Journal homepage https://jsmc.univsul.edu.iq
Journal of Sulaimani Medical College
ISSN:2223-148X

Original Article

Comparative Efficacy and Safety of Oral Tranexamic Acid, 1% Arbutin Cream, and Their Combination in the Treatment of Melasma in Sulaymaniyah City: A Randomized Controlled Trial

Hanaa Jaafar Hama Rashid[1]*, Darsim Mohammed Abdalla Maarouf[2]
[1]: Sulaimani Directory of Health, Sulaimani, Kurdistan Region, Iraq
[2]: Department of Clinical Science, College of Medicine, University of Sulaiamni, Kurdistan Region, Iraq

Article Info.

Article History
Received: 29/6/2025
Revised:17/8/2025
Accepted: 17/9/2025
Published online 21/12/2025

Key words:
Arbutin,
Combination Therapy,
Melasma,
mMASI score,
Tranexamic acid.

Abstract

Background: Melasma represents the most prevalent form of acquired pigmentary disorder, as mainly seen in women of Fitzpatrick skin types III-VI. Due to repeated recurrences after different possible treatment modalities, full resolution is often elusive. The purpose of this study was to assess the efficacy and safety of oral tranexamic acid (TXA), topical 1% arbutin cream, and their combination on the long-term outcome of melasma.

Patients and Methods: One hundred and twenty melasma patients were enrolled in a 1:1 ratio open-label RCT at Shahid Jabar Dermatology Center, Sulaymaniyah (Dec 2024–Jun 2025). Randomization into 3 groups: Group A (Oral TXA), Group B (topical 1% arbutin), and Group C (both). The severity of melasma was evaluated at baseline and at 1, 2, and 3 months. Patient satisfaction (with the 5-point Likert scale) and adverse effects were also evaluated. After stopping treatment, follow-up was performed over 3 months.

Results: The mMASI scores at baseline were similar between the groups. This decrease was most significant in Group C (4.25 ± 2.13), followed by Group A (5.70 ± 3.15) and Group B (5.96 ± 2.99) at 3 months. The highest patient satisfaction (42.5%) and the lowest recurrence rate (15%) were found in Group C. Adverse events were infrequent: upper gastrointestinal symptoms in Groups A (20%) and C (17.5%), and inflammation in Group C (2.5%). When comparing with Group B, ratios in Group C had a significant improvement (P = 0.007).

Conclusion: The combination of oral TXA and topical arbutin was more effective, had greater patient satisfaction, and lower recurrence compared to monotherapy, providing a more durable option for the treatment of melasma.

DOI: 10.17656/jsmc.10496
Corresponding author: Hanaa Jaafar Hama Rashid hanaj935@gmail.com

Introduction

Melasma is a benign, acquired condition characterized by facial hyperpigmentation and usually appears as asymmetrical, primarily facial, hyperpigmented macules or bordered areas (1). This condition can be distressing and significantly impact patients' quality of life (2). Melasma can be classified according to its distribution area: centrofacial (encompassing the forehead, cheeks, nose, upper lip, and

chin), malar (involving the cheeks and nose), or mandibular (along the mandible). The prevalence of melasma can vary from 1% in the normal population to 50% in the high-risk population. The difference in the prevalence of melasma in different nations can be attributed to ethnicity, genetics, and the degree of sun exposure. As it has been reported, the prevalence of melasma is much higher in the Middle East and South East Asians, Hispanic Americans, Mediterranean, Africans, and also Brazilians (3).

The pathogenesis of melasma is complex and not fully understood. Major contributors are chronic ultraviolet (UV) exposure, hormones (pregnancy or oral contraceptive use), genetic susceptibility, and inflammatory stimuli (4).

Recent evidence highlighting the importance of vascular and inflammatory mediators in the process of coronary artery disease. Vascular endothelial growth factor (VEGF), an important angiogenic factor, is significantly elevated in melasma lesions (5).

These cleavage leads to matrix-bound VEGF (vessel endothelial growth factor) that are released by the action of plasmin and local angiogenic variants rapidly diffused. VEGF (Vascular Endothelial Growth Factor) is a potent pro-angiogenic cytokine that is essential for vascular remodeling and neovascularization. In melasma, elevated levels of vascular factors including VEGF are thought to be important in pathogenesis by inducing expansion of dermal vascular supply and enhancing melanogenesis by endothelial-derived paracrine signals such as nitric oxide and endothelin-1(6).

In the melasma treatment, tranexamic acid is considered to have a dual mechanism of action, concurrently reducing pro-melanogenic signals and mitigating erythema and vascularity (7). Tranexamic acid is a synthetic form of the amino acid lysine, mainly used to prevent or reduce bleeding. In melasma, TXA helps lighten skin by blocking the plasminogen–plasmin pathway, which reduces the production of substances that trigger melanin formation (8).

Natural skin-lightening substances like arbutin can be found in a variety of plant species, including marjoram, blueberries, cranberries, and several pear species. Arbutin effectively decreases melanin production by blocking the tyrosinase enzyme. There are two isoforms of arbutin: α-arbutin (4-hydroxyphenyl-α-D-glucopyranoside) and β-arbutin (4-hydroxyphenyl-β-D-glucopyranoside).

