Original Research Article

Study on treatment regimes using low dose Tranexamic acid for longer duration along with oral antioxidants, topical broad spectrum sunscreen and newer safer depigmenting topical agents in refractory Melasma patients with history of topical steroid abuse at Telangana, India

Vimala Manne[1*], Anchala Parthasaradhi[2]

[1]Associate Professor, Department of DVL, Dr. VRK Women's Medical College,Teaching Hospital and Research Centre, Hyderabad,Telangana, India
[2] Anchala Skin Institute & Research Center, Hyderabad, Telangana, India

Received: 23-09-2020 / Revised: 26-10-2020 / Accepted: 22-11-2020

Abstract

Melasma is a common dermatological pigmentary disorder that can be very difficult to treat. Topical bleaching agents and stringent photoprotection, along with other treatment modalities, such as chemical peels and laser treatments, have been shown to provide only minimal improvements in this dyspigmentation. Of late, tranexamic acid has shown promise. Usage of different formulations of tranexamic acid-like topical, intradermal, and oral have been studied for Melasma, with oral formulations demonstrating the highest, although temporary, improvement. The efficacy of oral Tranexamic acid in the daily dose of 500mg for 3 to 6 months in Melasma patients has been established in various studies. Documented evidence of side effects with a higher dose of Tranexamic acid is present. There are also many published articles on the efficacy of oral sunscreens and antioxidants in preventing the exacerbation of Melasma in various studies. Topical corticosteroids (TCS) are widely misused on face especially by patients of refractory Melasma. Such patients cannot tolerate topical creams with strong bleaching agents. There are many topical agents which help in the treatment of Melasma without using topical steroids or strong bleaching agents like Hydroquinone which are misused by the rural population who visit our DVL outpatient department. Oral Tranexamic acid at a dose of 500 mg in 2 divided doses will give a response but recurrence after stopping the drug after 6 months usage occurs. In this study oral Tranexamic acid dose has been reduced and an oral antioxidant like Vitamin C, Lycopene, Red Orange Complex, Polypodium Leucotomos has been added in refractory Melasma patients to reduce the side effects of oral Tranexamic acid and without compromising its efficacy, as an adjunct in the treatment of Melasma; along with the use of broad spectrum sunscreen spf 50 plus which blocks both Ultraviolet radiation and visible light and milder topical agents containing Silymarin, PteroWhite, Soy extract, Niacinamide, Kojic acid and Mandelic acid which can be well tolerated on patients with a history of steroid abuse delivering promising results.

Keywords: Melasma, oral Tranexamic acid, oral Antioxidants, topical steroid abuse, Vitamin C, Niacinamide,Red-orange complex, Polypodium Leucotomos(PL), Silymarin.

**Correspondence*
Dr. Vimala Manne
Associate Professor,
Department of DVL, Dr. VRK Women's Medical College,Teaching Hospital and Research Centre,
Hyderabad,Telangana, India
E-mail: manne.vimala@gmail.com

Introduction

Melasma is a common dermatological pigmentary disorder that can be very difficult to treat. Topical bleaching agents and stringent photoprotection, along with other treatment modalities, such as chemical peels and laser treatments, have been shown to provide only minimal improvements in this dyspigmentation. Of late, tranexamic acid has shown promise.

Aim of the study

To use low dose Tranexamic Acid, oral Antioxidants and non-steroidal topical agents for long term use to treat refractory Melasma in patients who have a history of topical steroid abuse and also to prevent worsening of Melasma in them.

Methods

Study conducted from January 2018 to July 2019 to DVL outpatient Department .

