Brief Report

Efficacy of Oral, Topical, and Intradermal Tranexamic Acid in Patients with Melasma — A Meta-Analysis

Abstract

Background and Objective: Tranexamic acid (TXA) has recently shown promising results in the treatment of melasma. The objective of this study was to generate statistical evidence on the efficacy of TXA with different routes. **Materials and Methods:** We searched studies in PubMed, Cochrane, ClinicalTrials.gov, and Scopus using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. A change in melasma area and severity index (MASI)/modified MASI score from the baseline at the end of 8 and 12 weeks was seen. Inverse variance method was used for continuous data to measure standard mean difference (SMD) at a 95% confidence interval (CI). RevMan version 5.4 was used for analysis, and statistical heterogeneity across studies was reported using I^2 statistics. $P < 0.05$ was considered significant. **Results:** Totally, 28 randomized control trials were included. At 8 weeks, oral TXA showed a significant change in SMD of 1.61, 95% CI 0.44–2.79, $P = 0.007$; at 12 weeks, oral TXA showed SMD of 2.39, 95% CI 1.42–3.35, $P < 0.00001$ compared to adjuvant treatment. At 8 weeks, topical TXA did not show a significant change with SMD of -0.05, 95% CI -1.08–0.97, $P = 0.92$; at 12 weeks, topical TXA did not show a significant change with SMD of 0.66, 95% CI -0.10–1.42, $P = 0.09$ compared to adjuvant treatment. Similarly, for intradermal TXA at 8 weeks, results were not significant with SMD of 1.21, 95% CI -0.41–2.83, $P = 0.14$, and at 12 weeks, SMD was -0.55, 95% CI -2.27–1.18, $P = 0.54$ compared to adjuvant treatment. **Conclusion:** Tranexamic acid in an oral formulation can be used along with adjuvant treatment for the management of melasma. Data are still required for topical and intradermal routes. Owing to the fact that our included studies had a lot of heterogeneity, more research is needed along with addressing the adverse effects of tranexamic acid as well as its variation in different skin colors.

Keywords: *Intradermal, melasma, oral, topical, tranexamic acid*

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Introduction

Melasma is a common skin condition that causes blue-gray to brown patches and spots, usually on the sun-exposed areas of the face and neck, predominantly affecting women with darker skin types such as Fitzpatrick skin types IV, V, and VI.[1,2] The exact pathogenesis is unknown; however, it has been hypothesized that melasma is induced by biologically active melanocytes, and increased vascularity and elevated expression of angiogenic factors in the affected epidermis have also been found.[3-5] These factors may play an important role in the development of melasma. Melasma is associated with some factors like genetic susceptibility, ultraviolet (UV) light exposure, pregnancy, sex hormones, contraceptive pills, cosmetics, phototoxic drugs, and inflammatory processes.[6-10] Melasma significantly affects a patient's appearance and quality of life.[11-13] For many years, the treatment of melasma has been centered around topical creams, avoiding sunlight, use of vitamins, or even use of lasers to help decrease the pigmentation. Melasma area and severity index (MASI) is the most commonly used outcome measure for melasma. While the MASI score is a subjective assessment, it is calculated as a combination of three separate factors (total area of involvement, darkness, and homogeneity) and is considered a reliable, semi-objective tool in the analysis of melasma. Lately, Pandya and colleagues have proposed the modified MASI score (mMASI), which removes the homogeneity in its calculation because it had the lowest inter-rater agreement. Hence, MASI or mMASI, either of the scores, can be used for melasma.[14]

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Recently, the US Food and Drug Administration has approved a modified combination of Kligman's formulation containing 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide.[15] Broad-spectrum sunscreens' protection from UV radiation is useful in the management of melasma, but they usually fail to prevent relapse.[16] The use of tranexamic acid (TXA) has been a recent therapy for treating it. Tranexamic acid (trans-4-aminomethyl cyclohexane carboxylic acid) is a synthetic lysine analog that is mainly used for its antihemorrhagic and antifibrinolytic properties. Tranexamic acid can inhibit UV-induced pigmentation by reducing plasmin via reversible blockade of the lysine-binding site on plasminogen to these cells, decreasing free arachidonic acid, diminishing the production of prostaglandins, and eventually reducing melanogenesis in melanocytes; it also has anti-inflammatory and whitening effects.[17-20] According to recent studies, different routes of administration, such as oral, topical, intradermal injections, micro-needling, and iontophoresis, as well as different formulations of tranexamic acid, have been used for treating melasma with promising results.[21] Through a meta-analysis, we aimed to assess the therapeutic efficacy of different formulations of tranexamic acid in treating patients with melasma.