Although their rotational configurations differ, α and β-arbutin share the same chemical formula structure (9). β-arbutin is extracted from fruit peels and the leaves belonging to various plants. Microbial enzymes or microorganisms can biosynthesize α-arbutin, which is not found naturally (10). The fact that α-arbutin inhibits tyrosinase activity far more effectively than natural arbutin is interesting. Tyrosinase's active site exhibits a higher affinity for the α-glucoside bond than the β-glucoside bond (10).

This study aims to compare the safety and efficacy of topical arbutin, oral tranexamic acid, and their combined application in melasma treatment. By addressing gaps in long-term therapeutic strategies.

Patients and Methods

Study design and setting

This open-label, single-center randomized controlled trial (RCT) was conducted at the Shahid Jabar Dermatology and Venereology

Teaching Center in Sulaimani, Sulaimani, Kurdistan Region, Iraq. The research was conducted over a period of six months, between December 2024 and June 2025. Methods: One hundred twenty patients diagnosed with clinically positive melasma patterns and confirmed by Wood's lamp examination were included. Patients with chronic sarcoid uveitis were randomly assigned to three study arms, and 40 patients were included in each group.

Inclusion criteria

Adult patients of any sex with clinically diagnosed melasma confirmed by a Wood's lamp examination and by written informed consent for inclusion. With these criteria, the study populations were homogeneous, and an assessment of efficacy could be reliable.

Exclusion criteria

Pregnant or breastfeeding patients, patients on OCP, those with hypersensitivity to planned medications, or possessing prothrombotic medical conditions, recent users of treatment for melasma/participants in other trials were excluded to guarantee both safety and baseline equivalency.

Patient Groups and Randomization

Randomization was performed through a computer-generated randomization program to balance the three treatment arms of the study. Group A was treated with oral Tranexamic Acid (250 mg) twice a day, Group B with 1% Arbutin cream applied to the area involved twice a day, and Group C with both treatments combined, twice daily. During the treatment period, all participants were instructed to apply broad-spectrum sunscreen daily, avoid prolonged sun exposure, and wear sun-protective items (eg, sunglasses and hats). Due to the open-label design of the study, both participants and researchers were aware of their treatment assignments.

Baseline Assessment and Follow-Up

In a cross-sectional study, we examined the patients for the type and severity of melasma using Wood's lamp and a structured questionnaire that documented the patients' demographics, medical history, and melasma characteristics. At each follow-up visit (duration interval is three months), this questionnaire was re-evaluated to measure treatment response, adverse effects, and satisfaction, scored with a 5-level of Likert scale. Standard daylight conditions were used for the pictures.

The protein C and S levels were screened for patients in groups A and C (protein C and Protein S are natural anticoagulants, vitamin K, K-dependent plasma proteins that regulate blood clotting by inactivation of factors Va and VIIIa. Indeed, such deficiencies increase the relative risk of thromboembolic events, a concern when pre-treatment with antifibrinolytic agents such as tranexamic acid and the potential coagulation effects they have (11). The Modified Melasma Area Severity Index (mMASI) scores of area involvement and pigmentation were recorded at baseline, 1 month, 2 months, and 3 months to assess melasma severity.

.

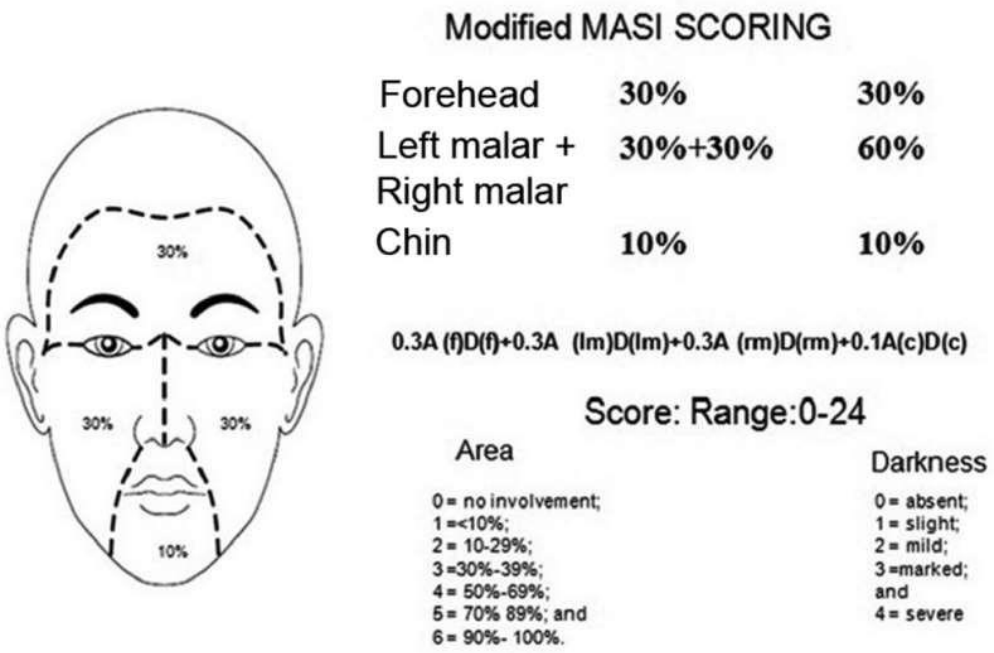

Figure 1. The modified Melasma Area and Severity Index (mMASI) score assessment (12). where (A) denotes the area of involvement and (D) represents the degree of darkness in the forehead (f), right malar (rm), left malar (lm), and chin (c). Scores range from 0 to 24, with higher values indicating greater pigmentation severity.

