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Review Article

Assessment the efficacy of tranexamic acid for reduce melasma using MASI/mMASI score: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Melasma is a commonly acquired pigmentary disorder, appearing as brown macules and patches on sun-exposed areas of the face and neck. Many treatments have been attempted to reduce melasma, however there has been no universally impactful procedure to show promising results. In recent studies, tranexamic acid (TXA) oral, injection, or topical has been used for treating/ reducing melasma with promising results. Tranexamic acid's main effect on skin is a whitening effect either systematically or topically preparation. We aim to provide the latest evidence on the clinical efficacy of TXA in the treatment of melasma by pooling data from cohort studies.

Methods We performed a comprehensive search on topics that assesses tranexamic acid to reduce melasma from inception up until May 2023.

Results There were 21 studies out of a total of 1167 patients reported the changes of MASI/mMASI score after using oral, topical, and injection TXA at 4 weeks, 8 weeks, and 12 weeks. The pooled analysis showed the significance of reduction in melasma area severity index/modified melasma area severity index (MASI/mMasi) scores at 4 weeks (MD: 3.58; 95% CI, 2.15-5.01;I2 = 92%), 8 weeks (MD: 5.08; 95% CI, 3.34–6.81;I2=96%) and 12 weeks (MD: 4.89; 95% CI, 3.80–5.97;I2=91%) after treatment were all less than the baseline scores, regardless of the delivery route.

Conclusion The objective of this thorough examination and analysis is to present the available information regarding the application of TXA as a treatment option for individuals with melasma. Additional extensive randomized controlled trials (RCTs) are required to determine the most effective dosage and treatment plan for TXA.

Key words
Tranexamic acid; Melasma; MASI/mMasi; Meta-analysis; Systematic review.

Introduction

Melasma is a commonly acquired disorder of skin pigmentation that is characterized by the presence of brown macules and patches on the exposed areas of the face and neck.[1] This condition is often caused by factors such as exposure to ultraviolet (UV) radiation, sex hormones, genetic predisposition, and the use of cosmetics.[1,2] Various treatments have been explored to reduce melasma, including chemical peeling and laser therapy, but none of these procedures have yielded universally satisfactory results.[2]

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Tranexamic acid (TXA) or (trans-4-(aminomethyl) cyclohexane carboxylicacid), a synthetic analogue of lysine, has shown potential in inhibiting UV-induced pigmentation by blocking the binding of lysine and reducing plasmin. TXA's has main effect on skin is a whitening effect either systematically or topically preparation.[2,3] TXA has been found to have a whitening effect on the skin when applied topically or taken orally. Recent studies have investigated the use of TXA in the treatment of melasma, either through oral ingestion, injection, or topical application, and have shown promising results.[3,4] However, there is currently no definitive consensus on the use of TXA for melasma treatment.[5] Consequently, this systematic review and meta-analysis aims to provide the latest evidence on the clinical efficacy of TXA in the treatment of melasma by pooling data from cohort studies.

Method

This meta-analysis through various stages: **(Figure 1).**

Search strategy We conducted a thorough investigation on the topic of melasma in 2023, specifically focusing on the use of tranexamix acid (TXA). We employed various keywords such as "TRANEXAMIC ACID" or "TXA," "Melasma," and "Chloasma," along with their relevant synonyms. The search spanned from the inception of relevant literature up until May 2023, utilizing electronic databases including Pubmed, Cochrane Central Database, ClinicalTrials.gov, and Mendeley. In order to determine the suitability of the retrieved records, we followed a systematic evaluation process using predefined inclusion and exclusion criteria. The initial search, which involved reviewing all abstracts to identify pertinent studies, was independently performed by two authors (MT and RM). In case of any discrepancies, final judgments and assessments of eligibility from full-text articles were made by all authors involved (MT, RM, and YK), applying a similar process for resolving potential disagreements. A diagram illustrating the literature search strategy for the systematic reviews is presented as **Figure 1**, following the preferred reporting items for systematic reviews guidelines.