2 groups of 25 refractory Melasma patients each with a history of topical steroid abuse for 1 year between 25 to 35 years both men and women were selected after stopping the use of topical steroids for 3 months. 2 groups of 25 Melasma patients between 25 to 35 years both men and women were selected. Patients with Melasma who had normal Complete Blood count, Coagulation profile, Liver function test, ECG. In Group A 3 men and 21 women were enrolled for the study and in Group B 2 men and 23 women were enrolled in the study. Group A patients were Advised to take 250 mg oral Tranexamic acid twice daily for 3 months duration and advised to use Broad spectrum sunscreen of spf 50 plus with Ultraviolet and Visible light protection,religiously and topical cream containing Silymarin, PteroWhite, Soy extract, Niacinamide, Kojic acid and Mandelic acid for 6 months duration on the affected area at night. In Group B, first, 3 months patients were on 250 mg oral Tranexamic acid daily, on a capsule of oral antioxidants daily containing Red-orange complex 100 mg, Polypodium Leucotomos 250mg, Vitamin C 75mg and Lycopene 6mg, daily topical Broad-spectrum sunscreen with both organic and inorganic components which block Ultraviolet radiation & visible light and topical night cream daily containing Silymarin, PteroWhite, Soy extract, Niacinamide, Kojic acid and Mandelic acid on the Melasma affected area.

Duration of the Study: 18 Months

Inclusion criteria

Age 25 to 35 Skin types I through VI (all skin types). Moderate or severe refractory Melasma who had a history of topical steroid abuse at least 1 year and more. They were all made to stop using topical steroids for 3 months.

Exclusion criteria

Current use of hormonal birth control medication or any hormonal therapy, Pregnant or nursing women, Use of topical steroids within 1 month of study enrollment, Use of topical hydroquinone within 3 months of study enrollment, History of laser or dermabrasion to the face within 6 months of study enrollment, Current treatment with blood thinning medications, History of thrombosis or thrombophilia History of thromboembolic disease, such as deep vein thrombosis, Occupation involving primarily outdoor activities, pulmonary embolism and or cerebral thrombosis, History of stroke, History of >2 spontaneous abortions, Family history of thromboembolic disease, History of kidney dysfunction, History of subarachnoid haemorrhage, History of cancer, Smoking Significant cardiovascular or respiratory disease (end-stage congestive heart failure or chronic obstructive pulmonary disease), History of acquired disturbances of colour vision, Known allergy to tranexamic acid.

Results

In Group A,1(4.55%) male patient lost to follow up and 2(9.1%) female patients stopped treatment due to side effects 1(4.55%) had severe palpitations and the other had Gastrointestinal disturbances. Other minor side effects encountered were erythema, burning sensation, oligomenorrhea in 1(4.55%) each and none had hypopigmentation. In Group B 2(9.1%) had Erythema, 1 (4.55%) had a burning sensation, while none had Gastrointestinal disturbances, palpitations, oligo-menorrhea and hypopigmentation.

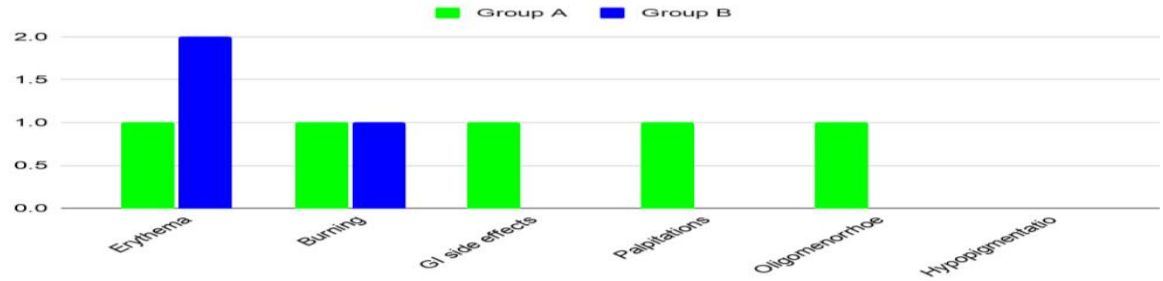

Fig 1:Comparative study of adverse effects among both groups

In Group A, out of 22 who remained till the end of the study, 4(18.2%) had Malar type, 14(63.6%) had Centrofacial type and 4(18.2%) had Mandibular type of refractory Melasma with topical steroid abuse for at least 1 year or more.In Group B, out of 22 who remained till the end of the study, 5(27.7%) had Malar type, 13(59.1%) had Centrofacial type and 4(18.2%) had Mandibular type of refractory Melasma with topical steroid abuse for at least 1 year or more.