Statistical analysis

The statistical analyses were carried out in IBM SPSS 26 with non-parametric tests given the non-normal distributions (Kolmogorov-Smirnov test). Continuous variables were compared between groups using the Kruskal-Wallis and Mann-Whitney U tests, and differences in mMASI scores were determined within groups using the Wilcoxon signed-rank test. Chi-square Test for Categorical Variables. Results are expressed as mean ± SD or (%). P≤0.05 indicates a statistically significant difference.

Ethical Consideration

Ethical approval for this study was obtained from the Ethics Committee of the College of Medicine, University of Sulaimani (Approval Code: 370, November 3, 2024). Informed consent was obtained in writing from all participants prior to entry into the study.

Results

The study enrolled 120 patients equally randomized to receive oral tranexamic acid (TXA) and topical 1% arbutin cream, or a combination of both. There were no statistically significant differences between groups at baseline. Mean age varied from 33.27 ± 6.96 to 35.37 ± 6.25 years (p 0.330). Females made up 95.0% of the population, and there was no statistically significant difference between the treatment groups in the proportion of females (p = 0.591). Regarding occupational status, 85.8% of the study population were indoor workers and 14.2% were outdoor workers, with no intergroup distinction (p = 0.079). Distribution of marital status was also similar [85.0% vs 12.5% vs 2.5% and p=0.290 (balance between married, single, and divorced)]. These results confirm demographic comparability of the groups studied, thus spanning the introduction of potential bias due to confounding when interpreting outcomes. As shown in Table 1.

Table 1. Sociodemographic Characteristics of Patients Across Treatment Groups.

Sociodemographic profile	**Group A** Oral TXA	**Group B** Topical 1% Arbutin	**Group C** Oral TXA with Topical 1% Arbutin	**Total**	**P value**
Age (year)					
Mean ± SD	35.37 ± 6.25	33.27 ± 6.96	34.26 ± 5.54	34.3 ± 6.29	0.330 ns
Min/Max	23/54	20/50	19/46	19/54	
95%CI	33.38 – 37.37	31.05 – 35.50	32.46 – 36.05	33.16 – 35.44	
Gender, n (%)					
Female	37 (92.5%)	39 (97.5%)	38 (95.0%)	114 (95.0%)	0.591 ns
Male	3 (3 (7.5%)	1 (2.5%)	2 (5.0%)	6 (5.0%)	
Occupation, n (%)					
Indoor worker	34 (85.0%)	38 (95.0%)	31 (77.5%)	103 (85.8%)	0.079 ns
Outdoor worker	6 (15.0%)	2 (5.0%)	9 (22.5%)	17 (14.2%)	
Marital state, n (%)					
Single	3 (7.5%)	8 (20.0%)	4 (10.0%)	15 (12.5%)	0.290 ns
Married	35 (87.5%)	32 (80.0%)	35 (87.5%)	102 (85.0%)	
Divorce	2 (5.0%)	0 (0.0%)	1 (2.5%)	3 (2.5%)	

TXA: Tranexamic acid; n: Number; SD: Standard deviation; Min: Minimum; Max: maximum; CI: Confidence interval; ns: no significant difference using Kruskal-Wallis test (age) and Chi-square test (others).

Baseline Clinical Profile

The melasma-related characteristics at baseline were similar among treatment groups (Table 2). Family history of melasma was present in 59.2% of patients (p = 0.639), and 53.3% reported irregular sunscreen use (defined as applying fewer than five days per week) (p = 0.529). Majority of patients had Fitzpatrick skin phototype III (59.2%) and IV (30.8%); types II (7.5%) and V (2.5%) comprised a lower number of patients (p = 0.199) The most common subtype was mixed melasma (40.8%), followed by dermal melasma (33.3%), and epidermal melasma (25.8%) (p = 0.163). Melasma was of variable duration between groups (p = 0.025), with the majority (70.8%) of patients having symptoms present for greater than two years. Centrofacial distribution was most common (83.3%), while malar (13.3%) and mandibular (3.3%) distributions were less common (p = 0.239). The most commonly listed predisposing factors were pregnancy (47.5%) and sun exposure (41.7%); hormonal therapy and combined hormonal-pregnancy exposure were infrequently cited.

Table 2. Baseline Clinical Characteristics of Patients Across Treatment Groups.

