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ORIGINAL ARTICLE

Comparative efficacy of topical 10% versus 5% tranexamic acid in treatment of women with melasma: a double-blind randomized controlled trial

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ABSTRACT

BACKGROUND

Melasma is a highly prevalent chronic pigmentary disorder. The pathogenesis is unknown but melasma often occurs in photo-exposed areas, e.g., cheeks, upper lip, chin, and forehead. Tranexamic acid (TA), a plasmin inhibitor, aids in the inhibition of UV-induced plasmin activity and melanogenesis, making it a favorable therapeutic option for melasma. Tranexamic acid may be administered through various routes, *e.g.*, topical. This study aimed to compare the efficacy of topical 10% versus 5% TA in women with melasma.

METHODS

This double-blind randomized controlled trial included 16 females with epidermal type melasma who were randomized into two groups to receive either topical 10% TA (n = 8) or 5% TA (n = 8) applied twice daily for eight weeks. Prior to intervention and at 8 weeks after intervention, the intensity and extension of melasma were assessed based on melasma area and severity index (MASI) score and pigmentation score.

RESULTS

Mean MASI and pigmentation scores in both treatment groups were similar at base-line ($p>0.05$). The reduction in MASI and pigmentation scores in the topical 10% TA and 5% TA groups was similar and statistically not significant after 4 and 8 weeks of treatment ($p>0.05$). There were no drug-related adverse reactions or complications.

CONCLUSION

This study demonstrated that topical 10% TA and 5% TA were effective in treating women with melasma. The utilization of topical 5% TA for melasma is a promising alternative therapeutic option without the need to increase the concentration of the formulation.

Keywords: Melasma, topical, tranexamic acid, MASI, pigmentation, women

INTRODUCTION

Melasma is an acquired pigmentary disorder characterized by light to dark brown macules, which may be confluent or discrete in typical locations, most often on the cheeks, upper lip, chin, and forehead or other photo-exposed areas, although they may also be found in non-exposed areas.[1] The exact pathogenesis is unknown, but it has been hypothesized that biologically active melanocytes induce melasma, increased vascularity, and elevated expression of angiogenic factors in the affected epidermis.[2] Melasma is a chronic disorder and tends to recur, especially among women of reproductive age, individuals with dark skin tone, and those living in areas with high sun exposure.[1,3]

Globally, melasma has been reported to be one of the most common dermatoses. Countries across Asia have a high prevalence of melasma, *i.e.*, 6.8% in Nepal and 13.61% in China.[4] A retrospective study conducted in RSUD dr. Saiful Anwar Malang, Indonesia, across the period of 2015-2017, reported that 159 (0.66%) outpatients out of a total of 24,048 patients were diagnosed with melasma.[5] However, the actual number of patients with melasma may be underreported due to use of over-the-counter medications by the patients.

Melasma management consists of the use of sunscreens and photoprotection, topical therapy (*e.g.*, hydroquinone, kojic acid, azelaic acid, retinoid, arbutin, niacinamide, or tranexamic acid [TA]), chemical peeling, laser, and/or combination therapy.[1-3] Tranexamic acid has recently been proposed as an effective treatment in melasma, as an alternative to hydroquinone. It may be administered through topical, intradermal, and oral routes. In one study, varying concentrations (2-5%) of TA have been used for patients with melasma.[6] Studies comparing the efficacy of topical 5% TA versus topical hydroquinone, a considered gold standard and frequently studied topical melasma therapy, have reported that topical 5% TA is as effective as 2-3% hydroquinone.[7,8] However, a direct comparison of different concentrations of topical TA has yet to be conducted.

The concentration of a drug in a formulation is important. A proportional increase or decrease in flux can be obtained by increasing the concentration of a dissolved drug.[9,10] It is noteworthy to evaluate whether a higher concentration of TA has a more favorable outcome, *i.e.*, shorter treatment duration from baseline to effect. There is a paucity of data on the efficacy and safety of topical TA in Indonesia. This study aimed to determine the comparative therapeutic effect of topical 10% versus 5% TA in women with melasma, particularly among those of Indonesian skin type, by examining the melasma area and severity index (MASI) and pigmentation scores.

