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Treatment of Verrucous Epidermal Nevus Using Long Pulsed Nd: YAG Laser

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Abstract

Background:

Verrucous epidermal nevi (VEN) are benign congenital epidermal hyperplasia and they constitute the most frequent form of epidermal nevi. Verrucous epidermal nevi lesions typically occur on the trunk or extremities but may also occur on the face and neck. The lesions may vary from skin colored to brown. No ideal treatment is yet available.

Objective:

To evaluate the efficacy and safety of long pulsed Nd: YAG laser (1064 nm) in treatment of verrucous epidermal nevus.

Patients and methods:

This study was conducted on twenty-one patients with verrucous epidermal nevi. They were subjected to treatment with long pulsed Nd: YAG laser (1064 nm) with 5mm spot size, 110J-150J/cm² fluence and 20-40msec pulse duration. A part of each lesion was subjected to laser treatment and the other part was left untreated as a control. Sessions were performed monthly for a maximum of 6 months.

Evaluation included clinical, histological, and patient self assessment. Follow up was carried for 6 months after the last session.

Results:

Patients received a mean of 4.48 ±1.33 sessions. Eight patients (38.1%) showed an excellent improvement, 9 patients (42.9%) had good improvement, and 4 patients (19%) had moderate improvement. Hypopigmentation was reported in one patient with skin type V. No recurrence was reported during the follow up period. After treatment with Nd: YAG laser, the histopathology revealed orthokeratosis, a thinned epidermis, sparse superficial perivascular lymphohistiocytic infiltrate and a normal capillaries appearance. Before treatment the mean ±SD of epidermal thickness was 169.5±22.9µm (range 209-138 µm) which reduced significantly to 69.8±15.5 after treatment (P<0.001).

Conclusion:

Long pulsed Nd: YAG laser is successful modality for treatment of verrucous epidermal nevus with no scarring and less downtime healing. However, further studies are necessary to refine the procedure and to confirm the present encouraging findings; also longer periods of follow up are needed.

Introduction

Epidermal nevi are hamartomas of the skin and have multiple clinical variants, including a verrucous type [1]. Verrucous epidermal nevi (VEN), constitute the most frequent, form, however, three other forms of epidermal nevi can be distinguished; inflammatory linear verrucous epidermal nevus (ILVEN), Darier-like epidermal nevus and linear porokeratosis [2].

Verrucous epidermal nevi occur in circumscribed patches or more often, in linear streaks or whorls following Blaschko's lines [3]. The lesions typically occur on the trunk or extremities, but may also occur on the face and neck [1]. Clinically, flat, velvety, papillomatous nevi developed in the newborn and have been distinguished as 'soft', whereas, more keratotic, verruciform lesions occurred during adolescence and were described as 'hard' [1,2]. The lesions may vary from skin-colored to brown [2].

Histologically, keratinocytic, or verrucous epidermal nevi are characterized by acanthosis, orthohyperkeratosis, papillomatosis, and an expanded papillary dermis which is sharply demarcated from the surrounding normal skin [2]. Analyzing 167 biopsy specimens from 160 patients with epidermal nevi, excluding nevus sebaceous, verruca-like features were described in (2%) and dilatation of blood vessels have been found [4].

Patients usually seek advice because of the disfiguring cosmetic appearance [2]. No ideal treatment is yet available, the topical treatments such as combined therapy of retinoic acid and 5-fluorouracil, dithranol, occlusive topical steroids, chemical peels and podophyllin may improve the keratotic surface however, they

always correlate with high rate of recurrence [5]. On the other hand, more aggressive approaches such as cryosurgery, electro-cautery and dermabrasion are used but recurrence is common if the damage is superficial and hypertrophic or hypopigmented scarring can occur if a significant proportion of reticular dermis is removed [6]. In the last three decades, multiple modalities of laser treatment have been tried; however, very few studies reported comparative results. Based on selective photothermolysis, pigment-specific lasers can be used to achieve significant cosmetic improvement of dark epidermal nevi with a reduced risk of scarring, but successful treatment was not achieved in non-pigmented or keratotic lesions [7]. Ablative lasers, such as CO_2 laser and erbium-YAG laser have been used for the treatment of superficial epidermal pigmented lesions [6,8]. Their wavelengths are absorbed by both intra- and extracellular water of the epidermis and dermis, which results in a non-specific destruction [8-10]. There is a relatively narrow margin of safety when treating epidermal nevi; if the treatment is too superficial with removal of the epidermis only, the nevus will recur and if it goes too deeply into the reticular dermis, hypertrophic scaring may develop [11]. In Previous studies, 585-nm Pulsed dye laser (PDL) has been used successfully in treatment of inflammatory linear verrucous nevus (ILVEN), which is a variant of epidermal nevi, by destructing the dilated blood vessels and decreasing the inflammatory process [12,13]. Based on the postulation that oxyhemoglobin in blood vessels has strong absorption peaks at wavelengths ranging from 585 to 595 nm of PDL and moreover has a significant, albeit more modest, absorption peak between 800 and 1,100 nm, long pulsed Nd -YAG laser (1064nm) have been used in the treatment of vascular defects as telangiectasia, portwine stains, haemangioma, spider nevi, varicose veins [14,15] and other entities with an associated blood supply including verrucous lesions such as warts [16]. Therefore, this study was designed to evaluate the efficacy and safety of long pulsed Nd: YAG laser in treatment of verrucous epidermal nevus with the target its blood vessels.