Clinical characteristics	**Group A** Oral TXA	**Group B** Topical 1% Arbutin	**Group C** Oral TXA with Topical 1% Arbutin	**Total**	**P value**
Family history of melasma, n (%)					
No	17 (42.5%)	18 (45.0%)	14 (35.0%)	49 (40.8%)	0.639 ns
Yes	23 (57.5%)	22 (55.0%)	26 (65.0%)	71 (59.2%)	
Using sunscreen, n (%)					
No	24 (60.0%)	21 (52.5%)	19 (47.5%)	64 (53.3%)	0.529 ns
Yes	16 (40.0%)	19 (47.5%)	21 (52.5%)	56 (46.7%)	
Fitzpatrick skin type, n (%)					
II	2 (5.0%)	4 (10.0%)	3 (7.5%)	9 (7.5%)	0.199 ns

III	20 (50.0%)	26 (65.0%)	25 (62.5%)	71 (59.2%)	
IV	15 (37.5%)	10 (25.0%)	12 (30.0%)	37 (30.8%)	
V	3 (7.5%)	0 (0.0%)	0 (0.0%)	3 (2.5%)	
Type of melasma, n (%)					
Epidermal	12 (30.0%)	5 (12.5%)	14 (35.0%)	31 (25.8%)	0.163 ns
Dermal	14 (35.0%)	14 (35.0%)	12 (30.0%)	40 (33.3%)	
Mixed	14 (35.0%)	21 (52.5%)	14 (35.0%)	49 (40.8%)	
Duration of melasma, n (%)					
<6 months	1 (2.5%)	2 (5.0%)	2 (5.0%)	5 (4.2%)	0.025 *
6 months – 1 year	3 (7.5%)	0 (0.0%)	1 (2.5%)	4 (3.3%)	
1-2 years	8 (20.0%)	15 (37.5%)	3 (7.5%)	26 (21.7%)	
>2 years	28 (70.0%)	23 (57.5%)	34 (85.0%)	85 (70.8%)	
Pattern of melasma, n (%)					
Centrofacial	31 (77.5%)	36 (90.0%)	33 (82.55)	100 (83.3%)	0.239 ns
Malar	7 (17.5%)	2 (5.0%)	7 (17.5%)	16 (13.3%)	
mandibular	2 (5.0%)	2 (5.0%)	0 (0.0%)	4 (3.3%)	
Predisposing factor of melasma, n (%)					
No	2 (5.0%)	0 (0.0%)	2 (5.0%)	4 (3.3%)	0.109 ns
Sun exposure	11 (27.5%)	23 (57.5%)	16 (40.0%)	50 (41.7%)	
Pregnancy	21 (52.5%)	16 (40.0%)	20 (50.0%)	57 (47.5%)	
Hormonal therapy	4 (10.0%)	1 (2.5%)	2 (5.0%)	7 (5.8%)	
Pregnancy with hormonal therapy	2 (5.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	

TXA: Tranexamic acid; n: Number; ns: no significant difference; *: Significant difference using chi-square test.

Treatment Efficacy Based on mMASI Scores

Treatment efficacy was evaluated using the modified Melasma Area and Severity Index (mMASI) at baseline and at monthly intervals up to three months (Table 3, Figure 2). At baseline (Day 0), mean mMASI scores were comparable across all groups: Group A (oral TXA) 9.38 ± 4.11, Group B (topical 1% arbutin) 9.02 ± 3.30, and Group C (combined therapy) 9.29 ± 3.84, with no statistically significant differences between any groups (Group A vs. B: Pa = 0.920; A vs. C: Pb = 0.963; B vs. C: Pc = 0.940).

One month later, a mild decrease was marked in all groups, but again intergroups difference were not significant even (Pa= 0.654, Pb= 0.618, Pc= 0.965). In the second month, Group C demonstrated a notable decrease (5.65 ± 2.51) that was significantly different from Group B (Pc = 0.040) and Group A (Pb = 0.044).

Group C (4.25 ± 2.13) also showed the largest reduction at three months, compared to Group B (Pc = 0.007) and trended towards improvement compared to Group A (Pb = 0.047, significant).

The within-group improvements over time in all arms were highly statistically significant ($p < 0.001$) between administrations as shown by intragroup comparisons demonstrating the cumulatively progressive effectiveness of each treatment arm. Of note, combination therapy was consistently superior to the monotherapies

at later time points, which reinforces the greater clinical effectiveness of this approach to treat melasma. Table 3 provides details on these results.

Figure 2. Comparative facial improvements following different treatment modalities.The right side of a 36-year-old female patient's face showed visible improvement after 12 weeks of oral tranexamic acid therapy (B) compared with baseline (A). Likewise, a 23-year-old male exhibited improvement after 12 weeks of topical 1% arbutin cream treatment (D) relative to baseline (C). Additionally, the left side of a 31-year-old female's face demonstrated progress following combined therapy for 12 weeks (D) compared with its initial state (E).

Table 3. Modified Melasma Area and Severity Index (mMASI) Scores Over Time Across Treatment Groups.

mMASI score (Mean ± SD)	**Group A** Oral TXA	**Group B** Topical 1% Arbutin	**Group C** Oral TXA with Topical 1% Arbutin	**P a**	**P b**	**P c**
Day 0	9.38 ± 4.11	9.02 ± 3.30	9.29 ± 3.84	0.920 ns	0.963 ns	0.940 ns
After 1 month	9.13 ± 4.65	8.15 ± 3.11	8.31 ± 3.47	0.654 ns	0.618 ns	0.965 ns
After two months	7.79 ± 4.14	7.35 ± 3.68	5.65 ± 2.51	0.801 ns	0.040 *	0.044 ns
After three months	5.70 ± 3.15	5.96 ± 2.99	4.25 ± 2.13	0.599 ns	0.047 ns	0.007 *
P value	<0.001 **	<0.001 **	<0.001 **			

TXA: Tranexamic acid; n: Number; SD: Standard deviation; ns: no significant difference. Intergroup comparisons were performed using the Mann-Whitney U test, with the following results: Group A (Oral TXA) vs Group B (Topical Arbutin) (Pa): No significant differences at any time point ($P > 0.05$). Group A vs Group C (Oral TXA + Topical Arbutin) (Pb): Significant improvement in Group C at 2 months ($P = 0.040$), but not at 3 months ($P = 0.047$, ns due to borderline significance). Group B vs Group C (Pc): Group C showed significantly better improvement than Group B at 3 months ($P = 0.007$). For intragroup comparisons (Wilcoxon signed-rank test), all treatment groups (A, B, and C) demonstrated highly significant reductions in mMASI scores over time ($P < 0.001$, marked as **), indicating progressive efficacy within each group.