METHODS

Research design

This was a prospective, double-blind, single-center randomized controlled trial conducted from April 2023 to November 2023 at a tertiary hospital in Manado, North Sulawesi, Indonesia. The reporting of this study adhered to the CONSORT 2010 checklist for reporting a randomized trial.[12]

Research subjects

In this experimental analytical study, a total of 16 subjects were randomized 1:1 to 2 groups, with eight in each of the two treatment groups: Group 1 (topical 10% TA) or Group 2 (topical 5% TA). A sample size of 8 per group was required to achieve a 95% difference in MASI and pigmentation scores at eight weeks between Group 1 and Group 2 for the efficacy of topical TA with 5% alpha and 80% power.[11] Consecutive non-random sampling was performed, i.e., we enrolled all new female cases of epidermal type melasma who met the inclusion criteria for admission at the Dermatology and Venereology outpatient clinic of RSUP Prof. Dr. R. D. Kandou, Manado. The inclusion criteria were female melasma patients aged 25-64 years, with no active skin disorder on the face, and previously treated cases of melasma who were off melasma medication for at least one month before entry. Pregnant and lactating women, patients on contraceptive pills, and patients on systemic therapy (e.g., phenothiazine [chlorpromazine], amiodarone, tetracycline, minocycline, chloroquine, cytostatics, heavy metals, inorganic arsenic) and/or anticonvulsant therapy (e.g., hydantoin, dilantin, phenytoin, and barbiturate) were excluded.

Interventions

Subjects were treated with topical 10% TA (Group 1) and topical 5% TA (Group 2). The drug was applied twice daily, at 6 a.m. and 6 p.m., respectively, for eight weeks. In the morning, after applying the respective allocated topical concentration of TA on the affected melasma area,

the patient applied sunscreen thrice daily (15-30 minutes before activities) and was advised to avoid sun exposure. Subjects returned for follow-up visits at weeks 4 and 8.

Randomization and blinding

Before the start of the trial, 16 eligible subjects were divided into two groups of eight subjects per group according to the randomization. The subjects were randomly allocated to two groups using computerized blocked randomization with block size of 4, which was done by another consultant in the department who was not associated with the study.

The outer packaging and inner texture of the topical used in the two groups were the same. Both the patients and the investigators were blinded to the drug given.

Outcomes

The outcomes examined were the core outcome domains for melasma reduction. The degree of melasma severity was evaluated by the MASI score at baseline, week 4, and week 8. In brief, the MASI score was calculated according to the following formula: area (A) of involvement, darkness (D), and homogeneity (H), with the forehead (f), right malar region (rm), left malar region (lm), and chin (c), corresponding to 30%, 30%, 30%, and 10% of the total face, respectively. The area of involvement in each of these four areas was given a numeric value of 0 to 6 (0=no involvement; 1 = <10%; 2 = 10%-29%; 3 = 30%-49%; 4 = 50%-69%; 5 = 70%-89%; and 6 = 90%-100%). Darkness and homogeneity were rated on a scale from 0 to 4 (0 = absent;1 = slight; 2 = mild; 3 = marked; and 4 = maximum). The MASI score was calculated by adding the sum of the severity ratings for darkness and homogeneity, multiplied by the value of the area of involvement, for each of the four facial areas.[12] All scores (mean ± SD) were evaluated by three dermato-venereologists.

The secondary outcome of this study were skin pigmentation and adverse reactions. Patients were examined with a skin analyzer (A-One simple ® [Bomtech South Korea]) to determine the pigmentation score (range = 0-10; higher score referring to severe pigmentation) at baseline, week 4, and week 8. Post-treatment photographs were taken to assess visual outcomes and comparisons in each patient. Adverse reaction during the treatment phase was recorded using a questionnaire.

