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The Effectiveness of Tranexamic Acid in the Treatment of Lichen Planus Pigmentosus and Erythema Dyschromicum Perstans in a tertiary care centre

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ABSTRACT
Background: Lichen planus pigmentosus (LPP) and erythema dyschromicum perstans (EDP) (also known as ashy dermatosis (AD)) are two conditions on the spectrum of dermal pigmentary disorders.There are currently no effective treatments for lichen planus pigmentosus (LPP) and erythema dyschromicum perstans (EDP).Lichen planus pigmentosus (LPP), is a fairly frequently encountered disorder of hyperpigmentation in Indians.Tranexamic acid, which downregulates pigmentation through a reduction in plasmin, can be a promising agent in these disorders. M**aterial and methods:** Place of study: Department of Dermatology, Nalanda Medical College & Hospital, Patna. Type of study: Interventional Study. Study Design: Allocation: N/A, Intervention Model: Single Group Assignment, Primary Purpose: Treatment, Masking: None (Open Label). Intervention Model Description: This a proof-of-concept study. 20 subjects (10 + 10 each) of LPP and EDP will be enrolled and all 20 will receive tranexamic acid. Actual Study Start Date: 19 April 2020, Estimated Study Completion Date: 30 April 2021. **Results:** In LPP ten patients were enrolled, one male and 9 women, mean age 42.80 ± 11.24-years, from 26 to 64-years. The mean duration of the disease was 7.50 ± 7.12 years. In EDP ten patients were enrolled, three male and seven women, mean age 42.00 ± 10.34-years, from 29 to 80-years. The mean duration of the disease was 8.50 ± 6.12 years In LPP good or favourable result was found in 70 percent of cases & rest shows unfavourable result, similarly in EDP good or favourable result was found in 80 percent of cases & rest shows unfavourable result after taking Tranexamic acid for 6 months. **Conclusion:** Based on the available data in the literature, it is recommended that oral TXA should only be used in cases of LPP & EDP that are unresponsive to topical hydroquinone and combination topical therapy over a period of approximately 12 weeks and if there are no contraindications to oral TXA. However, large-scale, randomized controlled trials are warranted to better characterize the role of oral TXA in the therapeutic ladder of LPP & EDP.

Key words: Lichen planus pigmentosus, Erythema Dyschromicum Perstans, Tranexamic acid

I. INTRODUCTION:

Lichen planus pigmentosus (LPP), is a fairly frequently encountered disorder of hyperpigmentation in Indians. Although initially described in Indians, this disorder has subsequently been seen in other racial and ethnic groups [1-2]. Several pigmentary illnesses with identical symptoms have been described in the literature under various names, including ashy dermatosis [3], erythema dyschromicum perstans [4], lichen pigmentosus [5], and 'lichen invisible pigmentogene' [6], with significant clinical overlap [7-11]. Vega et al. [9] reported in 1992 that LPP and ashy dermatosis are distinct entities and presented clinical and histopathological differences between the two. Convit and colleagues used the term EDP in 1961 in a report of five cases in which the disease was characterized by numerous small and large macules of a grayish color of varying intensity, sometimes becoming confluent covering extensive areas of the body. When the lesions were evolving, the macules had a slightly raised, firm, erythematous border that felt like a thin piece of string [4].

The etiology mostly remains unknown. The age range is from childhood through maturity, and both sexes are affected equally. Tranexamic acid, which may down regulate pigmentation through a reduction in plasmin, has been shown to decrease pigmentationin patients with melasma,

another pigmentary disorder [5]. Tranexamic acid (TA) is a synthetic analog of lysine, and serves as a fibrinolytic agent by binding lysine sites on fibrinogen. Commonly used in surgery to prevent bleeding, it has recently been used in dermatology for the treatment of melasma. Melasma is a pigmentary disorder characterized by hyperpigmented patchesin sun-exposed areas, often in response to hormones, sunlight, and other factors. The proposed mechanism of action of tranexamic acid in decreasing pigmentation in this condition is that it decreases inflammation by decreasing dermal angiogenesis and inhibits UV induced plasmin activity in keratinocytes [6]. In a study by Lee et al., when administered orally at a dose of 250mg twice daily over approximately 4 months, 89.7% of patients had documented improvement in pigmentation. Of those who improved, the median lightening was approximately 50%, which is significant. Other studies have also shown promising results [12].

This present study was done to demonstrate effectiveness of TA over LPP & EDP in a prospective cohort.

II. MATERIAL AND METHODS:

Place of study: Department of Dermatology, Nalanda Medical College & Hospital, Patna. **Type of study:** Interventional Study. **Study Design:** Allocation: N/A, Intervention Model: Single Group Assignment, Primary Purpose: Treatment, Masking: None (Open Label). **Intervention Model Description:** This a proof-of-concept study. 20 subjects (10 + 10 each) will be enrolled and all 20 will receive tranexamic acid.