Patient-Reported Satisfaction Outcomes

Patient satisfaction on a five-point Likert scale (1 = very dissatisfied; 5 = very satisfied) in the three treatment groups. There were no participants who reported "very dissatisfied with their experience", which suggests a good response to treatment. Dissatisfaction was limited and evenly distributed, with 2.5% in each group selecting "dissatisfied." Ratings of score = 3, or "neutral," were more common in groups B (30.0%) and A (25.0%) than in group C (15.0%), suggesting differences in patient-perceived effectiveness between treatments.

In Group A, 47.5% of patients reported that they were “satisfied” (score = 4), compared to 45.0% in Group B and 40.0% in Group C; conversely, “very satisfied” (score = 2.5) was more prevalent (42.5%) in Group C than in either Group A (25.0%) and Group B (22.5%). Intergroup analysis revealed statistically significant differences in satisfaction scores (Group C had better CS in overall satisfaction score compared with Group B [p = 0.032] and Group A [p = 0.018], while the comparisons between Group A with Group B were not significant (p=0.804). Mann-Whitney U test; Table 4, Figure 2).

Table 4. Patient Satisfaction Levels Across Treatment Groups Based on the Likert Scale.

Likert Scale n (%)	**Group A** Oral TXA	**Group B** Topical 1% Arbutin	**Group C** Oral TXA with Topical 1% Arbutin	**P a**	**P b**	**P c**
Very dissatisfied	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Dissatisfied	1 (2.5%)	1 (2.5%)	1 (2.5%)			
Neutral	10 (25.0%)	12 (30.0 %)	6 (15.0%)	0.804 ns	0.032 *	0.018 *
Satisfied	19 (47.5%)	18 (45.0%)	16 (40.0%)			
Very satisfied	10 (25.0%)	9 (22.5%)	17 (42.5%)			

TXA: Tranexamic acid; n: Number; %: Percentage; ns: no significant difference; *: Significant difference using Chi-square test. Pa = Group A vs. Group B; Pb = Group A vs. Group C; Pc = Group B vs. Group C.

Safety and Adverse Events Profile

All treatment arms monitored adverse effects, and differences in reported events were clinically significant but not clinically important and generally mild. In Group A (oral TXA monotherapy), 8 of 40 patients (20%) reported epigastric discomfort. Group B (1% arbutin topically, monotherapy) had the best safety profile, with only 1 of 40 patients (2.5%) in the group reporting mild skin irritation. Notably, Group C (combination therapy) accounted for 7 of the 40 patients (17.5%) experiencing epigastric pain, comparable to the gastrointestinal symptom profile of the oral TXA group.

There were no statistically significant differences between groups in the incidence of adverse effects (p = 0.163), suggesting that the combination regimen was not associated with increased risk of

adverse effects attributable to the treatments. (Figure 3).

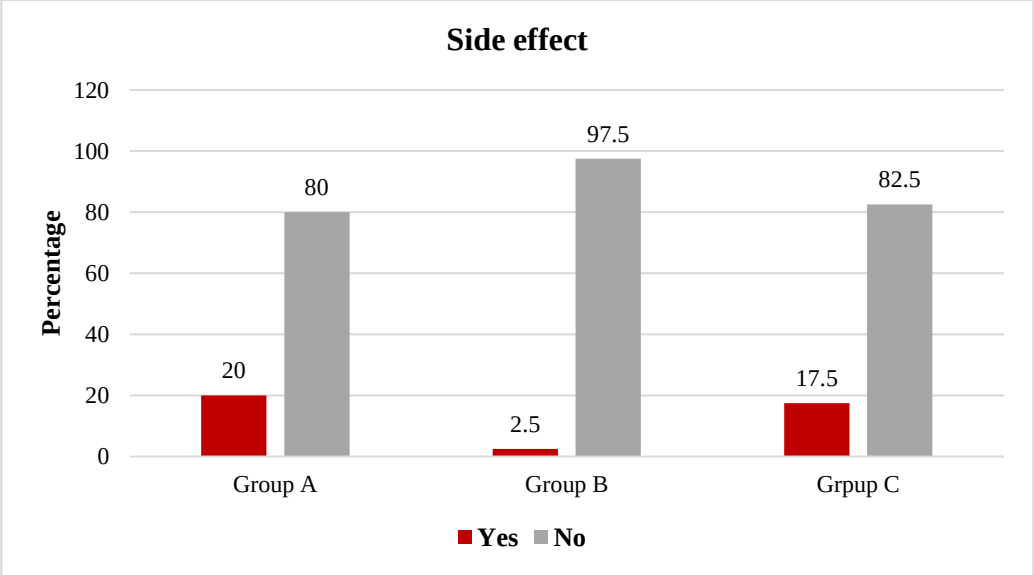

Figure 3. Side effect comparison between the groups. Group A: Oral tranexamic acid (TXA) monotherapy 250 mg taken twice daily, Group B: Topical 1% arbutin cream applied twice daily to affected areas, Group C: Combination therapy oral TXA (250 mg twice daily) plus topical 1% arbutin cream (twice daily)