Patients and Methods

During the period from September 2008 to August 2009, this study was conducted on twenty-one patients (9 males, 12 females), with verrucous epidermal nevi in the Outpatient Clinics, National Institute of Laser Enhanced Sciences, Cairo University, Egypt. The age of the patients ranged from 5-20 years. The duration of the disease ranged from 2 -16 years. Patients were of skin type III, IV, and V. No previous treatment had been received by any of the patients. Lesions distribution is shown in **table 1**.

Before starting treatment, an informed written consent was obtained and photo documentation was carried out. They were subjected to treatment with long pulsed Nd: YAG laser (1064 nm Cool Glide Excell; Altus Medical Burlingam, CA) with 5 mm spot size, 110J-150J/cm² fluence and 20-40 msec pulse duration with contact cooling. The fluence and pulse duration differed for each patient, depending upon thickness of the lesions, skin type and a previously performed spot test. Flat, velvety Lesions were treated with lower fluences and short pulse duration (110J-130J/cm2, 20-30ms), whereas, hard hyperkeratotic lesions were treated with higher fluences and longer pulse duration (130J-150L/cm2, 30-40ms). Patients with skin type V were treated with lower parameter settings even when their lesions were hard and hyperkeratotic.

The laser beam was fired through a cooled sapphire window with a diameter of 10 mm. For each laser pulse, pre-cooling of the lesion was achieved by contact cooling using the gold plated cooling head of the laser's hand piece for 3-5 seconds; the window was kept in contact of the skin surface for 5 seconds. The laser pulse was delivered followed by cooling for additional 2 seconds. The process was repeated in the same manner before and after application of each laser pulse to protect the epidermis. The sapphire window was continuously cooled by a surrounding gold-platted copper ring containing circulating water at approximately 51◦C. Overlapping of 2-3 pulses were needed in order to establish the grayish discoloration of the lesion that marks the end point of the treatment session.

Steel eye shield was used during laser session for one patient with infra-orbital lesion to protect the eye globe while the rest of the patients had their eyes protected by the ordinary opaque plastic goggles. Treatment was carried out under local anesthesia with lidocaine/prilocaine (EMLA) cream applied in an occlusive dressing approximately 1 hour before the start of the laser session.

For larger lesions, a representative part of the lesion was treated and similar size was left as a control according to the size and location of the lesions. Sessions were performed monthly for a maximum of 6 months. Patients were evaluated at 5 to 10 days after treatment to identify any adverse events. Patients stopped to receive sessions at any time during the protocol of treatment when no further improvement was observed by either doctors or patients for 2 subsequent sessions. After treatment, a cream (Fusidic acid 2%+Betamethasone 0.1% preserved with chlorocresol) was prescribed to patients for 2-3 days following each session. Sunscreen creams were also recommended depending upon the exposure of the lesion site to sun. Follow up was carried for 6 months after the last session.

Evaluation procedures

Clinical assessment: This included photographic documentation with digital camera; Kodak DX 3700, 3.1 Mega pixels, 3xs zoom was conducted before and after treatment. Patients were asked to report any adverse effect. The degree of improvement was determined as the percent of reduction in the clinical signs; which include reduction in the size, pigmentation and texture relative to the control (untreated site) in gradation of 10% to 100% rating. Excellent improvement is considered to be from 90%-100%, good improvement from 50%-89%, moderate improvement from 20%-49%, and poor from 0-19% [17]. The percentage reduction evaluations were based on the subjective appearance of the treatment sites, not on actual measurements.

Histopathological assessment: This was done using three mm punch biopsies, obtained from lesions before and after treatment, stained by hematoxylin and eosin (H&E).