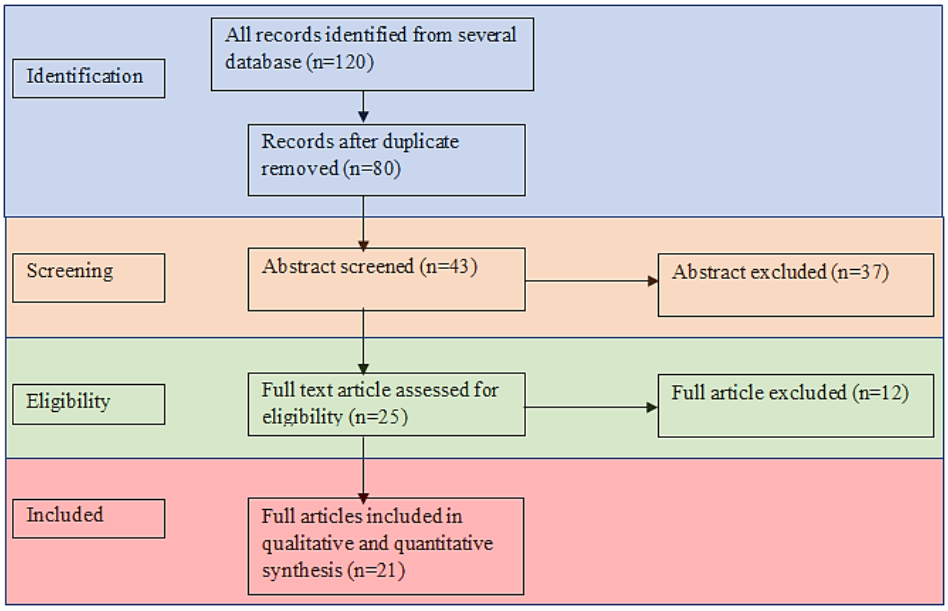

Figure 1 The flow diagram of meta-analysis.

Selection Criteria All studies examining the effectiveness of TXA in reducing melasma were considered for this study, regardless of how it was administered (orally, through intradermal/ injection, or topically). The selected publications had to be randomized controlled trial (RCT) studies. On the other hand, studies that did not focus on melasma with TXA, and those that were review articles, meta-analyses, epidemiological studies, abstracts only, non-English manuscripts, or editorials were excluded from this study.

Data extraction Three separate authors (MT, YK, and RM) performed data extraction and quality evaluation using a standardized approach. **Table 1** presents the relevant features of the studies included, highlighting the primary outcomes analyzed in the meta-analysis. These outcomes focused on calculating the mean difference and standard deviation of TXA related to the reduction of melasma, as assessed through MASI or mMASI scores before and after treatment, conducted over a duration of 4 weeks, 8 weeks, and 12 weeks.

Statistical Analysis The statistical analysis was performed using Revman 5.4 (used for continuous data).

Bias Analysis The risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) analysis was used to evaluate bias in various journals. As shown in **Table 1**, the analysis revealed that all the journals had explicitly defined population, intervention, comparison, and outcome criteria. Among these journals, the original studies were the most prevalent.

Table 1 ROBINS-I Analysis.