Materials and Methods

A meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) guidelines.[22]

Search strategy and selection criteria

We systematically searched PubMed, Cochrane Library, ClinicalTrials.gov, Google Scholar database, and ctri.nic.in for including relevant clinical trials published till 2021. Search terms included the following: ""Tranexamic acid," "TXA," "Melasma," "Melasma Area and Severity Index (MASI)," "Modified Melasma Area and Severity Index (mMASI)," "Hyperpigmentation," "Chloasma," "Oral tranexamic acid," "Topical tranexamic acid," "Intradermal tranexamic acid," "Hydroquinone," "Vitamin C," "Triple regimen/Modified Kligman's regimen," "Cysteamine," "Mesotherapy," and "randomized clinical studies."

In the primary screening, all the studies that were relevant and were using tranexamic acid in any one of the routes (oral, topical, or intradermal injection) with ongoing medical treatment in a study group of 18 years or older with clinically diagnosed melasma, which were double-blind, single-blind, or unblinded, were included.

Studies with secondary screening with those who included comparison of tranexamic acid in doses of "oral 250 mg twice or thrice daily with or without other treatment in the study group," "topical tranexamic acid in 2%, 3%, 4%, 5%, or 10% cream twice or thrice daily with or without other treatment in the study group," "intradermal injection of tranexamic acid at every 4-week interval with medical treatments which included any one of the following: hydroquinone cream, vitamin C, 5% cysteamine, triple regimen/modified Kligman's regimen which includes giving hydroquinone cream 2% w/w + tretinoin 0.05% w/w + fluocinolone 0.01% w/w, normal saline or distilled water, sunscreen, 1064-nm Q-switched neodymium-doped yttrium aluminum garnet laser (QSNY laser) in the study group" and those studies which provided any available information on MASI or mMASI in quantitative terms like frequency, numbers or percentages were included in the analysis.[14] Those studies in which tranexamic acid was the only treatment, studies without any control group, any group including pregnant patients, lactating females, patients with a history of thrombosis or an abnormal bleeding profile in the study group, any unpublished research work, preclinical studies, or observational studies were excluded from the analysis.

Study selection

After the removal of duplicate and irrelevant studies, each potential article was examined by two investigators independently to see if the study fit the predetermined inclusion criteria. Any disagreement was settled through discussion.

Data collection

From the included studies, data regarding patient characteristics and outcome of interest were collected. The study characteristics, which were publication year, country of origin, sample size, age, and outcome data, were extracted.

Endpoint

The primary efficacy endpoint was assessed by a change in the mean value of MASI or mMASI scores. MASI is a clinical score used for grading pigmentation in melasma ranging from 0 to 48, taking into consideration "area of involvement," "degree of pigmentation," and "homogeneity," while modified MASI (mMASI) eliminates the homogeneity of MASI, at the same time not affecting the reliability or validity of the measures.[14] Change in MASI/mMASI was obtained between pre- and post-treatment with oral, topical, and intradermal tranexamic acid compared to the change in the MASI/mMASI scores with adjuvant treatment at the end of 8 weeks and 12 weeks from the baseline.

Quality assessment of included studies

The quality of the included studies was reviewed independently by two reviewers following the guidelines mentioned in the Cochrane Handbook for Systematic Reviews of Interventions, and the risk of bias was assessed which included different parameters such as selection bias, allocation concealment, blinding of participants and the

personnel, attrition bias as incomplete outcome data and selection reporting bias, and other biases were graded as low, unclear, or high risk.

Statistical analysis

Inverse variance method was used for continuous variables to obtain standard mean difference (SMD) along with a 95% confidence interval (95% CI) to describe the change in MASI/mMASI score from the baseline at the end of 8 and 12 weeks as our primary endpoint.[14] Review Manager version 5.4 was used for analysis, and statistical heterogeneity across studies was reported using I^2 statistics. I^2 statistics of >75% were considered significant. Random effect models were used to estimate the overall effect and to give an accurate estimation of SMDs and 95% CI irrespective of the heterogeneity. $P < 0.05$ was considered significant.