Microscopic Image analysis for histopathological samples: The data were obtained using Leica Qwin 500 image analyzer computer system (England). The image analyzer consisted of a colored video camera , colored monitor, hard disc of IBM personal computer connected to the microscope , and controlled by Leica Qwin 500 software The image analyzer was first calibrated automatically to

convert the measurement units (pixels) produced by the image analyzer program into actual micrometer units.

The epithelial thickness was measured in each specimen using the interactive measuring menu with an objective lens of magnification 10 i.e. of total magnification 100. Readings were obtained from each specimen & the mean values were calculated in pre & post laser treatment. The data obtained were subjected to statistical analysis using Student's t- test

Patient self assessment: This was conducted to grade the overall satisfaction with treatment one month after the last session. The satisfaction scale simply was done asked each patient about being very satisfied, satisfied, or not satisfied with the degree of lesion regression by comparing lesions photographs before and after treatment .

Statistical analysis:

The data were coded and tabulated using the statistical package SPSS version 17.0.The data were described using the percent for qualitative data. "Pearson's product moment correlation coefficient" test is used to measure the correlation (linear dependence) between two variables giving a value between +1 and -1 inclusive.

Results

Clinical results:

Twenty-one patients presented with lesions of verrucous epidermal nevi of different sizes, thickness and at different anatomical sites. The mean age of patients was 12.76 ± 4.4 years (range 5-20 years). They were 12 females (57.1%) and 9 males (42.9%). Fitzpatrick skin type III was in 6 patients (28.6%), IV in 12 patients (57.1%), and V in 3 patients (14.3%). Mean duration of lesions was 7.48 ± 3.9 years (range 5-20 years). The most frequent location was on the trunk in 5 patients (23.8%), followed by the face in 4 patients (19%), upper limbs (arms) in 3 patients (14.3%), axilla in one patient (4.8%), lower limbs (2 thighs ,1 leg) in 3 patients (14.3%), genitalia (2 vulva, 1 scrotum) in 3 patients (14.3%), and buttocks in 2 patients (9.5%).Clinical data of patients and lesions distribution were shown in **table 1**.

Assessment of clinical improvement:

Site of lesions

Out of 21 patients; 8 patients (38.1%) showed excellent improvement, 9 patients (42.9%) had good improvement, and 4 patients (19%) had moderate improvement **(table 2)**. Excellent results were achieved in 8 lesions; 3 (14.3%) lesions on the face, 2 (9.5%) on the buttocks, and 3 (14.3%) on the genitalia (2 vulva, 1 scrotum). Good results were achieved in 9 lesions; 4 lesions (19%) on the trunk, 2 (9.5%) lesions on the upper limb (arms), and one lesion (4.8%) on each of

the following sites; the face, lower limb (thigh) and axilla. However, moderate results were obtained in 4 lesions; 2 lesions (9.5%) on the lower limbs (leg and thigh), and 2 lesions (9.5%) on the trunk and arm **(fig 1)**.

There were no treated sites that showed no improvement or poor results were obtained in this study. Improvement of the hard elevated lesions was gradual flattening of the lesions followed by shrinkage of the lesion. Improvement of soft velvet lesions were elicited by a decrease in size. Hypopigmentation was reported in one patient (4.8%) with skin type V. Clinical assessment efficacy was supported by comparing the pre and post treatment photographic documentation **(fig 2-4)**. In comparison the untreated control sites showed no improvement. Follow up the patients was carried on for 6 months after the last laser session without recurrence.

Variable		Patients number	Percentage
Gender	**female**	12	42.90%
	male	9	57.10%
Skin type	**III**	6	28.60%
	IV	12	57.10%
	V	3	14.30%
Site of lesions	**Face**	4	19%
	Trunk	5	23.80%
	Upper limb	3	14.30%
	axilla	1	4.80%
	Lower limb	3	14.30%
	genitalia	3	14.30%
	buttocks	2	9.50%