Post-Treatment Recurrence Analysis

There were significant differences in recurrence rates of melasma among treatment arms (Figure 4.6). Recurrence was defined by an increase in the mMASI score at the third month of follow-up. In terms of proportion, the group receiving oral tranexamic acid (TXA) monotherapy had a recurrence rate of 30% (12 from 40), whereas the group receiving topical 1% arbutin monotherapy had a slightly higher recurrence rate of 37.5% (15 from 40) (Table 5). Interestingly, the combination therapy group (oral TXA + topical 1%arbutin) had the best results, as only 15% (6 out of 40) of patients met recurrence.

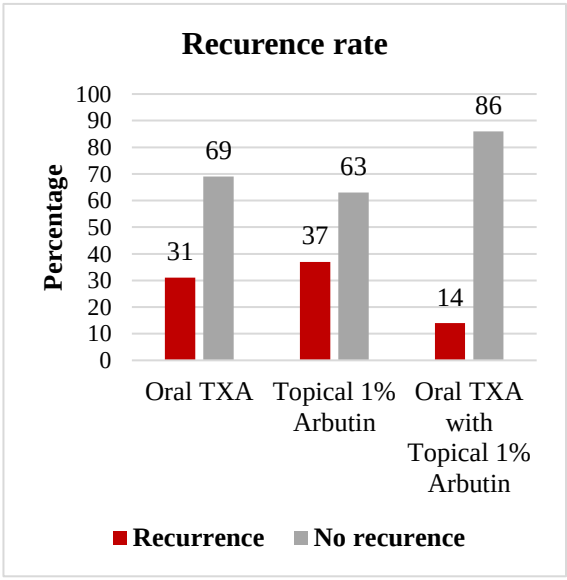

Figure 4. Recurrence rate among different treated groups.
Note: oral TXA: oral tranexamic acid

Discussions

Melasma is one of the most prevalent forms of acquired pigmentation disorder in women, as well as in men, but less fairly, which owes to more frequently seen in Fitzpatrick skin types III to VI. It presents as macules and patches of hyperpigmentation that are usually seen on the sun-exposed areas of the face and neck. The management of melasma has been a challenging process for the clinician and patient alike, since always, complete clearing of lesions is usually not possible, and relapses are common even after successful initial treatment (13, 14). The aim of this study was to compare the efficacy of oral tranexamic acid (TXA), 1% arbutin cream, and their combination in the treatment of melasma in Sulaymaniyah, divided into three groups: Oral TXA (monotherapy) group, topical 1% arbutin (monotherapy) group, & combination therapy (oral TXA with 1% arbutin cream).

In the current study, both oral tranexamic acid (TXA) and topical 1% arbutin significantly improved melasma severity. The combination group (Group C) showed a 54.3% reduction in mMASI scores at 12 weeks compared with 39.2% and 33.9% in the TXA (Group A) and arbutin (Group B) groups, respectively ($p < 0.001$). Philipp-Dormston et al., conducted a study on this as well. (2024) highlighted multimodal combination therapy, advocating that TXA and tyrosinase inhibitors (eg, arbutin) be preferred over hydroquinone due to the established safety profile (15). Similarly, Latha et al., (2025) proved through a comparative study, proved that the combination of oral TXA with topical agents achieved a quicker and more stable decrease in melasma severity, as the improvement in the mean MASI scores was highly significant ($P < 0.001$) (16).

Furthermore, Cassiano et al., (2022). in their review on melasma treatments, they found that oral TXA improved the effectiveness of topical depigmenting agents, indicating that the earlier benefits seen in other studies when topical treatments were combined with oral agents may be manifested earlier when topical treatments are combined with oral agents (17).

The superiority response of combination therapy may be due to the dual action of each agent in the regimen: TXA inhibition of UV-induced melanogenesis through blockade of plasminogen–plasmin system and vascular mediators like VEGF (6), and arbutin, indirect inhibition of tyrosinase, resulting in decreased melanin production (10). This complementary action likely enhances treatment durability and depth of pigment reduction.

Oral TXA (Group A) in our study produced statistically significant reductions in pigmentation, but the improvement was slower compared with Group C, where the combination application showed the rates of improvement in pigmentation. This is supported by the findings of Atefi et al. (2017), who demonstrated that tranexamic acid is highly effective in treating melasma by inhibiting melanogenesis through various mechanisms, such as reducing plasmin activity, inhibiting vascular endothelial growth factor (VEGF), and blocking inflammatory mediators (18). It's possible that the direct inhibition of tyrosinase, the enzyme involved in melanin production, by 1% arbutin aided even more improvement in Group C (10). The study by Rivas et al., (2013) also

highlighted the effectiveness of topical agents like arbutin, reporting significant reductions in melasma severity. These findings are in line with our results, where arbutin alone (Group B) led to some improvement in pigmentation, though it was less effective than the combined therapy. The combination therapy appears to provide a more comprehensive approach to melasma treatment, addressing both the underlying vascularity and melanin production (19).