Study	*Confounding Bias*	*Participants Bias*	*Intervention Bias*	*Missing Data Bias*	*Outcome Bias*	*Reporting Bias*	*Overall Risk Bias*
Padhi, 2015	No	No	No	NI	No	No	Low
Lajevardi, 2017	No	No	Yes	NI	No	Yes	Low
Minni, 2020	No	No	No	NI	No	No	Low
Karrabi, 2020	No	Yes	No	NI	No	No	Low
Zhao, 2020	No	No	No	NI	No	No	Low
Banihashemi, 2015	No	No	No	Yes	No	No	Low
Janney, 2019	No	No	No	NI	No	No	Low
Kanechorn, 2012	No	No	No	NI	No	No	Low
Kaur, 2020	No	Yes	No	NI	No	No	Low
Laothaworn, 2018	No	No	No	NI	No	No	Low
Shamsi, 2020	No	Yes	No	NI	No	No	Low
Wanitphakdeedecha 2020	No	No	No	NI	No	No	Low
Karn, 2012	No	No	No	NI	No	No	Low
Shin, 2013	No	No	No	NI	No	No	Low
Malik, 2019	No	No	No	NI	No	No	Low
Colferai, 2018	No	No	No	NI	No	No	Low
Del Rosario, 2018	No	No	No	Yes	No	No	Low
Shihab, 2020	No	No	No	NI	No	No	Low
Steiner, 2009	No	No	No	NI	No	No	Low
Atefi, 2007	No	No	Yes	NI	No	Yes	Low
Chung, 2016	No	No	No	NI	No	No	Low

Note: Bias analysis showed that all journals have clear population, intervention, comparison, and outcome. These journals were mostly the original study for this research. There were 3 journals with participants data bias, 2 journal with intervention bias, 2 journal with missing data bias, and 2 journal with reporting bias. All of the included studies have a low score according with overall risk bias.

However, some journals displayed bias in different aspects. Three journals exhibited bias in participant data, two journals had bias related to the intervention, two journals had biases due to missing data, and two journals had biases associated with reporting. Overall, all of the included studies were found to have a low score indicating the risk of bias.

Result

Study selection A summary of the study selection process can be found in **Figure 1**. After removing duplicate articles, a search of multiple databases produced 120 articles, out of which 80 were considered potentially relevant. Further evaluation of the titles and abstracts led to the exclusion of 49 articles that did not meet the eligibility criteria. Eventually, 21 studies were identified that met the criteria and underwent full-text reading. There were no conflicts during the study selection process. The bias analysis of all these journals is presented in **Table 1**.

Baseline Characteristic

According to 21 studies involving a total of 1167 patients **(Table 2)**, it has been found that melasma is most commonly observed in individuals up to the age of 35. The use of tranexamic acid (TXA) through oral intake (250mg), injection (0.05-4ml), or topical application (2-5% TXA) has shown significant effectiveness in reducing melasma symptoms, as assessed by the MASI/mMasi score, at 4 weeks, 8 weeks, and 12 weeks compared to the baseline. Among the included studies, only two did not mention any associated side effects. Some common side effects of oral TXA include heartburn, nausea, and abdominal pain, while those related to topical and intradermal injection of TXA include redness, irritation, and pain.

Meta-Analysis of MASI/mMASI Score There were 21 studies **(Figure 2)** reported the changes of MASI/mMASI score after using TXA oral, topical, and injection TXA at 4 weeks, 8 weeks, and 12 weeks. The pooled analysis showed the significance of reduction in MASI/mMasi scores. Scores at 4 weeks (MD: 3.58; 95% CI, 2.15-5.01;I^2 = 92%), 8 weeks (MD: 5.08; 95% CI, 3.34–6.81;I^2=96%) and 12 weeks (MD: 4.89; 95% CI, 3.80–5.97;I^2=91%) after treatment were all less than the baseline scores **(Figure 2A–C)**, regardless of the delivery route.

Oral TXA showed at 4 weeks (MD: 7.51; 95% CI, 2.52–12.5;I^2=94%) the reduction of MASI/mMASI score higher than at 8 weeks (MD: 6.8; 95% CI, 0.37–13.23;I^2=99%) and 12 weeks (MD: 6.19; 95% CI, 4.09–8.29;I^2=92%. Injection TXA reported the MASI/mMASI score similarly higher at 8 weeks (MD: 4.66; 95% CI, 3.49–5.841;I^2=0%) and 12 weeks (MD: 4.4; 95% CI, 0.04–8.76) than 4 weeks (MD: 2.78; 95% CI, 1.1–4.45;I^2=30%). Topical TXA has a higher MASI/mMASI score at 8 weeks (MD: 4.12; 95% CI, 2.64–5.61;I^2=90%) than at 4 weeks (MD: 2.29; 95% CI, 1.1–3.49;I^2=84%) and 12 weeks (MD: 3.95; 95% CI, 2.74–5.16;I^2=88%).