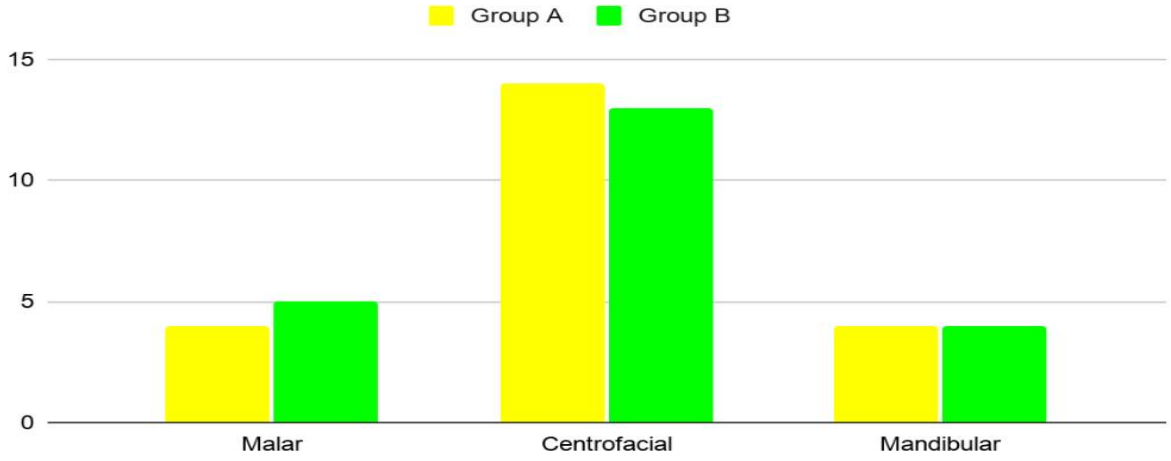

Fig 2:Types of recalcitrant melasma with topical steroid abuse who were till the end of the study

Group A patients were advised to use broad spectrum specific sunscreen which blocks both UV light & Visible light daily, topical night cream daily containing Silymarin, Niacinamide, Soy extract, MA, KA and petrowhite and Tranexamic acid 500 mg on weekends for next 3 months.22 Patients were analyzed by Physician Global Assessment into Excellent (>90% improvement), Good (>60% improvement), Moderate (>30% improvement), Mild (<30% improvement) in group A after 1 month, 3 months, 6 months and followed up to 1 year. In Group A, At 3 months follow up 3(13.6%) patients had Excellent results, 14(63.6%) Good, 5(22.7%) Moderate and 1(4.5%) had Mild results. In Group B, At 3 months follow up 1(4.5%) had Excellent results, 12(54.5%) Good, 7(31.8%) Moderate and 2(9.1%) had Mild improvement.

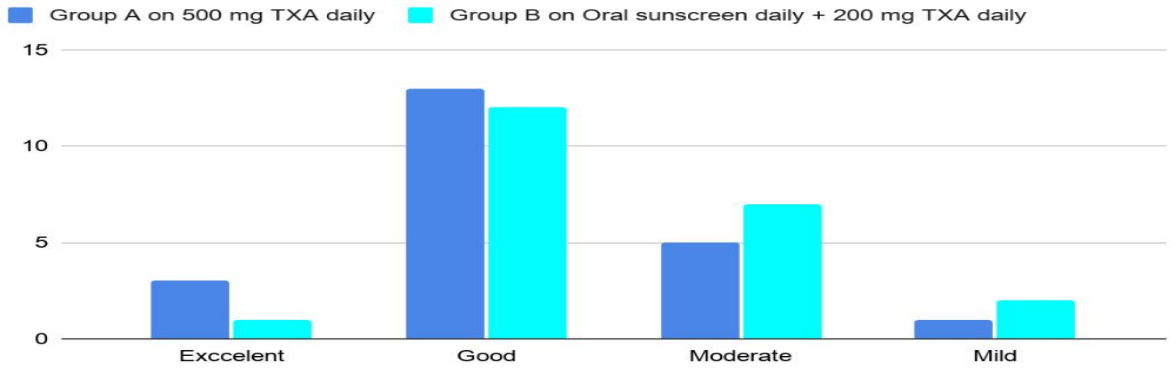

Fig 3:Physician global assessment after 3 months of treatment in Group A and Group B