Results

Baseline characteristics

Initially, a total of 29 studies were included through an electronic or manual search and were selected for a full-text review based on the title and abstract details. However, a study done by Wanitphakdeedecha *et al*. (2020) was excluded as they only had a graphical representation of MASI/mMASI score.[23] Ultimately, 28 studies met the inclusion criteria.[24-51] Among these, a study by Sahu *et al*. used both the oral and topical routes of tranexamic acid.[34] All the studies provided data relevant to the primary outcome. We chose three routes of administration of tranexamic acid: oral, topical, and intradermal injection. The relevant features of the studies included in the meta-analysis are provided in Figure 1 and Supplementary Table. In the end, thirteen studies evaluated the efficacy of oral TXA, nine studies evaluated the efficacy of topical TXA, and seven studies evaluated the efficacy of intradermal injections of TXA.[24-51]

Primary efficacy endpoints in oral TXA

Mean changes in MASI/mMASI score were reported in all 13 studies at 8 weeks and 12 weeks after the beginning of treatment with oral tranexamic acid compared to the other treatment. At 8 weeks, in random effect, SMD was 1.61 and 95% CI was 0.44 to 2.79. *P* value in random effect at 8 weeks was 0.007, which was significant, as shown in Figure 2. The heterogeneity between studies was 98% ($P < 0.00001$). At 12 weeks, in random effect, SMD was 2.39 and 95% CI was 1.42 to 3.35. *P* value in random effect at 12 weeks was < 0.00001, which was again found significant, as shown in Figure 3. The heterogeneity between studies was 95% ($P < 0.00001$).

Primary efficacy endpoints in topical TXA

Mean changes in MASI/mMASI score were reported in all nine studies at 8 weeks and 12 weeks after the beginning of treatment with topical tranexamic acid compared to the other treatment. At 8 weeks, in random effect, SMD was -0.05 and 95% CI was -1.08 to 0.97. *P* value in random effect at 8 weeks was 0.92, which was not significant, as shown in Figure 4. The heterogeneity between studies was 99% ($P < 0.00001$). At 12 weeks, in random effect, SMD was 0.66 and 95% CI was -0.10 to 1.42. *P* value in random effect at 12 weeks was 0.09, which was again not significant, as shown in Figure 5. The heterogeneity between studies was 92% ($P < 0.00001$) as shown in Figure 5.

Primary efficacy endpoints in the intradermal injection of TXA

Mean changes in MASI/mMASI score were reported in all seven studies at 8 weeks and 12 weeks after the beginning of treatment with intradermal injection of TXA compared to the other adjuvant treatment. At 8 weeks, in random effect SMD, was 1.21 and 95% CI was -.041 to 2.83. *P* value in random effect at 8 weeks was 0.14, which was not significant, as shown in Figure 6. The heterogeneity between studies was 96% ($P < 0.00001$). At 12 weeks, in random effect, SMD was -0.55 and 95% CI was -2.27 to 1.18. *P* value in random effect at 12 weeks was 0.54, which was also not significant, as shown in Figure 7. The heterogeneity between studies was 98% ($P < 0.00001$) as shown in Figure 7.

Discussion

In 1979, Sadako first showed the use of oral tranexamic acid for melasma in Japan.[23] It can also be administered as an intradermal injection or a topical formulation.[38,52-54] The role of tranexamic acid in human cell cultures was studied by Maeda *et al*., in which they revealed that tranexamic acid inhibits melanin synthesis in epidermal melanocytes by blocking the interaction of melanocytes and keratinocytes by inhibition of the plasminogen system.[55] Tranexamic acid has currently become more widely used in the treatment of disorders of pigmentation, especially in Japan.[56] Even in the Chinese population, the use of oral tranexamic acid for melasma has been tried for its effectiveness and safety, as recommended by some authors. However, the dose of oral tranexamic acid used in the treatment of melasma is far less than the dose used for its hemostatic action.[57]

In our meta-analysis, the clinical effectiveness was considered in terms of showing a reduction in MASI/mMASI score at 8th and 12th week from the baseline. We found that oral route of tranexamic acid showed a significant reduction when compared to other adjuvant treatment (8 weeks, SMD was 1.61 and $P < 0.007$; 12 weeks, SMD was 2.39 and $P < 0.00001$), while topical route and intradermal route did not show a significant reduction in MASI/mMASI scores when compared to other adjuvant treatment.