Across treatment groups, we see an increase in patient satisfaction, confirming the improved effectiveness of combination therapy. Another indication that all interventions were tolerable is the lack of very dissatisfied patients. Although the neutral response also differed between groups, 42.5% of patients in Group C were "very satisfied," which reinforces the synergistic effect of adding oral tranexamic acid with topical arbutin.

The differences in satisfaction level were statistically significant (P = 0.032 for Group B vs Group C; P = 0.018 for Group A vs Group C) and indicative of the patient's perception of difference in satisfaction with combination therapy, and further bolsters the superiority of combination therapy for melasma. These findings align with Philipp-Dormston (2024), studies that highlight multimodal approaches as more effective in achieving patient-centred outcomes.(20)

A meta-analysis by Gonçalves et al., (2024) demonstrated that oral tranexamic acid (TXA) as an adjuvant to triple combination topical treatment significantly improved Melasma Area and Severity Index scores and reduced recurrence rates (21).

In our findings, both treatments appeared to be safe in our study. Both treatments in this study had side effects that were not severe. Oral TXA commonly reported side effects were mild gastrointestinal discomfort, and skin irritation in the arbutin group was temporary and mild... These results are consistent with previous studies evaluating the safety of oral tranexamic acid (TXA) and topical arbutin in melasma treatment. A study by Latha et al., (2025) compared oral TXA with a triple combination cream, reporting minimal adverse effects, primarily mild gastrointestinal symptoms in the TXA group and transient skin irritation in the topical treatment group (22).

Similarly, a review on depigmenting agents highlighted that arbutin is generally well-tolerated, with temporary erythema or irritation being the most commonly observed side effect (23). Additionally, tranexamic acid's safety profile has been extensively studied, with common side effects including mild gastrointestinal discomfort, headache, and rare thrombotic events (24).

Topical 1% arbutin demonstrated a favorable safety profile, with only mild skin irritation and transient erythema reported. These findings align with existing literature on arbutin’s safety profile. According to the Scientific Committee on Consumer Safety (SCCS), alpha-arbutin is considered safe when used in face creams up to 2% and body lotions up to 0.5%, with minimal risk of adverse effects (25). Additionally, a review by Chandorkar et al., (2021), highlights that alpha-arbutin is a well-tolerated skin-lightening agent, primarily acting through tyrosinase inhibition, with transient erythema and mild irritation being the most commonly reported side effects (26).

A large variation in treatment groups was observed for recurrent melasma. Recurrence as determined by four standardized criteria: aggravation in mMASI score, clinical assessment pigmentation, Physician Global Assessment, and photography. 31% recurrence rate after oral tranexamic acid (TXA); 37% recurrence rate after topical 1% arbutin monotherapy. In contrast, the best result were obtained with combination therapy (oral TXA + 1% arbutin topical), with only 14% of patients reporting recurrence. These findings align with existing literature on melasma recurrence rates and the effectiveness of combination therapy. A review by Gan c. et al. (2024), highlights that melasma remains a challenging condition with a high recurrence rate, particularly when treated with monotherapy approaches (27).

Similarly, a study by Parać et al., (2024), discusses the multifactorial nature of melasma recurrence, emphasizing the importance of targeting multiple pathways, including vascular and melanogenic mechanisms (28).

The lower recurrence rate observed in the combination therapy group (14%) supports previous findings that integrating systemic and topical treatments enhances long-term efficacy. These results further validate the clinical advantage of multimodal approaches, reinforcing the need for personalized treatment strategies to minimize recurrence.

Conclusions

Compared with monotherapy, oral TXA＋ topical arbutin combination therapy proved to be more effective, had higher patient satisfaction, and lower recurrence rates. It targets vascular and melanogenic components; therefore, it provides optimal long-term results and has a good safety profile. Because melasma is multifactorial, a personalized multimodal approach is associated with the best long-term results. A larger sample size with longer follow-up is needed to succeed in defining the best treatment options.

Recommendations

High efficacy and lower recurrence rates of topical arbutin after MTX and oral TXA therapy suggest the future focus would be on the combination therapy of oral TXA and topical arbutin as first priority treatment. However, treatment should be personalized according to skin type, background, and response. Further studies are needed to assess long-term outcomes, perform comparative experiments with other depigmenting agents, and evaluate the optimal dose to mitigate side effects.

Limitations

The three-month follow-up in this study limits our understanding of long-term recurrence patterns, and the fact that the study was done at a single centre limits generalizability to wider populations. This was an open-label trial, which introduces the potential for observer and performance bias, and a larger, multi-centre trial would provide greater statistical robustness. More importantly, mechanistic analyses should be performed to elucidate the mode of action of TXA and arbutin to treat melasma.

Conflict of Interest Statement: None
Funding: No Funding was received

References

1. Vitale MD. Management of mixed melasma on darker phototypes: A new and safe laser therapy treatment. IJCMCR. 2024;37(3):1-6.