In Group A, At 3 months follow up, these patients were advised to continue broad spectrum specific sunscreen which blocks both UV light & Visible light daily, same topical night cream daily and Tranexamic acid 500 mg on weekends for next 3 months. At the end of 6 months of study,1(4.5%) had Excellent results,11(50%) Good, 8(36.4%) Moderate improvement and 2(9.1%) had Mild improvement.In Group B, At 3 month follow up after analyzing the results the patients were asked to continue oral Tranexamic acid 250mg daily with oral

Anti oxidant daily, and continue both specific broad spectrum specific sunscreen spf 50 plus which blocks both UV light & Visible light daily, and same topical night cream on the Melasma affected area daily. In Group B, at 6 months follow up 4(18.2%) had Excellent results, 14(63.6%) Good, 3(13.6%) Moderate and 1(4.5%) had Mild improvement.

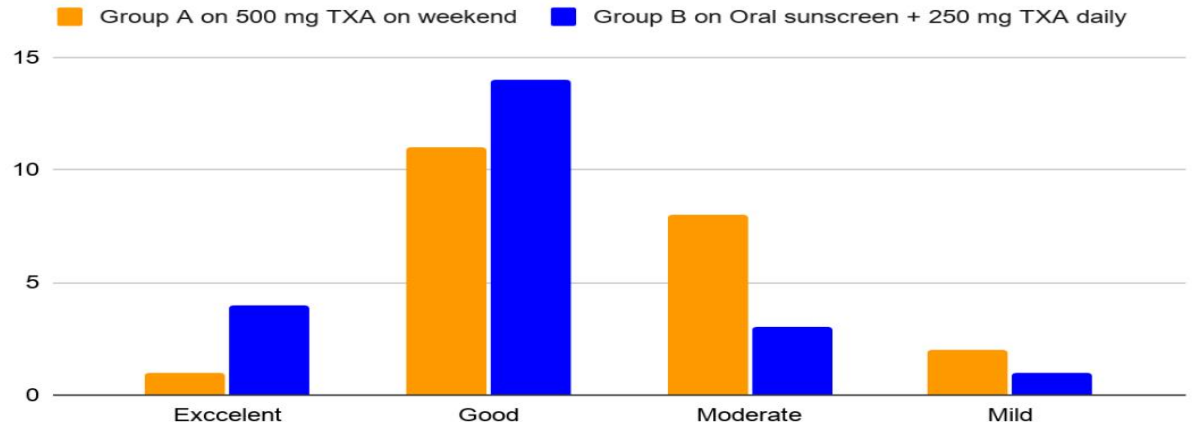

Fig 4:Physician Global Assessment after 6 months of treatment in Group A and B

In Group A at 6 months follow up after analyzing the results, the patients were told to continue daily usage of same broad spectrum specific sunscreen of spf 50 plus which blocks both UV light & Visible light daily, and continue oral Tranexamic acid 500mg in 2 divided doses at weekends and same topical night cream alternate on the Melasma affected area. At the 12th month follow up, none had Excellent results,9 had Good,7(31.8%) Moderate,6 had Mild improvement. In group B, at 6 months follow up after analyzing the results the patients were advised to continue daily usage of a broad spectrum specific sunscreen which blocks both UV light & Visible light daily, and continue oral Tranexamic acid 250mg daily, oral Antioxidant capsule daily and same topical night cream on the Melasma affected area on alternate days. In Group B, at 12 months follow up 3(13.6%) had Excellent results, 15(68.2%) Good, 2(9.1%) Moderate and 2(9.1%) had Mild improvement.