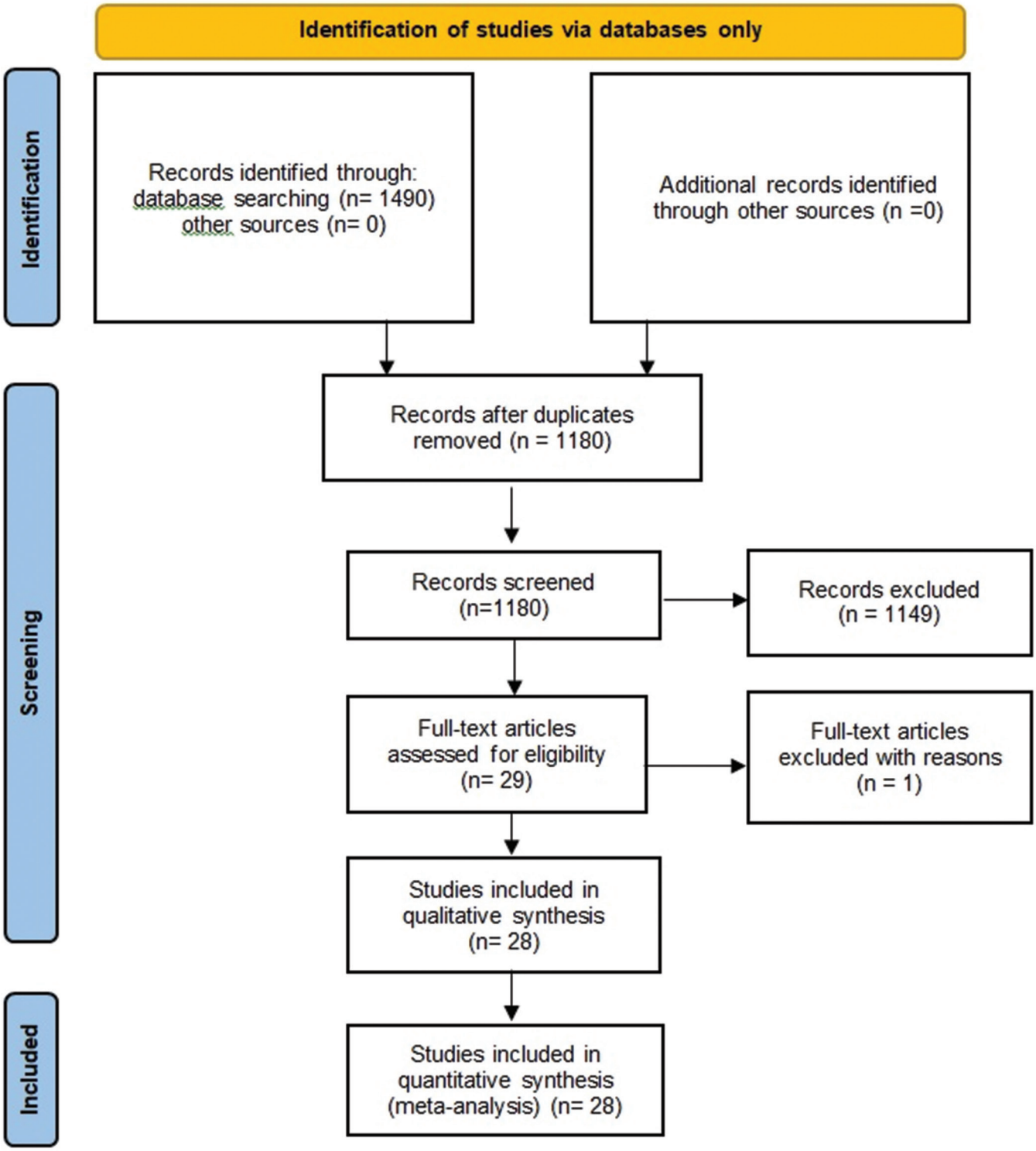

Figure 1: PRISMA flow diagram of included studies

Various routes of administration have been described for the use of tranexamic acid in the treatment of hyperpigmentation, including a topical liposomal formulation and intradermal microinjections.[58,59] Hajime *et al*. used oral tranexamic acid for 10 weeks, during which they showed a reduction in the severity of melasma.[60] Similarly, results were outlined by Higashi *et al*.[61] In a study by Cho *et al*. in 2011 which used 500 mg/day of tranexamic acid as an additional therapy to the patients treated with intense pulsed light (IPL) or Nd:YAG laser as compared to patients treated with only IPL or Nd:YAG laser showed that modified MASI score was lower in the tranexamic acid group ($P < 0.005$).[62] In a triple-blinded randomized control trial by Minni *et al*., it was shown that oral tranexamic

