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Comparative Study of Combination of Oral Tranexamic Acid with Modified Kligman's Formula Versus Oral Tranexamic Acid with Azelaic Acid 15% in the Treatment of Melasma

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Melasma refers to acquired hyper-pigmentary condition effecting skin. Owing to its multifactorial causation and chronicity, there is an increased need for new multimodality therapies to treat melasma more effectively and to prevent the side effects seen with the conventional modalities of treatment.
Objectives: Compare efficacy of combining oral Tranexamic Acid and Azelaic Acid 15% with that of Oral Tranexamic Acid (TA) and Modified Kligman's Formula. Also, to record any adverse effects of combining these agents.
Methods: Patients having Melasma who will be coming to Dermatology OPD, AVBRH, Sawangi, Wardha, will be enrolled after considering the various inclusion and exclusion criteria. A detailed history will be asked, which will be followed by a cutaneous examination that includes the calculation of MASI (Melasma Area and Severity Index).
One Group (A) - participants will receive - Oral 500 mg Tranexamic acid OD plus Modified Kligman's Formula (fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2%) cream one time at night only.

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Second Group (B)- participants will receive - Oral 500 mg Tranexamic Acid OD plus Azelaic Acid 15% gel once daily at night only.
Both groups will also receive Broad-spectrum sunscreen SPF-30 daily (3 hourly).
Patients will be called for regular follow up at 4 weeks and 8 weeks (for early results). Clinical photos will be clicked at every follow-up visit and MASI score shall be doocumented.
Expected Results: To analyze efficacy of combining Oral TA along with Azelaic Acid 15% and if it provides better results, we can avoid the undesirable side effects that are seen on prescribing the Modified Klingman's Formula, in Melasma patients.
Conclusion: This study will help us in analyzing efficacy of combining Oral TA with Azelaic Acid 15%, therefore will provide a newer treatment modality with lesser side effects and maybe better results than the gold standard- Modified Klingman's Formula.

Keywords: Melasma; Klingman's formula; tranexamic acid; comparison.

1. INTRODUCTION

Melasma is an acquired condition causing hyper-melanosis that tends to occur in areas of skin exposed to solar radiation [1]. Common cutaneous disorder and accounts for 4% cases in Dermatology setups in South Asia. Among Indians, Melasma is commonest pigmentary condition [2,3]. Morphologically, it appears in the form of symmetric patches that are hyperpigmented with irregular borders. The usual sites are on the centrofacial region, cheeks and mandible. Melasma commonly affects dark/dusky skin but it can occur in every kind of skin [4,5,6]. Various patterns of melasma seen - Centrofacial: involves forehead, cheeks, upper lip, nose, chin and is the commonest. Malar: cheeks along with nose. Mandibular: mandibular ramus [7]. Treatment of melasma should ideally be a multifaceted approach that includes sun-protective therapy along with antioxidant agents and skin brightening creams. Exfoliants and resurfacing methods should be used as and when needed. Studies on Melasma suggest first-line therapeutic modalities should consist of strong sun-protection plus topical lightening formulations [8,9,10,11]. Hydroquinone (HQ) is most often the main component of different combinations of topicals that are used along with - glycolic, azelaic and kojic acid, retinoic acid, or sometimes even corticosteroids [1]. Most commonly studied and prescribed combination, 'triple combination', has HQ, retinoic acid, corticosteroids. Proposed initially by Kligman and Willis [12]. Kligman's Formula (original) consisted 5% HQ, 0.1% tretinoin, 0.1% dexamethasone. Found effective in treating Melasma as well as post-inflammatory hyperpigmentation. It's capability of causing irritation due to high tretinoin concentration was an issue and many modifications have been tested and have given good results in long-term clinical studies that have been performed. Ideally recommended first-line treatment modality in melasma is topical therapy, which are preferably triple combinations [13].

Azelaic acid is known to competitively inhibit tyrosinase. It induces cytotoxic effects directly to melanocytes by inhibiting DNA synthesis plus mitochondrial enzymes [14]. Azelaic Acid also helps by reducing free radical generation, since they are hypothesized to cause hyperpigmentation [15]. Tranexamic acid (TA) is derived synthetically from lysine. Conversion of plasminogen into plasmin in inhibited by it since it is a fibrinolytic agent and further cause blocking of attaching of plasminogen with keratinocyte. Eventually, causes decline in prostaglandin as well as fibroblast growth factor formation. Both are responsible for melanin synthesis stimulation [16].