Statistical analysis

Statistical analyses were performed using Statistical Packages for Social Sciences version 25.0 (IBM Corp., Release 2022, Armonk, NY, USA). Data were presented as mean ± SD or n (%), as appropriate. Statistical analysis was performed with the Chi-square test and independent t-test to determine the significant differences between the two groups. A p value of <0.05 was considered statistically significant.

Ethical clearance

This clinical study was reviewed and approved by the Health Research Ethical Committee of Prof. Dr. R. D. Kandou, Manado (Ref: No. 181/EC/KEPK-KANDOU/X/2022). All participants provided written consent after a detailed discussion about the treatment plan, expected outcome, benefits, and risk of treatment.

RESULTS

From April 2023 to November 2023 a total of 37 patients were recruited, with 21 subjects not meeting the inclusion criteria. There were no dropouts in the study. Thus, 16 subjects were included in the study and were analyzed for primary and secondary outcome measures (**Figure 1**). There were no reported adverse events during the 8-week follow-up. No clinical signs of allergic contact dermatitis were reported. At base-line, the two groups were matched for mean age (50.00 ± 5.81 vs. 52.00 ± 7.05 years, p=0.283.) The mean MASI scores at baseline in groups I (TA 10%) and II (TA 5%) were 19.93 ± 10.62 and 24.26 ± 5.93, respectively, with no significant difference between the groups (p=0.330). Similarly, no significant difference was found in the mean score of pigmentation between groups I (4.50 ± 2.07) and II (5.88 ± 2.70) before the intervention (p=0.272) (Table 1).

Response to treatment

The patients were monitored every four weeks for the MASI and pigmentation scores and evaluation of side effects and complications of the drugs. The mean MASI scores in group I at the end of 4 and 8 weeks were 16.76 ± 10.51 and 12.80 ± 9.95, respectively, whereas the values were 19.50 ± 5.37 and 14.70 ± 4.27 for group II, respectively. The MASI score across groups was statistically not significantly different between week 4 and week 8 (p>0.05) (Table 2).