2. Harumi O, Goh CL. The effect of melasma on the quality of life in a sample of women living in Singapore. The Journal of clinical and aesthetic dermatology. 2016;9(1):21.
3. Cestari T, Arellano I, Hexsel D, Ortonne J, Academy LAPD. Melasma in Latin America: options for therapy and treatment algorithm. Journal of the European Academy of Dermatology and Venereology. 2009;23(7):760-72.
4. Espósito ACC, Cassiano DP, da Silva CN, Lima PB, Dias JAF, Hassun K, et al. Update on Melasma-Part I: Pathogenesis. Dermatol Ther (Heidelb). 2022;12(9):1967-88.
5. Liu W, Chen Q, Xia Y. New Mechanistic Insights of Melasma. Clin Cosmet Investig Dermatol. 2023;16:429-42.
6. Kwon S-H, Hwang Y-J, Lee S-K, Park K-C. Heterogeneous Pathology of Melasma and Its Clinical Implications. International journal of molecular sciences. 2016;17(6):824.
7. Galache TR, Sena MM, Tassinary JAF, Pavani C. Photobiomodulation for melasma treatment: integrative review and state of the art. Photodermatology, Photoimmunology & Photomedicine. 2024;40(1):e12935.
8. Sirithanabadeekul P, Lapsomboonsiri S, Rungjang A, Thanasarnaksorn W. Split face comparison between common concentration vs double dilution of intradermal abobotulinum toxin type A (Dysport) injection for facial lifting in Asians. Journal of Cosmetic Dermatology. 2018;17(3):355-60.
9. Juliano CC. Spreading of dangerous skin-lightening products as a result of colourism: a review. Applied Sciences. 2022;12(6):3177.
10. Boo YC. Arbutin as a Skin Depigmenting Agent with Antimelanogenic and Antioxidant Properties. Antioxidants. 2021;10(7):1129.
11. Wu Y, Liu J, Zeng W, Hu B, Hu Y, Tang LV. Protein S Deficiency and the Risk of Venous Thromboembolism in the Han Chinese Population. Frontiers in Cardiovascular Medicine. 2022;Volume 8 - 2021.
12. Khurana VK, Misri RR, Agarwal S, Thole AV, Kumar S, Anand T. A randomized, open-label, comparative study of oral tranexamic acid and tranexamic acid microinjections in patients with melasma. Indian journal of dermatology, venereology and leprology. 2019;85:39.
13. Goel A, Trivedi N. Current updates on melasma treatments. Cosmoderma. 2023;3(79):84-90.
14. Neagu N, Conforti C, Agozzino M, Marangi GF, Morariu SH, Pellacani G, et al. Melasma treatment: a systematic review. Journal of Dermatological Treatment. 2022;33(4):1816-37.
15. Philipp-Dormston WG. Melasma: a step-by-step approach towards a multimodal combination therapy. Clinical, Cosmetic and Investigational Dermatology. 2024:1203-16.
16. Latha S. Comparative Study of Efficacy and Safety of Oral Tranexamic Acid with Topical Triple Combination Cream Containing Fluticasone Propionate 0.05%, Tretinoin 0.025% and Hydroquinone 2% Versus Topical Triple Combination Alone in the Treatment of Melasma: Rajiv Gandhi University of Health Sciences (India); 2019.
17. Cassiano DP, Espósito ACC, da Silva CN, Lima PB, Dias JA, Hassun K, et al. Update on melasma—part II: treatment. Dermatology and Therapy. 2022;12(9):1989-2012.
18. Poojary S, Minni K. Tranexamic acid in melasma: A review. Pigment Disord. 2015;2(12):228.
19. Rivas S, Pandya AG. Treatment of melasma with topical agents, peels and lasers: an evidence-based review. American journal of clinical dermatology. 2013;14:359-76.
20. Ribeiro Gonçalves O, de Souza MCF, Rocha AV, Alves GS, Freitas JLR, de Azevedo BB, et al. Assessing the efficacy of oral tranexamic acid as an adjuvant to triple combination topical treatment in melasma: a meta-analysis of randomized controlled trials. Clinical and Experimental Dermatology. 2024;49(12):1518-24.
21. Latha S. Comparative Study of Efficacy and Safety of Oral Tranexamic Acid with Topical Triple Combination Cream Containing Fluticasone Propionate 0.05%, Tretinoin 0.025% and Hydroquinone 2% Versus Topical Triple Combination Alone in the Treatment of Melasma: Rajiv Gandhi University of Health Sciences (India); 2019.
22. Galappatthy P, Rathnayake D. Depigmenting agents. Pigmentary Skin Disorders. 2018:261-80.
23. Murdaca G, Greco M, Vassallo C, Gangemi S. Tranexamic acid adverse reactions: a brief summary for internists and emergency doctors. Clinical and Molecular Allergy. 2020;18:1-4.
24. Bernauer U, Bodin L, Chaudhry Q, Coenraads P, Dusinska M, Ezendam J, et al. SCCS opinion on the safety of alpha-arbutin and beta-arbutin in cosmetic products: European commission; 2023.
25. Handorkar N, Tambe S, Amin P, Madankar CS. Alpha Arbutin as a Skin Lightening Agent: A Review. International Journal of Pharmaceutical Research (09752366). 2021;13(2).
26. Gan C, Rodrigues M. An update on new and existing treatments for the management of melasma. American Journal of Clinical Dermatology. 2024;25(5):717-33.
27. Parać E, Bukvić Mokos Z. Unmasking melasma: Confronting the treatment challenges. Cosmetics. 2024;11(4):143.