Discussion

Currently, this study represents the most comprehensive investigation of the effectiveness and safety of using Tranexamid Acid (TXA) as a treatment for melasma, a condition that causes psychological distress. The management of melasma remains challenging, and there is an on going search for a therapy that is both safe and effective. Fortunately, the findings of this study indicate that TXA may be a promising treatment option for adult patients with melasma, particularly when taken orally either alone or in conjunction with other treatments.

Table 2 Characteristic of all included studies.

No.	*Study*	*Population*	*Age (Mean±SD)*	*Preparation*	*Interventions*	*MASI/Mmasi (baseline)*	*MASI/Mmasi (4 w)*	*MASI/Mmasi (8 w)*	*MASI/Mmasi (12 w)*	*Outcome*	*Side effects*
1	Padhi,2015	40	35.85±7.614	Oral	Oral TA 250 mg bid plus cream VS cream	18.243±1.05	6.135±4.94	2.19±2.378		MASI	Oligomenorrhea
2	Lajevardi, 2017	88	35.4±5.7	Oral	Oral TA 250 mg bid plus sunscreen VS Sunsceen	14.4±8.4	5.1±4.8	N/A	5.9±3.9	MASI	Abdominal Pain
3	Minni, 2020	130	35.22±0	Oral	Oral TA 250 mg bid plus topical FbTC VS topical FbTC	10.45±4.51	6.16±3.94	4.32±5.11	2.26±2.29	mMASI	Erythema, burning
4	Karrabi, 2020	27	35.22±6.02	Injection	TA: 0.05 ml (4 mg/ml) VS cysteamine 5% cream, qn	10.43±2.69	7.03±3.19	5.52±2.55	N/A	mMASI	Erythema, Irritation, burning
5	Zhao, 2020	17	39.47±6.05	Injection	TA: 2ml (100 mg/ml) VS 2ml (400 mg/ml) VC	7.03±3.84	5.42±3.56	2.97±2.53	N/A	MASI	Erythema
6	Banihashemi,2015	23	N/A	Topical	5% liposomal topical TA bid, Vs 4% HQ	14.72±2.2	11.3±2.1	9.17±1.9	7.69±2.4	MASI	None
7	Janney,2019	50	35.86±7.51	Topical	5% topical TA qd, Vs 3% HQ qd	12.39±3.34	11.48±5	10.49±4.8	9.47±2.79	MASI	Irritation
8	Kanechorn, 2012	21	39.3±0	Topical	5% topical TA bid plus sunscreen Vs sunscreen only	3.75±1.22	3±1.1	2±1	1.6±0.8	MASI	Minor irritation
9	Kaur, 2020	40	33.15±0	Topical	Topical 10% TA plus micro-needling VS 2 weeks; vs micro-needling	4.31±1.77	2.54±1.26	15.2±7	N/A	mMASI	Erythema, dryness
10	Laothaworn, 2018	25	44.79±7.79	Topical	3% topical TA bid plus QSNYL VS QSNYL only	16.38±8	15.24±6	N/A	N/A	mMASI	None
11	Shamsi, 2020	60	26.1±0.6	Topical	Topical 4% TA plus micro-needling VS Topical HQ 4%	12.89±5.16	10.31±4.36	N/A	6.84±4.31	mMASI	Erythema
12	Wanitphakdeedecha, 2020	46	48.0±10.0	Topical	Topical 1.2% TA plus fractional thulium fibre 1972 nm VS Laser only	11.08±2.91	N/A	6.7±1.8	8.9 ±1.5	mMASI	None
13	Karn, 2012	260	N/A	Oral	Oral TA 250 mg bid plus topical HQ+Sunscreen VS HQ +Sunscreen	10.45±4.51	N/A	8.95±2.08	7.84±2.44	MASI	Oligomenorrhea, belching
14	Shin, 2013	44	44.4±7.9	Oral	Oral TA 750 mg per day plus QSNY laser VS QSNY laser	7.9±3.7	N/A	5±3.4	N/A	mMASI	Heartburn, nausea
15	Malik, 2019	100	N/A	Topical	Oral TA 250 mg bid plus 3% topical TA bid VS Vs oral TA 250 mg bid plus 20% azelaic acid qd	33.7±12	N/A	21.68±10.93	N/A	MASI	Not available
16	Colferai, 2018	37	43.97±0	Oral	Oral TA 250 mg bid plus sunscreen VS Sunsceen	20.9±9.1	N/A	N/A	10.8±4.6	MASI	Gastrointestional disturbance
17	Del Rosario, 2018	44	43.86±5.8	Oral	Oral TA 250 mg bid plus sunscreen VS Sunsceen	8.8±2.93	N/A	N/A	4.49±2.93	mMASI	Gastrointestional disturbance
18	Shihab, 2020	25	46.6±5.5	Oral	Oral TA 250 mg bid plus 4% HQ, Vs 4% HQ	8.96±2.45	N/A	N/A	4±1.6	mMASI	Menstruation disturabnce
19	Steiner, 2009	17	40.58±0	Injection	3% topical TA bid, Vs TA 4 mg/ml*0.05 ml/cm2 injection	12.2±5.35	N/A	N/A	9.9 ±7.07	MASI	Erythema, burning
20	Atefi, 2007	60	38.10±6.27	Topical	5% topical TA bid, Vs 2% HQ	4.8±1.06	N/A	N/A	2.33±0.71	MASI	Erythema, Irritation
21	Chung, 2016	13	41.38±4.37	Topical	2% topical TA per week plus IPL, Vs IPL only	14.77±4.55	N/A	N/A	9.38±5.49	mMASI	None