Table1. Clinical data of patients

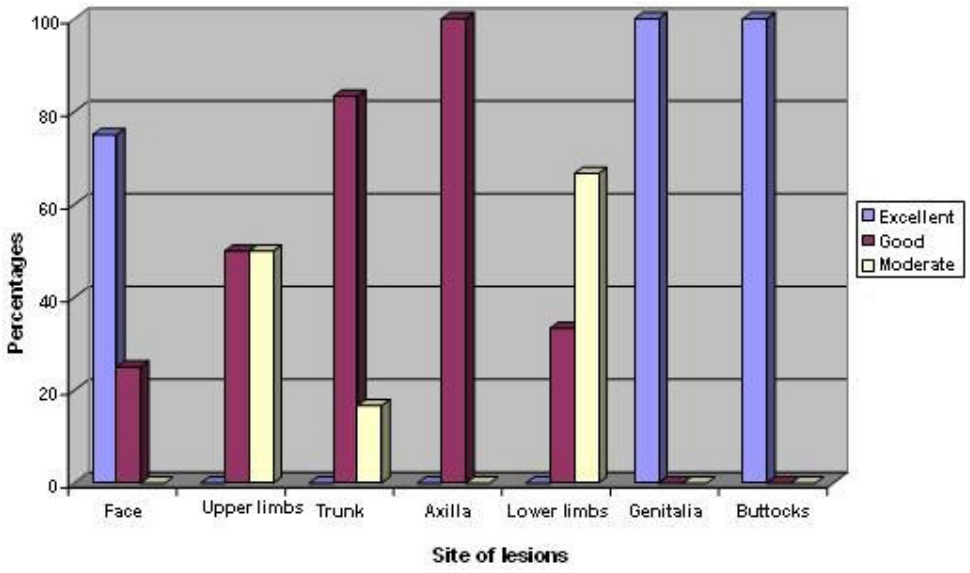

Fig 1: Percentages of the degree of lesions improvement in regards to lesions distribution.

Site of lesions	Number of Patients (percentage %)			
	Excellent	Good	Moderate	Total
Face	3 (14.9%)	1 (4.8%)	-	4 (19%)
Trunk		4 (19%)	1 (4.8%)	5(23.8%)
Upper limbs	-	2 (9.5%)	1 (4.8%)	3(14.3%)
Axilla	-	1 (4.8%)		1 (4.8%)
Lower limbs		1 (4.8%)	2 (9.5%)	3(14.3%)
Genitalia(vulva& scrotum)	3 (14.9%)	-	-	3(14.3%)
Buttocks	2 (9.5%)	-	-	2 (9.5%)
Total	8 (38.1%)	9 (42.9%)	4 (19%)	21(100%)
*Average improvement (percentage)	95%	70%	35%	

* Excellent improvement (90%-100%), good improvement (50%-89%), moderate improvement (20%-49%)

Table2: The number of patients (percentage) regarding the site of lesion and degree of improvement

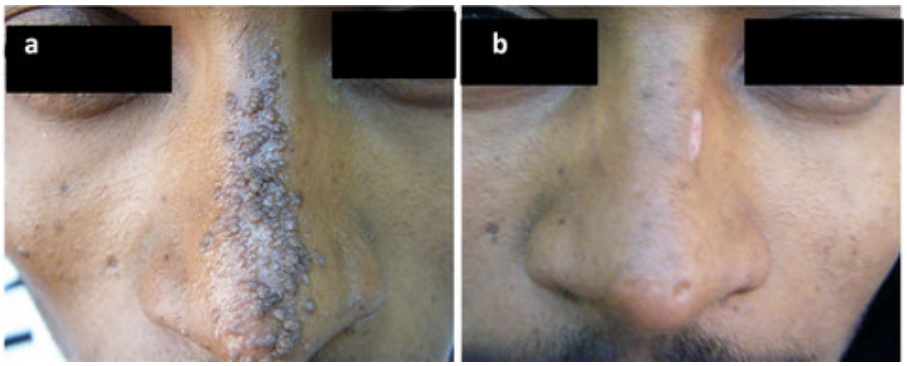

Fig 2: twenty years- old patient with VEN on the nose **(a)** before treatment and **(b)** excellent improvement after 4 sessions, hypo-pigmentation appeared in the upper right side.