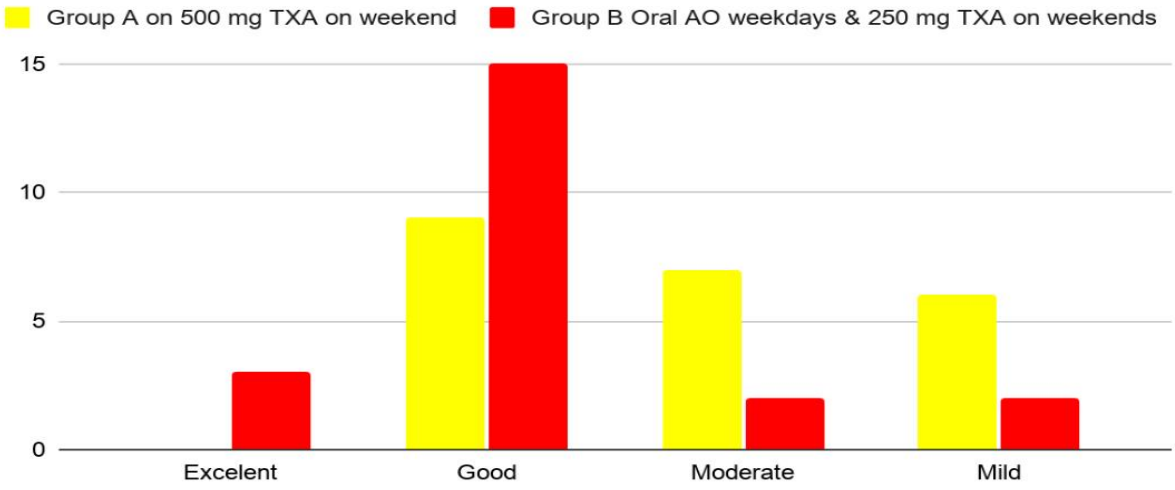

Fig 5:Physician Global Assessment after 12 months of treatment in Group A and Group B

In Group A at 12 months follow-up after analyzing the results, the patients were told to stop Tranexamic acid and continue applying the same broad spectrum specific sunscreen which blocks both UV light & Visible light, daily and topical night creams at weekends for next 6 months. At 18 months follow up,

none had Excellent results, 6(27.3%) Good,8(36.4%) Moderate and 8(36.4%) had Mild improvement in Group A. In Group B after analyzing the results, at 12 months the patients were told to use oral Tranexamic acid 250mg at weekends and continue using oral Antioxidants at weekends and to apply the topical night cream on Melasma affected area on weekends while continuing the use of same broad spectrum sunscreen.

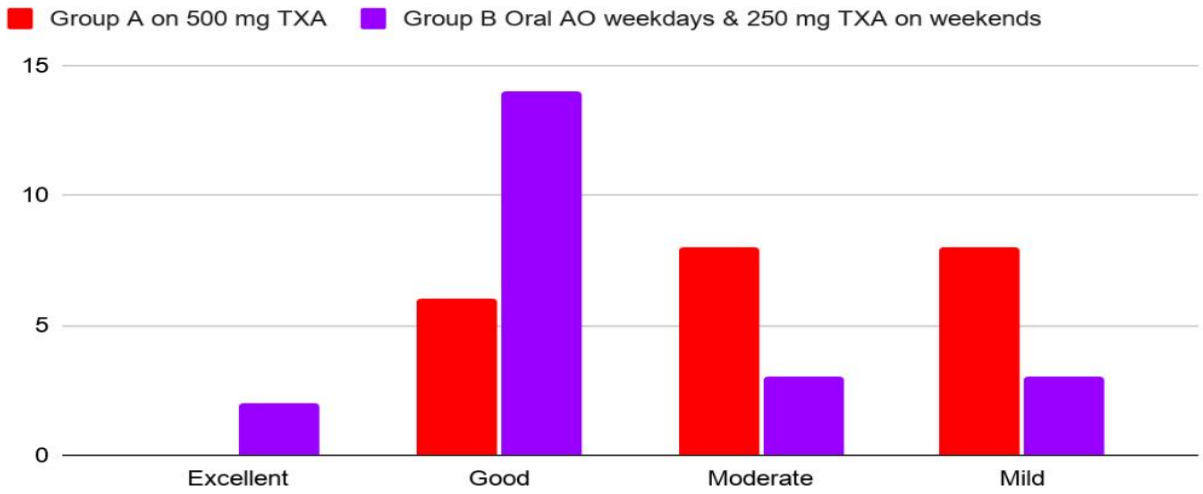

Fig 6:Physician Global Assessment after 18 months of treatment in Group A and Group B both on topical night creams