*SD: standard seviation, MASI: melasma area severity index, mMASI: modified melasma area severity index, TA: tranexamic acid, bid: twice a day, QSNY: low-fluence 1064-nmquality-switched neodymium-doped yttrium aluminum garnet, HQ: hydroquinone, IPL: intensed pulse light

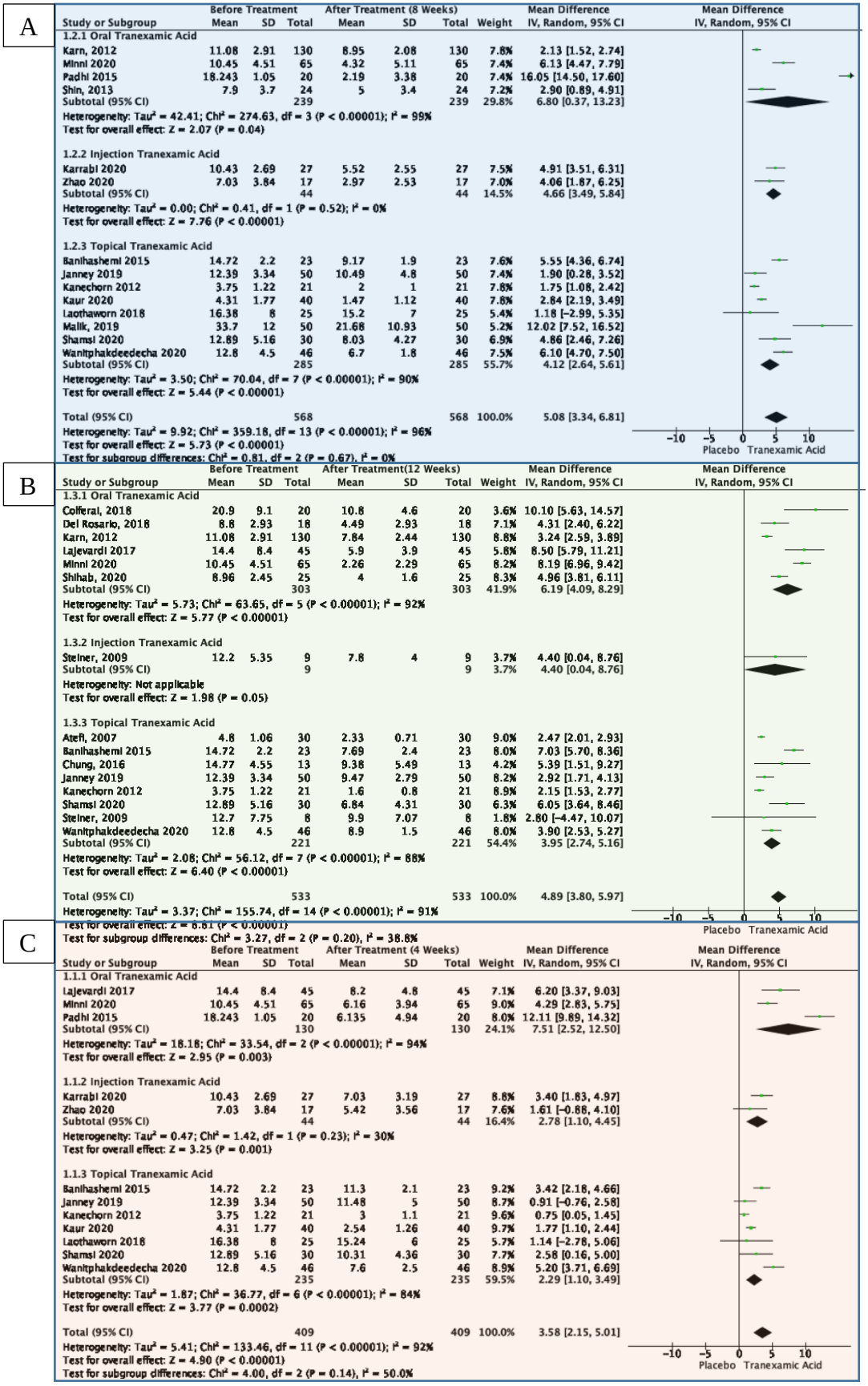

Figure 2. Forest plots reporting the MASI/mMASI score between pre- and post- tranexamic acid treatment at (A) 4 weeks, (B) 8 weeks, (C) 12 weeks

This study's results indicate that TXA may be promising in terms of its clinical effectiveness and tolerability for adult melasma patients. Furthermore, the study suggests that orally administered TXA may be more beneficial than topical or intradermal injection forms. In a study by Khurana V.[6] It was found that oral TXA had a more significant impact at 4 weeks compared to topical and injection forms. The oral dosage used in the study was 500 mg/day, much lower than the 2000 mg treatment dosage for haemostasis, resulting in minimal side effects.[6,7]

The underlying causes of melasma remain unclear, although increased dermal vascularity and the expression of angiogenic factors are known to play a role in pigment research.[7] Besides inhibiting melanin synthesis through the plasminogen–plasmin pathway, TXA has been shown to effectively modulate the numbers of vessels and mast cells in the dermal changes associated with melasma, as observed in histological evaluations conducted in some studies.[8]

The meta-analysis and systematic review performed in this study have some limitations. Firstly, the trials included in the analysis had varying follow-up durations, doses, and types of MASI score. Secondly, the quality of the studies was low, and the assessment of the MASI score may have been influenced by subjective factors. Additionally, there was significant heterogeneity in the MASI score, possibly due to differences in sample size and study quality. However, it is important to note that high heterogeneity is often observed when dealing with continuous variables.

Conclusion

The objective of this thorough examination and analysis is to present the available information regarding the application of TXA as a treatment option for individuals with melasma. Additional extensive randomized controlled trials (RCTs) are required to determine the most effective dosage and treatment plan for TXA.

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