Interventions: Drug Tranexamic acid tablets: 325mg of tranexamic acid twice daily for six months. **Experimental treatment:** All 20 subjects (10 + 10 each) will receive tranexamic acid tablets, 325mg twice daily for six months. **Actual Study Start Date:** 19 April 2020, **Estimated Study Completion Date:** 30 April 2021

Clinical Trial Outcome Measures

Primary Measures:

Change in Pigmentation using Colorimetry,

- Time Frame: 3 visits over 180 days
- Determine if there is a reduction in pigmentation in patients with LPP or EDP after administration of tranexamic acid using colorimetry.

Change in Pigmentation using Diffuse Reflectance Spectroscopy,

- Time Frame: 3 visits over 180 days
- Determine if there is a reduction in pigmentation in patients with LPP or EDP after administration of tranexamic acid using diffuse reflectance spectroscopy.

Secondary Measures:

Change in Erythema using Colorimetry,

- Time Frame: 3 visits over 180 days
- Determine if there is a reduction in erythema in patients with LPP or EDP after administration of tranexamic acid using colorimetry.

Change in Erythema using Diffuse Reflectance Spectroscopy,

- Time Frame: 3 visits over 180 days
- Determine if there is a reduction in erythema in patients with LPP or EDP after administration of tranexamic acid using diffuse reflectance spectroscopy.

Inclusion Criteria: Subject age 18 and older – Subject with a diagnosis of LPP or EDP–Subject able to understand requirements of the study and risks involved –Subject able to sign a consent form – Subject to have discontinued all topical or oral medications, with the exception of sunscreen, used to treat pigmentary abnormalities one month prior to treatment.

Exclusion Criteria: Personal history of clotting disorder or thromboembolic disease (deep vein thrombosis (DVT), stroke, etc) – Active malignancy, excluding non-melanoma skin cancer – Moderate to severe renal impairment – History of migraine with aura – Current anticoagulant therapy – Current use of hormonal contraception or hormone replacement therapy in the last 30 days – A woman who is lactating, pregnant, or planning to become pregnant

Conditions in This Trial: Lichen Planus Pigmentosus & Erythema Dyschromicum Perstans.

Data analysis: The collected data were analysed with IBM. SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the unpaired sample t-test was used. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value 0.05 is considered as significant level.

III. RESULTS:

A prospective study was conducted in the Department of Dermatology, Nalanda Medical College & Hospital, Patna, from April 2020 to April 2021. A total of 20 patients (10 + 10 each) of

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Lichen Planus Pigmentosus and Erythema Dyschromicum Perstans.

Table 1: Demographic and Clinical Data of 10 Patients with Lichen Planus Pigmentosus

S/N	Sex	Age in years	Phototype	Duration in years	Pruritus	Face	Peribuccal	Neck	FFA	TA	F/U after 6 months
1	**M**	**32**	**III**	**4**	+	+	+	+	-	+	**Good**
2	**F**	**33**	**V**	**2**	++	+	+	-	-	+	Unfavourable
3	**F**	**61**	**III**	**3**	+	+	-	-	-	+	**Good**
4	**F**	**52**	**III**	**11**	+	+	-	-	+	+	**Good**
5	**F**	**38**	**IV**	**8**	-	+	+	-	-	+	**Good**
6	**F**	**39**	**V**	**6**	-	+	-	-	-	+	**Good**
7	**F**	**29**	**IV**	**9**	-	+	+	+	-	+	Unfavourable
8	**F**	**26**	**IV**	**2**	+	+	-	+	-	+	Unfavourable
9	**F**	**64**	**IV**	**17**	-	+	+	+	+	+	**Good**
10	**F**	**54**	**III**	**13**	++	+	+	-	-	+	**Good**

FFA: Frontal Fibrosing alopecia

Ten patients were enrolled, one male and 9 women, mean age 42.80 ± 11.24-years, from 26 to 64-years. Four patients had phototype III, four phototype IV and two phototypes V. The mean duration of the disease was 7.50 ± 7.12 years (Table 1).

The face was the initial location in all patients, followed by the neck. At the examination, the lesions were located in the face in all patients, with the involvement of the peribuccal area in 6 cases (60.00%), the forehead in 1 cases (10.00%) and the temples in 1 cases (Figures 1 and 2). One patient had also bilateral hyperpigmentation of eyelids and one had cheilitis. The neck was involved in 4 cases (40.00%), the dorsum of the hands in one case; no flexural lesion was observed. The color of the lesions was brown or grew. Three patients had thyroiditis with hypothyroidism in one case; three other patients had diabetes mellitus. All patients had intense sun exposure but no fragrance application was reported. Good or favourable result was found in 70 percent of cases & rest shows unfavourable result after taking Tranexamic acid for 6 months.