Discussion

Melasma is an acquired condition of symmetric hyperpigmentation, typically occurring on the face, with higher prevalence in females and darker skin types.[1].Melasma is generally a clinical diagnosis consisting of symmetric reticulated hyper melanosis in three predominant facial patterns: centrofacial, malar, and mandibular (1), rarely extra -facial upper chest and extremities[1,2].Melasma can also negatively influence the quality of life and cause substantial psychological and social distress[3]. . Multiple factors have been incriminated in the causation of melasma which includes genetic factors, solar radiation, hormonal factors, pregnancy, changes in uterine or ovarian hormones, oral contraceptives, hepatopathies, and cosmetics, drugs and others (3) out of which exposure to sunlight is undoubtedly the most important factor and both Ultraviolet radiation and visible light. (3) The mainstay of treatment for melasma has been topical bleaching agents, like hydroquinone alone or in combination with retinoids and topical steroids[4,5]. and stringent photoprotection.[6]. The overall safety of these combinations has unfortunately never been studied in well designed clinical trials. What complicates the situation further is that these combinations are most often used for prolonged periods either by the patients themselves or from prescriptions by the treating physicians. The recommendation that the combination is stopped after about 4-8 weeks is followed rarely at all by the patients. [7] as most of them land into a relapse the moment they stop using the triple combination therapy and this invariably leads to continuing their treatment either with or against medical advice. When these patients seek medical advice after months of continuous use of a steroid -based combination treatment, their disease is almost invariably complicated by skin atrophy, telangiectasia, and other steroid adverse effects. [8, 9] The facial skin in these patients also shows extreme sensitivity to sun exposure, probably because of the skin atrophy associated with the prolonged use of the steroid in the triple combination treatment. Typically these patients also complain that the area of involvement of melasma has also increased with the prolonged or recurrent use of the triple combination treatment. This can also be explained based on the variable degree of skin atrophy associated with the prolonged use of the triple combination treatment. This skin atrophy usually does not remain localized to the area of application of the steroid and extends to some extent beyond it as well leading to the involvement of this atrophied skin by the original disease. The facial skin in these patients also becomes intolerant to commonly used drugs for melasma. [8, 7] Patients who had been using this triple combination treatment for more than a year