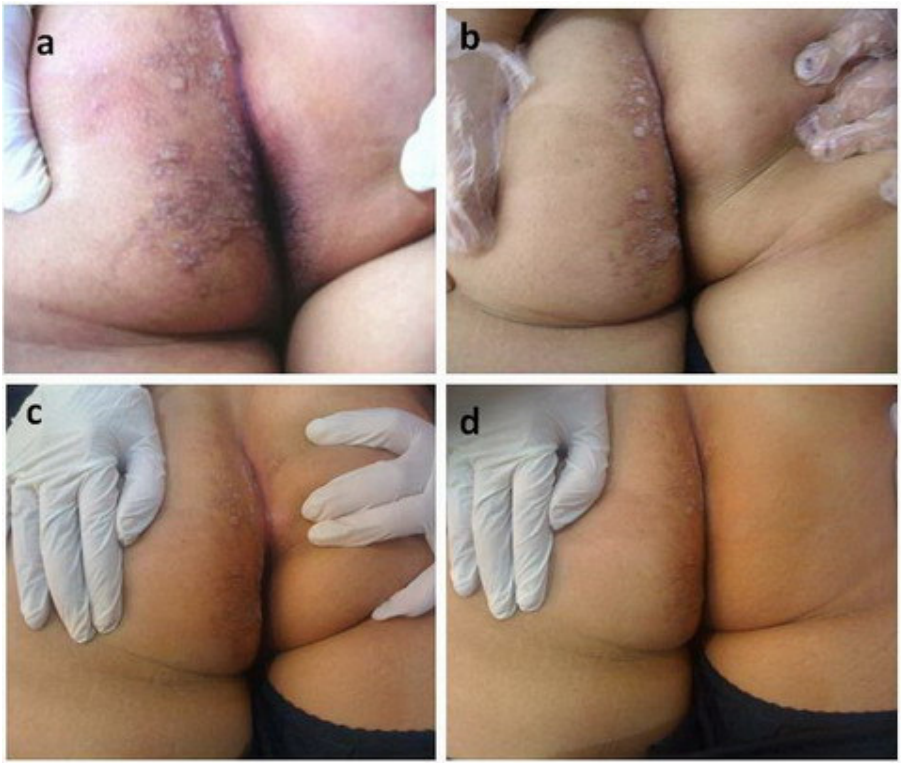

Fig 3: Twelve year-old female patient with VEN on the buttocks; **(a)**: before treatment, **(b)**: after 2 sessions, **(c)**: the left lower inner medial part is the control site and **(d)**: after treatment. The right lateral part has received 4 sessions showing excellent result.

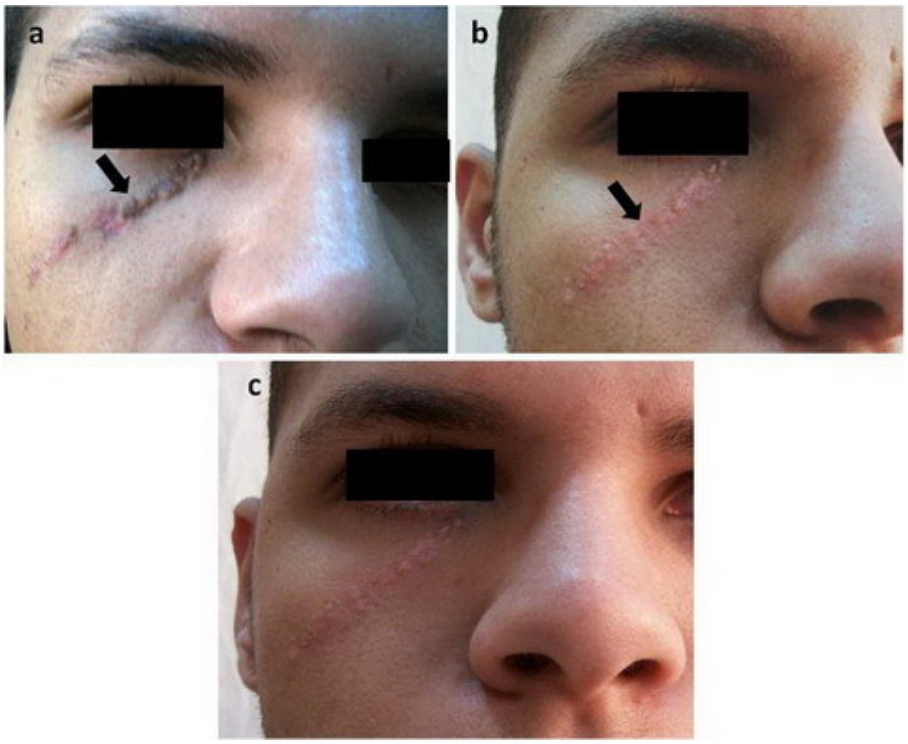

Fig 4: Nineteen year-old male patient with VEN on the face; **(a)**: the lower treated part after 2 sessions, **(b)** showed excellent improvement of the lower part after 4 sessions and **(c)** the upper part has been done for the patient during the follow up period to give him better cosmetic appearance (the arrow showed demarcation between lower part (treated) and upper part. The arrow pointed to the site of biopsy.

Number of sessions

Patients received a mean of 4.48 ±1.33 sessions (range 2-6 sessions). Four patients (19%) received 3 sessions, 9 patients (42.9%) received 4 sessions and 8 patients (38.1%) received 6 sessions. It has been observed that excellent improvement was obtained in 3-4 sessions in lesions located on the face, genitalia and buttocks however this was statistically insignificant. The relationship between the number of sessions, degree of clinical improvement and sites of the lesions was shown in **fig 5**.