Table 2: Demographic and Clinical Data of 10 Patients with Erythema Dyschromicum Perstans

S/N	Sex	Age in years	Phototype	Duration in years	Pruritus	Face	Trunk	Neck	TA	F/U after 6 months
1	**M**	**39**	**III**	**5**	-	-	+	-	+	**Good**
2	**F**	**80**	**V**	**18**	-	-	+	-	+	Good
3	**F**	**61**	**V**	**9**	-	-	+	-	+	**Good**
4	**F**	**55**	**III**	**7**	-	-	+	-	+	**Good**
5	**M**	**64**	**IV**	**5**	-	-	+	-	+	**Good**
6	**M**	**39**	**IV**	**3**	-	-	+	-	+	**Good**
7	**F**	**38**	**III**	**8**	+	-	+	+	+	Unfavourable
8	**F**	**33**	**IV**	**4**	-	-	+	-	+	Unfavourable
9	**F**	**29**	**V**	**3**	-	-	+	-	+	**Good**
10	**F**	**34**	**III**	**6**	-	-	+	-	+	**Good**

Ten patients were enrolled, three male and seven women, mean age 42.00 ± 10.34-years, from 29 to 80-years. Four patients had phototype III, three phototype IV and three phototypes V. The mean duration of the disease was 8.50 ± 6.12 years (Table 2). The trunk was the main location in all patients. At the examination, the lesions were located in the trunk in all patients, with the involvement of the neck area in only one case (10.00%). The color of the lesions was blue grey.

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Two patients had thyroiditis with hypothyroidism in one case; four other patients had diabetes mellitus. Good or favourable result was found in 80 percent of cases & rest shows unfavourable result after taking Tranexamic acid for 6 months.

IV. DISCUSSION:

Most of our patients were phototypes III or IV with a clear female predominance. In LPP, the lesions are irregularly shaped or oval, brown to gray macules or patches, located on sun-exposed areas or, less commonly, on intertriginous folds. In our series, the face was involved in all cases, mainly in the perioral area followed by the neck. Cutaneous lesions were overall bilateral with a patch pattern. We noticed only one case with associated lesions on the hands but no flexural lesions. Bilateral upper eyelid lesions can be, although rarely, the predominant location in LPP. Other rare clinical forms are reported in the literature as blaschkoid, zosteriform, segmental or mucosal LPP. Most of our patients had a chronic course of their disease and this is a common feature in LLP. Triggering factors were sun exposure with photoaggravation in some cases, presence of hepatitis C virus and application of mustard oil [13-16]. Similar results were also comparable in cases of Erythema Dyschromicum Perstans. In a study by Lee et al [12], when administered orally at adose of 250mg twice daily over approximately 4 months, 89.7 % of patients had documented improvement inpigmentation. Of those who improved, the median lightening was approximately 50%, which is significant. Other studies have also shown promising results.

Year	Study	No.of Cases vs Controls	TXA Arm (oral)	Duration (Wk)	Results	Additional Comments
1985	Hajime and Colleagues (Japan) [17]	40 cases, 0 Controls	1-1.5g daily	10	33 cases had a reported decreased severity	
1988	Higashi and colleagues (Japan) [18]	11 cases, 0 controls	0.75-1.5g daily	A couple of months	11 cases reported with decreased severity	Recurrence of melasma noted a few mo post cessation of treatment p<0.001
2008	Wu and colleagues (China) [19]	256 cases, 0 controls	500mg daily	24	10.5%>90%, 19%>60%, 51%, 30%	33% response 4 wk, 33% in 8 wk
2012	Wu and colleagues (China) [20]	75 cases, 0 controls	250 mg twice daily	24 (follow up at 6 months)	Excellent 10.8%, Good 54%, Fair 31.1%, Poor 4.1%	The recurrence rate noted in the trial was 9.5%. 82% of results were noted in first 4 wk.
2015	Padhi, Pradhan (India) [21]	20 case, 20 controls	250 mg twice daily	8	54.65% saw a decrease in in MASI (15.425–6.995), 88% saw a decrease in MASI (from 18.243 to 2.19)	TTC—faster, more sustained effect when TXA is added

2016	Lee and colleagues (Singapore) [12]	561	250mg twice daily	16	Improvement noted in 89.7% (50% lightening), 10.0% remained unchanged, 0.4% worsened.	1.8% were on monotherapy 94% were on depigmenting creams 35.5% had prior laser with TXA added on as an adjuvant 8 wk to response

V. CONCLUSION:

Tranexamic acid is the first systemic therapy to be studied for Lichen Planus Pigmentosus and Erythema Dyschromicum Perstans. It has clearly demonstrated the efficacy for hyperpigmentation in Asian skin, even in low doses (e.g., 500 mg daily) over short periods (8–12 weeks). It has also established itself as a safe therapeutic option, which is easy to administer with few, reversible, and mild side effects. Studies have shown that TXA does not increase thromboembolic risk, although patients should be screened carefully for contraindications and risk factors prior to commencement of the therapy. Patients was informed of the risks associated with therapy and counseled adequately prior to the initiation of therapy. Based on the available data in the literature, it is recommended that oral TXA should only be used only in cases of LPP & EDP that are unresponsive to topical hydroquinone and combination topical therapy over a period of approximately 12 weeks and if there are no contraindications to oral TXA. However, large-scale, randomized controlled trials are warranted to better characterize the role of oral TXA in the therapeutic ladder of LPP & EDP. Despite the plethora of studies now published on the successful use of oral TXA for the treatment of LPP & EDP, lrandomized, double-blinded, controlled trials and data from centers outside Asia are clearly needed to document safety and efficacy in Asian patients.

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