continuously or repeatedly and the management of the disease in such patients becomes a real challenge. [7]. Sunscreen with both UV + VL protection is an important adjuvant therapy to prevent the exacerbation of hyperpigmentation and to improve the appearance of these conditions.Sunscreen can improve melasma and oral antioxidants may also have a role in preventing photoexacerbation of Melasma. Photosensitive conditions such as melasma is exacerbated by exposure to ultraviolet (UV) rays and visible light making a broad spectrum sunscreen use an essential component of treatment[10]. Sunscreen with both UV + VL protection is an important adjuvant therapy to prevent the exacerbation of hyperpigmentation and to improve Melasma. Many topical agents like Hydroquinone, Azelaic acid, Kojic acid(KA), Glycolic acid, Salicylic acid, and Tretinoin. Of these treatments, Hydroquinone remains the gold standard. Multiple studies suggest that combination formulations offer the best results [11]**.** These triple combination formulas usually contain Hydroquinone, a Retinoid, and a Corticosteroid in varying concentrations. Newer agents targeting melanosomal transfer like topical Niacinamide or vitamin B3, the active amide of niacin, interferes with melanosomal transfer to the surrounding keratinocytes by inhibiting PAR-2[12]. Silymarin, derived from the milk thistle plant Silybum marianum (L) Gaertn is a natural polyphenolic flavonoid. Its main component silybin (silibinin), is considered to be the most biologically active with potent antioxidant properties. Cutaneous photoprotection mechanisms triggered by Silymarin and Silybin are numerous and mainly demonstrate their ability to reduce and suppress harmful effects of solar UV radiation, such as UV-induced oxidative stress, inflammation, immune responses and DNA damage as well as induction of apoptosis. Silymarin significantly prevented melanin production in a dose-dependent manner with an IC50 value (concentration producing 50% maximal inhibition) of 28.2 μg/ml, without effects on cell viability. Even in high doses, Silymarin does not show any toxic effects and has no harmful effects on the embryo. [13] Silymarin shows strong free radical-scavenging activity that is several folds greater than that of vitamin E . It inhibits lipid peroxidation and provides significant protection against UVB-induced depletion of catalase activity. Therefore, Silymarin can effectively terminate the harmful biochemical reactions by scavenging free radicals and ROS, and by strengthening the cellular antioxidant status . This may be the other mechanism of action of Silymarin in the treatment of Melasma.Silymarin inhibited l-DOPA oxidation activity of tyrosinase, the rate-limiting melanogenic enzyme, in cell based-systems, but it did not directly affect cell-free tyrosinase activity. Furthermore, Western blot analysis indicated that Silymarin decreased the expression of tyrosinase protein. This explains the exact main mechanism of action of Silymarin in the treatment of Melasma.[13]. Silymarin showed tremendous improvement of Melasma in a dose-dependent manner and was effective in the prevention of skin damage caused by U.V. sunlight. It is a safe new topical agent effective in treatment of melasma.[13]. Other adjuvant treatment modalities in recalcitrant Melasma include chemical peels, dermabrasion, and laser treatments, all of which have demonstrated limited efficacy(14). Of late, there has been an interest in studying the effects of tranexamic acid (TA) in melasma. TA has been evaluated for the treatment of melasma in various formulations, including topical, intradermal, and oral.TA is a fibrinolytic agent that has antiplasmin properties. It has been hypothesized that TA can inhibit the release of paracrine melanogenic factors that normally act to stimulate melanocytes. Oral TA has begun to show more promise for the treatment at a dosage of 500 mg daily for 3 to 6 month as per studies conducted by months [11-12]. However,72 percent of patients experienced a relapse of melasma within two months of stopping the oral TA. This occurred despite the use of combination skin lightening topical products. (18)conducted a placebo-controlled trial that demonstrated improved MASI scores after three months of using oral TA (49%) compared to placebo (18%). Again, improvements in those with severe melasma were lost after three months of discontinuation and switching to sunscreen alone[13]. Role of oral antioxidants like Vitamin C, Polypodium Leucotomos has been mentioned in the treatment of refractory Melasma[13]. Another recent study determined that the use of antioxidants protected UVA-induced delayed CPD (Cyclobutane Pyrimidine Dimers) formation by enhancing ROS(Reactive oxygen species) scavenging activity and melanogenesis inhibition. These are important considerations in the pathophysiology of melasma: therapeutic options should be adapted to target all the associated factors. There has been much interest recently in the use of Polypodium leucotomos (PL) as an adjunct photoprotective agent in melasma. Polypodium is a fern of the Polypodiaceae family that is unique to Central and South America. PL's mechanisms of action include the promotion of the p53 suppressor gene expression, modulation of inflammatory cytokines, upregulation of endogenous antioxidant systems, and blockade of UV radiation-induced cyclooxygenase-2

expression .Several recent studies have documented a beneficial effect in patients with melasma Molecular evidence that oral supplementation with Lycopene or Lutein protects human skin against ultraviolet radiation. There are also many published articles on the efficacy of oral sunscreens and antioxidants in preventing the exacerbation of Melasma in various studies.(J In recent years, there has been increasing public interest in plant antioxidants, Due to the potential anticarcinogenic and cardioprotective actions mediated by their biochemical properties. The red (or blood) orange (Citrus sinensis (L.) Osbeck) is a pigmented sweet orange variety typical of eastern Sicily (southern Italy), California, and Spain. Red orange complexes that include anticancer, anti-inflammatory, and cardiovascular protection activities. Moreover, the effects on health of its main constituents (namely, flavonoids, carotenoids, ascorbic acid, hydroxycinnamic acids, and anthocyanins) are described. The red orange juice demonstrates an important antioxidant activity by modulating many antioxidant enzyme systems that efficiently counteract the oxidative damage.Data obtained from in vivo studies showed that supplementation of red orange extract (100 mg/daily) for 15 days brought a significant reduction in the UV-induced skin erythema degree.So the combination of oral antioxidants consisting of Red orange complex (ROC*H), ,Vitamin C ,Lycopene by inhibiting photo induced inflammatory response, beneficial in protecting the skin from photo-ageing, helps in Acute UV-B skin induced damage, augments the photo protection process and not only Augments topical sunscreen therapy providing an optimum 360 degree protection from Sunlight. In this study oral Tranexamic acid dose has been reduced to 250 mg once daily for a longer duration of 1 year and an oral antioxidant has been added in refractory Melasma patients to reduce the side effects of oral Tranexamic acid and without compromising its efficacy, as an adjunct in the treatment of Melasma along with broad spectrum sunscreen spf 50 plus which blocks both Ultraviolet radiation and visible light and milder topical depigmenting agents. The results are satisfactory with no side effects even after using for 6 months daily 250 mg dose and next 6 months weekend dose. and most of the patients having good results even TA 18 months follow up with 13.6% percent having excellent results & 68.2 % having good results .