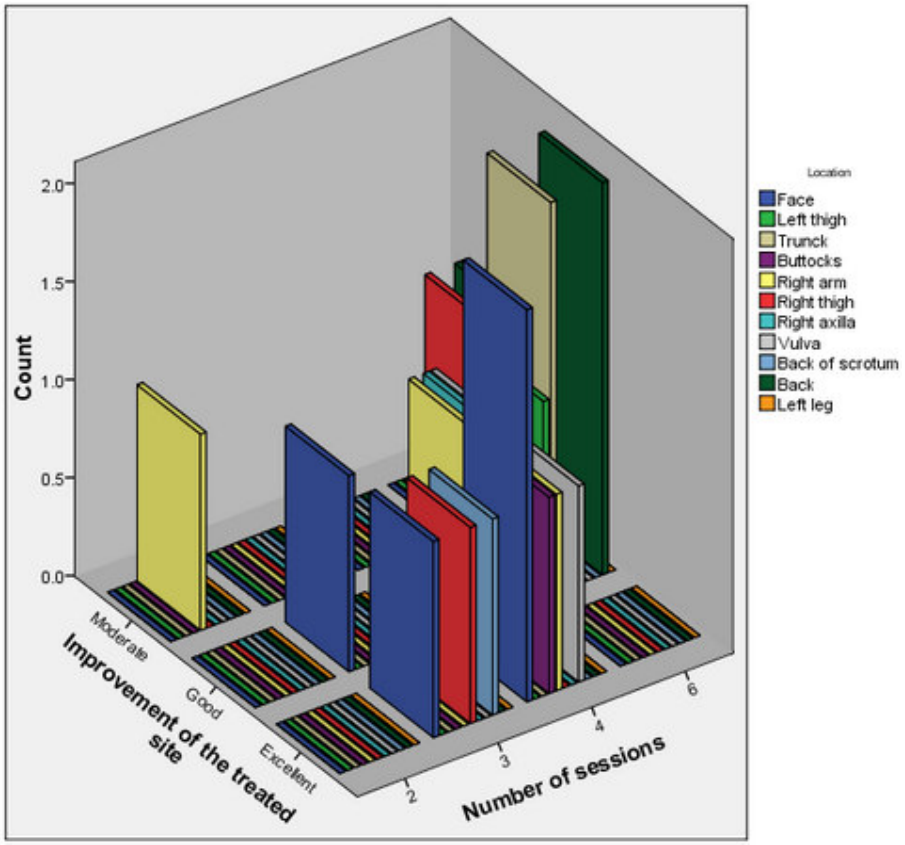

Fig 5: The relation between improvement of treated sites, number of sessions.

Correlations between the degree of improvement and site of lesions

"Pearson's product moment correlation coefficient" test was used to measure the correlation between the degree of improvement and the site of lesions. A positive correlation was found between the excellent degree of improvement and the face (r=0.959, p = 0.182), the genitalia (r=0.814, p= 0.394) and the buttocks (r=0.814, p= 0.394) however this was statistically insignificant **(table 3)**.

Site	R	*p*
Face	0.959	0.182
upper limbs	-0.814	0.394
Trunk	-0.094	0.94
Axilla	0.096	0.939
Lower limbs	-0.995	0.061
Genitalia	0.814	0.394
Buttocks	0.814	0.394

Table 3: Correlation between the degree of improvement and site of lesions done by Pearson's product moment correlation coefficient

Histopathological results: (fig 6)

Before treatment, histopathological examination showed epidermal hyperplasia, papillomatosis, hyperkeratosis, dilated blood vessels and perivascular lymphohistiocytic infiltrates in the superficial dermis **(fig 6 a, b)**. After treatment with Nd: YAG laser, the histopathology revealed orthokeratosis, a thinned epidermis **(fig 6 c, d)**, sparse superficial perivascular lymphohistiocytic infiltrate and a normal capillaries appearance. The papillary collagen was highly packed; coarse and clumped **(fig 6 c)**.

Epidermal thickness was measured before treatment and after Nd:YAG laser treatment as shown in **fig 7 a, b** . Before treatment the mean ± SD of epidermal thickness was 169.5 ± 22.9µm (range 209-138 µm) which reduced significantly to 69.8 ± 15.5 after treatment (P<0.001) **(table 4)**.