2. RATIONALE/NEED FOR THE STUDY

Melasma is still challenging to treat in dermatology outpatient department. It also has significant psychosocial implications on the patient's life. Treatment given can often vary in efficacy owing to various parameters including variations in clinical features of the patient and treatment response seen amongst different races, genders and also skin types. Since melasma has a multifactorial aetiology, there is need to have a multifaceted treatment modality so that different agents namely, photoprotection, vascularity, pigmentation and alteration in endocrinal effects are addressed [17]. The mainstay of the medical management for melasma is still with topical skin lightening treatment and these should be used as first-line agents. Hydroquinone, triple combination therapy, other agents and upcoming oral therapies will be used in combination in the

future [18]. Commonest topical therapy in melasma all over the world, is Kligman's formula which is triple combination drug regimen. Kligman had initially utilized a cream with dexamethasone 0.1% plus tretinoin 0.1% and hydroquinone 5% as constituents [19]. Till today, there have been a number of alterations in which dexamethasone is replaced with other steroids, mainly hydrocortisone, fluocinolone, and mometasone. Fluocinolone containing formulation (fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2%) was launched in our country, a while ago and is known to be better as well as safer option that showed lesser side effects in comparison to the original Kligman's formula [20]. Any steroid formulation is not advised to be applied on for long since it can lead to undesirable aftereffects namely, telangiectasia, hypopigmentation, hypertrichosis, acneiform eruptions plus atrophy [21]. Also, the continuing safety of Hydroquinone applied topically is controversial since has led to paradoxical hyperpigmentation, irritant contact dermatitis and confetti like depigmentation in a few cases [22]. According to various Clinical studies done on Melasma, treatment with 20% azelaic acid topically is reportedly greater than 2 percent hydroquinone and almost equally efficacious to 4% hydroquinone, plus without unwanted effects of hydroquinone [23]. Therefore, if this combination proves better, we can avoid the side effects such as guttate hypomelanosis and exogenous ochronosis that are seen with long term use of Hydroquinone.

Different formulations of tranexamic acid have been evaluated as a means of therapy for melasma. Oral TA has shown promising results whereas intradermal and topical therapies have not shown good results till now. Long-term maintenance of achieved results following the stoppage of oral TA should be included in future studies, as well as combination therapy with TA and other modalities [23].

Owing to the dearth of available research data on the combination of topical Azelaic Acid with oral tranexamic acid as well as the need for a combined modality approach towards the treating a case of Melasma, we propose this study to analyze the efficacy of combining these two agents. If it proves efficacious, the possible long term side effects of the gold standard-Kligman's Formula can be avoided in Melasma patients.

2.1 Aim

Compare efficacy of combining Oral Tranexamic Acid and Modified Kligman's Formula versus Oral Tranexamic Acid and Azelaic Acid 15%.

2.2 Objectives

1. To study the effectiveness of combining Oral TA and Modified Kligman's Formula in the therapy of Melasma.
2. To study the effectiveness of combining Oral TA and Azelaic Acid 15% in treating Melasma.
3. To compare effectiveness of combining Oral TA with Azelaic Acid 15% versus that of Oral Tranexamic Acid with Modified Kligman's Formula.
4. To record any adverse effects of combining these agents

3. METHODOLOGY

3.1 Materials

Place of study: Out-Patient Department (OPD) of Dermatology, Acharya Vinobha Bhave Rural Hospital (AVBRH), Sawangi, Wardha, Maharashtra, India.

Study design: Interventional Comparative study.

Period of Study: October 2020 to August 2022.

Period required for data collection**:** 2 years.

Study Population: All patients, including all genders falling in the age group of 18 – 50 years diagnosed as melasma, coming to the outpatient department of Dermatology, Venereology and Leprosy in Acharya Vinoba Bhave Rural Hospital (AVBRH), Sawangi, Wardha, Maharashtra, India

3.1.1 Sample size

Sample size formula with derived error of margin:

$$n=\frac{Z^2*P*(1-P)}{d^2}$$

Z=significance at 5% i.e 95% confidence interval=1.96
P=Prevalence =4%=.04
d= Desired error of margin=7%=0.07
$n= 1.96^2 *0.04 *(1-0.04)$
0.07^2

n= 30.10
n x 2 = **60 patients needed in the study.**

Sample size for this study will be 60 patients.

3.1.2 Inclusion criteria

- Patients including male/females of age group 18-50 years, having Melasma.
- Voluntarily participating patients in the study with their informed consent.
- Washout period of 1 month will be taken into consideration for patients who have previously taken other medications for Melasma.

3.1.3 Exclusion criteria

- Patients already on prior treatment for Melasma.
- Patients with severe systemic comorbidities
- Pregnant and lactating women.
- Patients who are known cases of any hepatic disease or coagulopathies.
- Patients on anticoagulants.

3.2 Methods

Patients having Melasma who will be visiting Dermatology OPD, AVBRH, Sawangi, Wardha, will be enrolled as per the various inclusion and exclusion criteria. History will be taken, along with cutaneous examination that includes calculating MASI (Melasma Area and Severity Index) score.

Calculation of MASI:

Gravity of the melasma is seen in four zones (forehead, right and left malar area,chin) and examined on three parameters: percentage of total area involved (A), darkness (D), and homogeneity (H) [24].