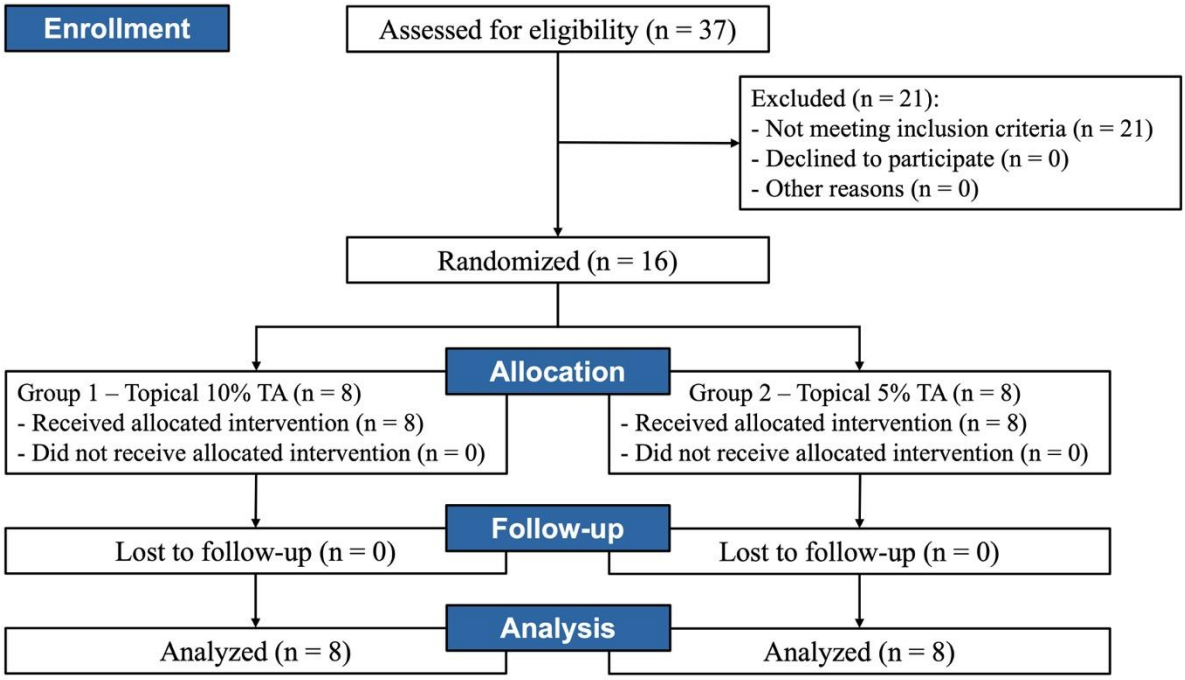

Figure 1. Flow chart of the participants

Table 1. Clinicodemographic characteristics of study subjects by treatment groups at baseline

Characteristics	TA 10% (n=8)	TA 5% (n=8)	p value
Age (years)	50.00 ± 5.81	52.00 ± 7.05	0.283
Pattern distribution of melasma			
Centrofacial	6 (75.0)	6 (75.0)	1.000
Malar	2 (25.0)	2 (25.0)	
MASI score	19.93 ± 10.62	24.26 ± 5.93 5.88	0.330
Pigmentation score	4.50 ± 2.07	± 2.70	0.272

Note: data presented as mean ± SD, except for pattern distribution of melasma n (%); TA: tranexamic acid; MASI: melasma area and severity index

Table 2. Comparison of melasma area severity index and pigmentation scores between 10% TA and 5% TA after 4 and 8 weeks of treatment

After intervention	TA 10% (n=8)	TA 5% (n=8)	p value
4 weeks			
MASI score	16.76 ± 10.51	19.50 ± 5.37	0.330
Pigmentation score	2.75 ± 0.89	3.25 ± 2.49	0.601
8 weeks			
MASI score	12.80 ± 9.95	14.70 ± 4.27	0.627
Pigmentation score	2.50 ± 1.20	3.13 ± 2.53	0.538

Note: TA: % tranexamic acid; MASI: melasma area severity index

The pigmentation scores for group 1 were 2.75 ± 0.89 and 2.50 ± 1.20 at week 4 and week 8, respectively; for group 2 they were 3.25 ± 2.49 and 3.13 ± 2.53 at week 4 and week 8, respectively. The reduction across groups was not statistically significant between week 4 and week 8 (p>0.05) (Table 2).

DISCUSSION

At the end of the study, satisfactory outcomes were obtained in both groups. Our study showed a reduction in MASI and pigmentation scores after treatment with 10% and 5% TA, as compared to those at baseline. These findings further

strengthen the utilization of TA as a therapeutic option in melasma.

However, at the end of the study, comparative results of the two groups for MASI and pigmentation scores were not statistically significant. The increment in TA concentration did not yield statistically significant results across groups. An increase in the concentration does not necessarily increase its efficacy in relation to its absorption. Several factors may be involved in drug absorption in skin, namely, the permeation through the skin (rate-limiting membrane stratum corneum), physiochemical properties of the drug (lipid-water partition coefficients, solubility, and molecular weight), excipients used in the formula, type of formulation, presence of enzymes in skin structures, application site, and skin type.[11, 13]

Regarding the time to therapeutic endpoint of topical TA, it was reported in one meta-analysis to be eight weeks, where it responded slowly in the first four weeks with only mild improvement or no response, while the improvement continued, with a moderate to good response in most patients at week 8.[14,15] This is in line with our findings, where the mean MASI and pigmentation scores were considerably reduced following the use of TA after 4 and 8 weeks treatment.