Conclusion

Low dose of 250 mg Tranexamic acid can be safely given for a longer duration than 6 months along with oral Antioxidants, along with topical broad spectrum sunscreen of spf 50 plus with Ultraviolet radiation and Visible light protection and milder depigmenting cream with newer ,affective, safe agents for long term use minimising side effects,optimising results with lesser chances of exacerbation or recurrence of refractory Melasma in topical steroid abuse patients .Many more studies in this direction will help us to provide better treatment modalities for long term use with optimal efficacy in such patients.

References

1. Tamega Ade A, Miot LD, Bonfietti C, Gige TC, Marques ME, Miot HA. Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. J Eur Acad Dermatol Venereol. 2013;27(2):151–156.
2. Guinot C, Cheffai S, Latreille J, Dhaoui MA, Youssef S, Jaber K, et al. Aggravating factors for melasma: a prospective study in 197 Tunisian patients. J Eur Acad Dermatol Venereol. 2010; 24(9):1060–1069
3. K.Aishwarya, Pradeep Vittal Bhagwat, Nimmi John, Current concepts in melasma - A review article, Journal of Skin and Sexually Transmitted Diseases,2020;2(1):13-7.
4. Shankar K, Godse K, Aurangabadkar S, Lahiri K, Mysore V, Ganjoo A, Vedamurthy M, Kohli M, Sharad J, Kadhe G, Ahirrao P, Narayanan V, Motlekar SA. Evidence-based treatment for melasma: expert opinion and a review. Dermatology and Therapy, 2014, 4(2):165-186.
5. Rationale for the use of topical corticosteroids in melasma Journal of drugs in dermatology: JDD 2004; 3(2):169-74.
6. Juan Pablo Castanedo-Cazares et al. Near-visible light and UV photoprotection in the treatment of melasma: a double-blind randomized trial Photodermatol Photoimmunol Photomed.2014; 30(1):35-42
7. Mometasone-based triple combination therapy in melasma: Is it safe? Imran Majid.Cutis.Indian Journal of Dermatology.2010;55(4):359-362
8. Soniya Meena, Lalit Kumar Gupta, and Garima Bhatri.Topical Corticosteroids Abuse: A Clinical Study of Cutaneous Adverse.2017;62 (6): 675
9. Abir Saraswat et al. Topical corticosteroid abuse on the face: A prospective, multicenter study of dermatology outpatientsIndian Journal of Dermatology, Venereology, and Leprology,2011; 77(2): 160-166
10. Sakeena Fatima, Taylor Braunberger,and Iltefat H Hamzavi The Role of Sunscreen in Melasma and

Postinflammatory Hyper pigmentation, Indian J Dermatol. 2020 ; 65(1): 5–10
11. Kelly D Werlinger et al. Prevalence of self-diagnosed melasma among premenopausal Latino women in Dallas and Fort Worth, Tex, Arch Dermatol. 2007;143(3):424-5.
12. Medical Lasers; Engineering, Basic Research, and Clinical Application 2015; 4(1): 39-44
13. Rashmi Sarkar, Anuva Bansal, Pallavi Ailawad Successful Treatment of Refractory Melasma Future therapies in melasma: What lies ahead? Indian J Dermatol Venereol Leprol.The treatment of melasma by silymarin cream. Targeted Altai.BMC Dermatol. 2012;12: 18.

Conflict of Interest: Nil
Source of support:Nil