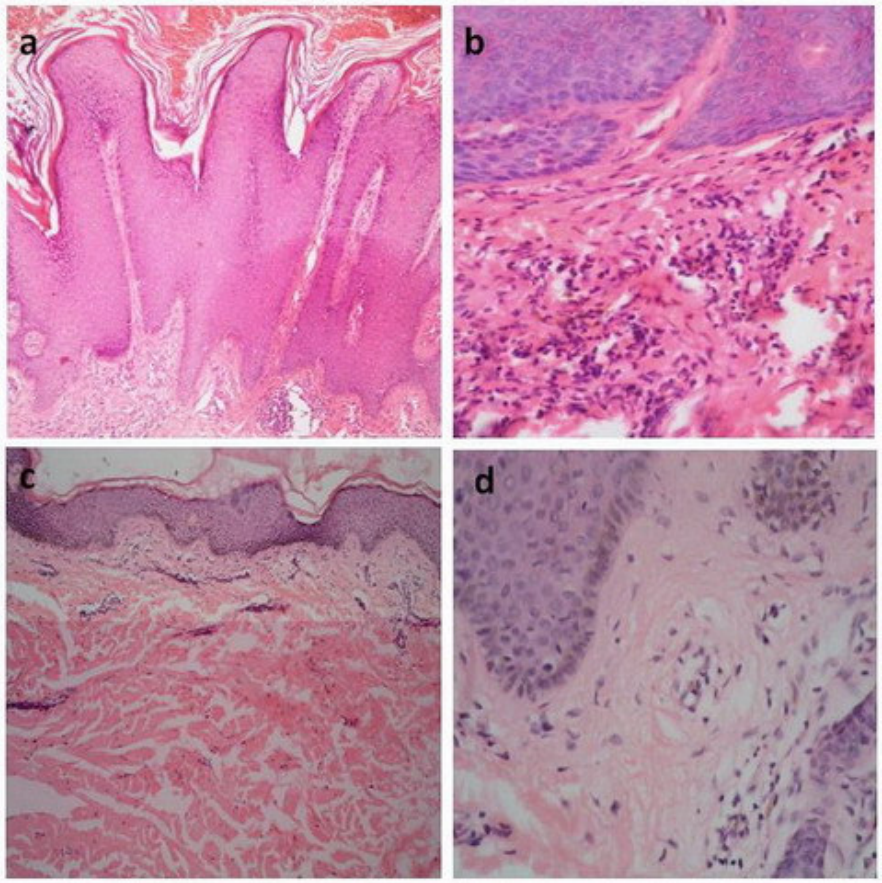

Fig 6: (a) before treatment showing epidermal hyperkeratosis, acanthosis and papillomatosis (H&E x100), **(b)** before treatment showing mild perivascular lymphohistiocytic infiltrates in the superficial dermis and dilated capillaries (H&E x400), **(c)** after treatment showing orthokeratosis and thinned epidermis with reduction of papillomatosis (H&E x100), **(d)** after treatment showing sparse superficial perivascular lymphohistiocytic infiltrates and a reduction in number of blood vessels (H&E x400).

*Epidermal thickness	Before treatment	After treatment
Maximum	209.03	91.1
Minimum	138.7	41.5
Mean±SD	169.5±22.9	69.8±15.5
P value	<0.001**	

* Epidermal thickness was measured in micrometer (µm)
** Highly significant

Table 4: Epidermal thickness measurements before and after laser treatment

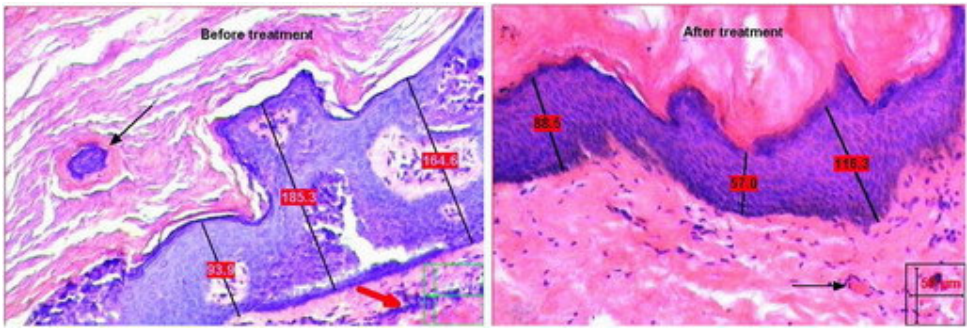

Fig 7: (a) showed measurements of the epidermal thickness at different points before treatment. The black arrow pointed to large thickened blood vessels. The red arrow pointed to the inflammatory infiltrates. **(b)** showed reduction in measurements of epidermal thickness at different points after treatment. The black arrow pointed to normal blood capillary (H&E x100).

Patients self assessment results

One month after the last laser session each patient graded his level of satisfaction regarding the improvement of cosmetic appearance using the photographs taken before and after treatment. Thirteen patients (61.9%) were very satisfied with the results of treatment, 5 patients (23.8%) were satisfied and asked for treatment of the whole lesion however and 3 patients (14.3%) were not satisfied.