Mathematical value for percentage area involved given as: 0=none; 1= <10% involved; 2= 10-29% involved; 3= 30-49% involved; 4= 50-69% involved; 5=70-89% involved; 6=90-100% involved [24].

Darkness in lesion (D) is co-related to normal cutis and graded as:

0=normal skin without hyper pigmentation;
1=hardly visible hyper pigmentation;
2=light hyper pigmentation;
3=moderate hyper pigmentation;
4=extreme hyper pigmentation [24].

Homogeneity of hyper pigmentation (H) graded on scale of 0 to 4 : 0=normal skin without hyper pigmentation; 1=involvement in specks; 2=small patchy areas involved; 4=uniform involvement without clear skin areas [24].

For calculating MASI, sum of severity grade for darkness (D) and homogeneity (H) is multiplied by number of areas (A) involved and by percentages of four facial zones (10-30%) [24].

Total MASI score: Forehead 0.3 (D+H)A + right malar 0.3 (D+H)A + left malar 0.3 (D+H)A + chin 0.1 (D+H)A [24]

After screening and including patients based on the inclusion criteria, at baseline, written informed consent will be obtained. Eligible study participants will be randomized equally (1:1 allocation ratio) into either treatment arm (group A or B) according to a system-generated random number table. The randomized allocation will be concealed by the SNOSE technique.

Group A participants will receive - Oral 500 mg Tranexamic acid OD plus Modified Kligman's Formula (fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2%) cream once every night only.

Group B participants will receive - Oral 500 mg Tranexamic Acid OD plus Azelaic Acid 15% gel once daily at night only.

Both groups will also receive Broad-spectrum sunscreen SPF-30 daily (3 hourly).

Patients will be called for regular follow up at 4 weeks and 8 weeks (for early results). Clinical photos will be clicked on every follow-up visit and MASI score shall be documented.

Following 2 months of above medical prescription, MASI score decrease will be documented as measure of primary outcome along with clinical evaluation of photographs.

3.3 Statistics

All standard parametric and non-parametric data will be assessed by standard statistical methods. *'p'* value of <0.05 considered significant.

4. EXPECTED RESULTS

This analysis will help us in comparing the efficacy of combining oral TA with two different topical agents namely, modified Kligman's Formula and Azelaic acid 15% and thus arrive at a better formulation amongst the two and also possibly ;with lesser side effects.

5. DISCUSSION

Sardesai et al. performed study with 160 cases (of all age groups) of all genders. The patients were given treatment consecutively that consisted of five distinct combination therapies for a time of three months. Response after therapy was calculated by MASI. Study suggested modified Kligman's formula as superior most. Although, it also showed a comparatively greater incidence of undesirable side effects and therefore, should be advised with caution and proper counseling [25].

Eunice Del Rosario et al did a study on patients of Melasma by giving 250 mg of Tranexamic Acid (TA) or a placebo (in form of capsule) two times every day for three months along with sunscreen and then 3 months sunscreen application only. Modified Melasma Area and Severity Index (mMASI) score was primary measure of outcome. Enrolled cases were 44 and about 39 completed study. 49% decrease was observed in mMASI score in TA arm whereas 18% seen in control group post 3 months. Three months post treatment, a 26% decrease in mMASI score was observed in TA group compared to initial values versus 19% decrease in placebo. Any kind of undesirable events not reported [26].

Nicholas J. Lowe et al analyzed the safety, efficacy, amount of tolerability of topical 20% azelaic acid when compared with vehicle for managing facial hyper pigmentation in people with dark skin. After a twenty four week period of treatment, azelaic acid caused greater reduction in pigmentation than vehicle on measuring by subjective scale and chromometer analysis. But it also produced a higher sensation of burning and stinging. Study suggested that the patients treated with azelaic acid noted as having much softer skin and were satisfied with their treatment in comparison to those treated with the vehicle [27].

Susan Farshi conducted a study on twenty-nine women with diagnosed case of melasma. Fifteen patients treated with 4% topical hydroquinone and 14 given topical azelaic acid for 60 days. Cream applied two times everyday. Both groups also applied a sunscreen. MASI scores were calculated before starting the therapy and also at every subsequent visit. Mean MASI prior to therapy was 7.2 in first group and 7.6 in the second group, without a significant distinction in two groups. Post 60 days, MASI score was 6.2 with hydroquinone whereas 3.8 with azelaic acid, significant statistical difference. Study concluded 20% azelaic acid applied two times every day may be superior to HQ 4% in decreasing mild Melasma [28]. Few of the related studies were reviewed [29-37].

6. CONCLUSION

This study will help us in analyzing efficacy of combining Oral TA with Azelaic Acid 15%, therefore will provide a newer treatment modality with lesser side effects and maybe better results than the gold standard- Modified Klingman's Formula.

ETHICAL APPROVAL AND CONSENT

Institutional Ethical Committee (IEC) clearance will be obtained. Written informed consent in their vernacular language will be taken from all the participants for voluntary participation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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