	40	3	15		
Marked = 51%–75%	2	10	8	40		
Excellent = 76%–100%	0	0	9	45		
Adverse effects						
Erythema	1	5	2	10	6.29	0.04 (S)
PIH	4	20	1	5		
Burning sensation	14	70	0	0		

Abbreviations: HS, highly significant ($p < 0.01$); NS, Non-significant ($p > 0.05$); S, significant ($p < 0.05$).

Various types of lasers have been investigated for the treatment of AN such as long-pulsed alexandrite laser, fractional 1550-nm erbium laser, and CO2 lasers.[8] Wijnberg et al.[14] have successfully treated a case of recalcitrant benign juvenile AN on the face, using two sessions of ablative CO2 laser under general anesthesia. Another case report by Rosenbach and Ram[15] showed a great improvement of a case of axillary AN using long-pulsed alexandrite laser. Ten treatment sessions were required to achieve 95% clearance of the pigmented AN lesions. A comparative study by Ehsani et al.[4] has demonstrated better results in the treatment of AN using long-pulsed alexandrite laser compared to topical retinoids. It acts through targeting melanin and inducing thermal healing leading eventually to tissue remodeling and pigment reduction. On the other hand, it is not a good option for dark-skinned patients for fear of possible PIH.[8]

Fractional lasers have also been successfully used in the treatment of AN. The laser beam is absorbed by water, creating microscopic columns of thermal damage. These columns act as 'melanin shuttles' that extrude thermally damaged components below the stratum corneum, known as micro-epidermal necrotic debris (MENDs).[16] These MENDS contain excess melanin that is further eliminated through the stratum corneum leading eventually to the improvement of pigmentary disorders.[17]

Leerapongnan et al.[18] have compared fractional 1550-nm erbium fiber laser (three sessions) versus topical tretinoin 0.05 for 12 weeks

in 18 patients with AN on the neck. Better improvement was noticed regarding the skin roughness and hyperpigmentation on the laser side with no reported adverse effects. They concluded that fractional erbium laser could be considered as an effective alternative treatment for AN.

A few reports have addressed the use of fractional CO2 laser in the treatment of AN.[19,20] Campos et al.[19] had treated a child with nevoid AN using two cycles of pulsed CO2 laser (2.6 J/cm^2), 2-month interval. No recurrence was noticed during 14 months follow-up. In the present study, the use of fractional CO2 laser resulted in marked improvement of both the texture and pigmentation of AN lesions. Moderate improvement was noticed in 15% of patients, marked improvement in 40% of patients, and excellent response in 45% of patients. Among the patients who had an excellent response after laser therapy, 20% had a recurrence of AN lesions during the 6 month follow-up period. Further laser sessions were performed to clear recurrent AN.

In a study by Zaki et al.,[20] 20 Egyptian patients with AN received three sessions of fractional CO2 on the right side of the neck versus glycolic acid peel 70% on the left side. Clinical improvement on the side treated by glycolic acid peel showed 43% compared to 19% improvement on the laser side. On the contrary, a higher statistically significant improvement was found in the AN lesions treated with CO2 laser compared to TCA peels in our study (p < 001). This could be attributed to different laser machines, laser parameters, and longer treatment duration in our study (four sessions).

Furthermore, laser therapy had shown better improvement regarding both the color and texture of AN lesions compared to TCA peels. The maxim peeling effect after TCA application was 7–14 days. On the other hand, fractional laser therapy was followed by mild desquamation of the treated skin in 5–7 days with no downtime and the patients could easily resume the daily activities without noticeable peeling effect. A few sessions were needed to achieve an excellent response with fractional CO2 laser (median = two sessions) while none of the patients treated with TCA peels had an excellent response after four treatment sessions.

The adverse effects were also significantly higher in the TCA group compared to the laser group. A burning sensation was noticed in 70% of the cases treated with TCA peeling, but it was tolerable and did not necessitate stoppage of treatment. Post-treatment erythema persisting >2 weeks was reported in 5% of the cases in the TCA group versus 10% in the laser group. However, it rapidly recovered with topical mid-potent steroids. Post-inflammatory hyperpigmentation was found in 20% of the patients in the TCA group versus 5% in the fractional laser group. Lower incidence of PIH with fractional CO2 laser can be explained by the rapid regeneration of the laser-ablated skin from the normal spared skin surrounding the MTZs that serve as a reservoir for tissue regeneration.[16] Therefore, fractional CO2 laser can be considered a safe option for the treatment of AN in dark-skinned population. Side effects as erosions, scarring, and secondary infection were not reported in our study.

To summarize, fractional CO2 laser therapy is a promising and effective treatment option for pseudo-AN. It is associated with higher clearance rates of AN lesions, a fewer number of sessions, and less adverse effects compared to TCA peels. Despite lower results, TCA peeling can be an easy, office-based, and cost-effective substitute for the treatment of pseudo-AN lesions.

CONFLICT OF INTEREST

No conflict of interest.

DATA AVAILABILITY STATEMENT

Authors elicit to not share data.

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