Tranexamic acid is a synthetic derivative of the amino acid lysine and acts as a plasmin inhibitor. Plasmin plays a crucial role in melasma since UV light enhances plasmin activity in keratinocytes, subsequently resulting in an elevation of melanocyte-stimulating mediators, such as arachidonic acid and α-melanocyte stimulating hormone. Topical TA is also postulated to inhibit plasminogen from binding to keratinocytes by interfering with the lysine binding sites on keratinocytes, which in turn downregulates prostaglandin, a stimulator of tyrosinase, resulting in a decline in tyrosinase activity and melanogenesis.[6,16,17]

Tranexamic acid may suppress melanin formation by the inhibitory release of paracrine melanogenic factors that generally act to stimulate melanocytes. Additionally, TA reduces the expression of vascular endothelial growth factor and endothelin-1, minimizing bleeding and hampering angiogenesis. Histologically, a significant reduction in the regions to which TA solutions have been applied in the basal layer of UV-exposed epidermis has been reported. Thus, TA aids in the inhibition of UV-induced plasmin activity, melanogenesis, and is anti-angiogenic, making it a favorable therapeutic option for melasma.[6,17-20]

Throughout the years, TA has been administered via different routes of administration, including oral and topical administration, intradermal injection, and microneedle administration, or in combination with Q-switched Nd:YAG laser or with routine topical agents, with promising outcomes. Recent meta-analyses have substantiated that TA is a secure and effective therapy for managing melasma.[19] Topical TA has showed its superior efficacy in treating epidermal-type melasma as compared with dermal-type and mixed-type melasma.[21] This finding rationalizes our utilization of topical TA in epidermal-type melasma.

A review article reported various topical formulations of TA that have been utilized, such as 2% emulsion, 3% cream, 5% solution, and 5% liposomal cream. Out of the six clinical investigations conducted, only one did not demonstrate a significant effect of topical TA in treating melasma. Nevertheless, in the latter study the limited number of participants or the heavy impact of sun protection in treating melasma may have contributed to the need for more statistically significant differences between TA and its vehicle. The efficacy of topical administration of TA was demonstrated, as was the effectiveness of topical hydroquinone alone, topical hydroquinone combined with dexamethasone, and intradermal injection of TA.[6] It is noteworthy that with continuous administration of topical TA, the pigmentation will gradually fade, suggesting that the duration of therapy rather than the provision of a higher dose makes the treatment more effective.[22] However, the use of topical TA may cause side effects, *e.g.*, skin irritation, xerosis, and scaling; nevertheless, topical TA has a lower rate of irritation compared with topical hydroquinone, making it a safe therapeutic option in melasma.[18,23]

Our study highlighted that an increase in topical TA concentration did not increase its efficacy. This finding implicated that following a routine application of topical 5% TA, topical 5% TA is a reasonable alternative to topical 10% TA in the management of epidermal-type melasma without the need to increase its concentration.

The present study had limitations, including the short length of the study follow-up and the absence of a control group receiving a placebo. Future experimental studies may investigate the different concentrations of topical TA with additional active ingredients and/ or other application methods.

Conclusions

Topical 10% TA and 5% TA were effective in treating women with melasma after 4- and 8-weeks intervention. A topical 5% is a reasonable alternative for the management of epidermal-type melasma without the need of a higher concentration.

Conflict of Interest

None declared.

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Author Contributions

FOM is the corresponding author who originated the research concept, prepared the study proposal, analyzed the data, wrote the draft, and finalized the manuscript document. MGK and HEJP drafted the research idea, developed the trial, interpreted results, and wrote the draft, and were involved in the evaluation and finalization of the article document. AIC, LT, and JAT, were in charge of subject recruiting, presented the discussion and wrote the draft. PMC advised on statistical issues, wrote the draft, and was involved in reviewing and finalizing the manuscript. All authors have read and approved the final manuscript.

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Data Availability Statement

The datasets generated and/ or analyzed during the current study are available upon request from the corresponding author.

Declaration of Use of AI in Scientific Writing

Nothing to declare.

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