Discussion

The treatment of verrucous epidermal nevus is difficult and often un-satisfactory. The multiple treatment modalities that have been used show that managing this disease is challenging. Ablative lasers such as CO_2 and Erbium-YAG laser have been considered as the gold standard for treatment of VEN [6,8]. However, vaporization should extend only into papillary dermis; thus, thick,

verrucous lesions may be unresponsive or produce hypertrophic scars, owing to the unpredictable penetration of the laser beam through the verrucous tissue [8]. In addition, the expected outcome after healing is hypopigmentation especially in dark skinned patients [6,9]. Hohenleutner et al [6] reported that poor results (partial or full recurrence, hypertrophic or keloidal, cosmetically unacceptable scar) were found in 5 of 12 patients after the continuous-wave CO_2 laser therapy of verrucous epidermal nevi. Literature relating to the erbium-YAG laser is mainly concentrated on resurfacing techniques; however, excellent cosmetic results without apparent scarring in patients with epidermal nevi located in problematic sites, such as the neck and upper chest have been documented [9]. These could be due to biases in the selection of cases with superficial or small lesions as thick, verrucous lesions may not respond or produce hypertrophic scars, owing to the unpredictable penetration of the laser beam through the warty tissue and 25% of patients can show a relapse within 1 year after the treatment [18]. In contrast, lasers such as the 585-nm PDL have shown good results in the treatment of ILVEN, which is a variant of epidermal nevi [12,19].

Sidwell et al [13] explained the success of pulsed dye laser in treatment of ILVEN by destruction of the dermal capillaries based on the theory of selective photothermolysis [20] and the reduction in the number of capillaries and inflammatory mediators reaching the epidermis supports this idea [19]. Two aspects can explain the mechanism of action of long pulsed Nd: YAG laser in treatment of VEN. First, ILVEN and VEP share the histopathological features of dermal involvement with a lymphohistiocytic inflammatory infiltration and dilated blood capillaries of the upper dermis [4].The Second explanation; oxyhemoglobin is a chromophore which absorbs both wavelengths; 585nm pulsed dye laser and to a lesser degree, the 1064nm Nd: YAG laser; allowing the 1064nm wavelength to penetrate deeper (from 3.7 up to 6 mm) into tissue than visible light, enabling heat delivery to occur more deeply into the dilated blood vessels [14]. Thus, selective thermal photocoagulation of dermal blood capillaries of VEN leads to regression of lesions that was elicited clinically, and confirmed histologically, where marked reduction in epidermal thickness and number of blood vessels was observed after end of treatment. Nd: YAG wavelength allows even deeper penetration into the dermis with relative sparing of the epidermis and because of the minimal-energy absorption by melanin occurs at this wavelength, darker skin types can be treated with minimal risk to the epidermis [14,17]. During the treatments the epidermis was effectively protected by the chilled cooling head of the laser's hand piece that is a component of this laser equipment thus, excellent pre-operative, and postoperative skin cooling was achieved together with a constant perfect view of the operative field. Our results showed healing with no scarring, no downtime a, and a low risk of adverse effects, compared to the results of the studies done on the ablative lasers such as CO_2 and erbium-YAG [6,8,11].

Hypo-pigmentation has been shown in one patient and it faded out after 4 months. High fluences (130J-150L/cm2) were used to compensate of for the possible loss of heat as thick hyperkeratotic epidermis increases the reflection of laser light [21,22]. Long pulse duration (30-40ms) was chosen to occlude large deep blood vessels nourishing the thicker hyperkeratotic epidermis [23]. Long pulsed Nd: YAG has been used safely with high fluence and with repeated overlapping pulses. It has been used for treating acne scars using 120J/cm2 fluence

where triple pulses were applied to each acne scar [24]. It was observed clinically that the face, buttocks and genitalia (vulva and scrotum) were the first sites to show the satisfactory results in the least number of sessions; however this was statistically insignificant due to small sample size. The elicited improvement can be explained by the fact that the skin is more vascular and the epidermis is thinner in these sites so it responded better [22]. Better results were obtained with early lesions, so early intervention was advised. Hohenleutner et al [6] conducted that soft lesions responded better to CO_2 laser than hard lesions; however, long pulsed Nd: YAG laser enabled effective treatment of both soft and hard lesions by selecting the proper fluence and pulse duration suitable for each type.

Conclusion

Long pulsed Nd: YAG is a successful modality for treatment of verrucous epidermal nevus with no scarring and minimal downtime. However, further studies are necessary to refine the procedure and to confirm the present encouraging findings, longer periods of follow up, are needed.

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