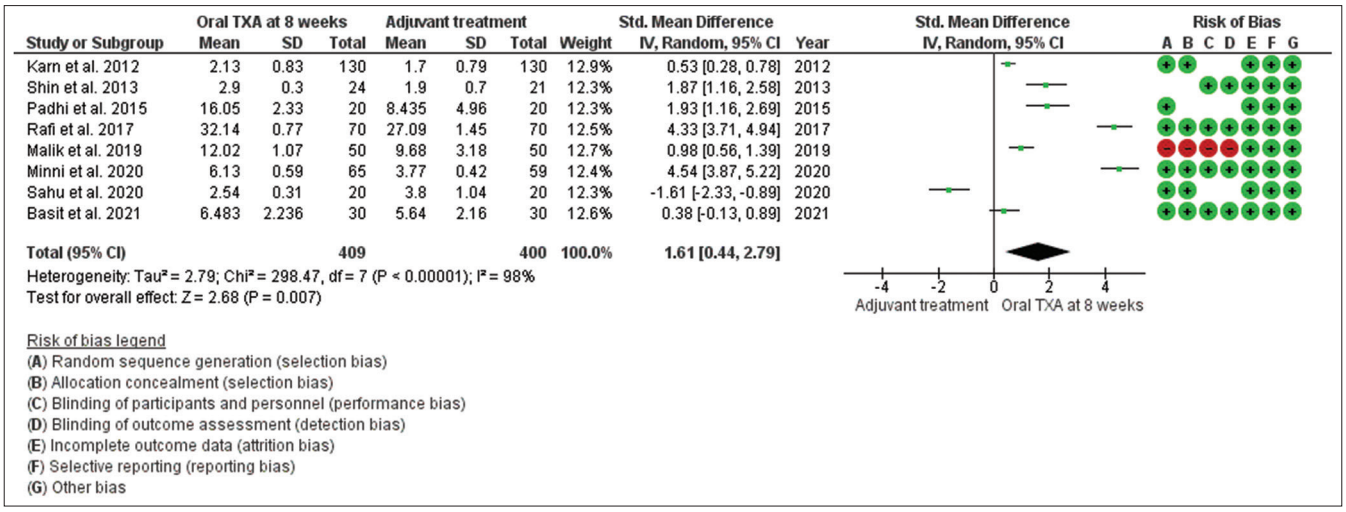

Figure 2: Funnel plot results of the efficacy of oral tranexamic acid in patients with melasma at 8 weeks

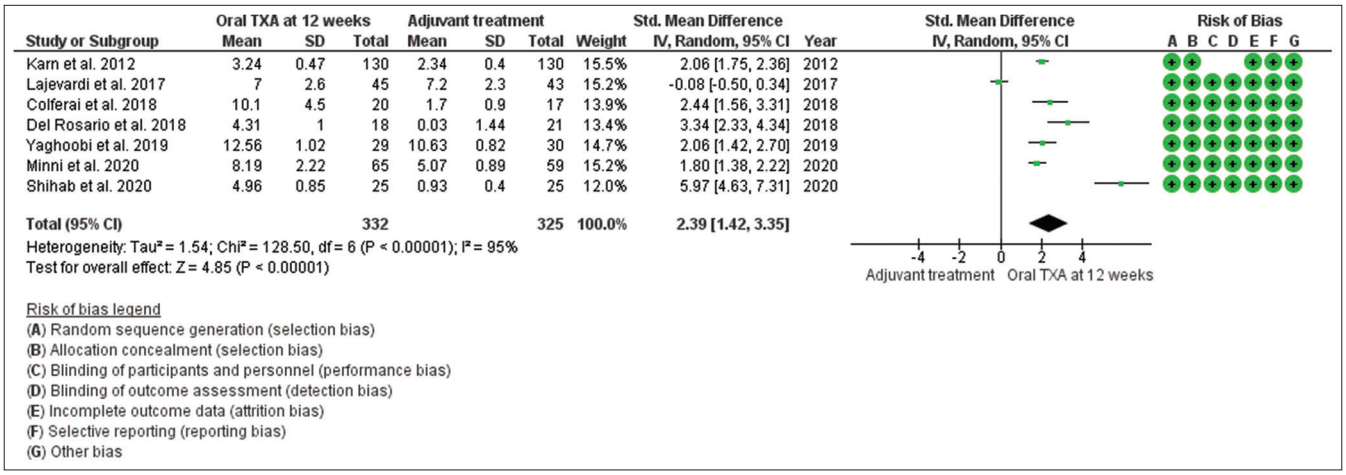

Figure 3: Funnel plot results of the efficacy of oral tranexamic acid in patients with melasma at 12 weeks

acid + fluocinolone-based triple combination cream (FbTC) results in early response and higher clearance of melasma at 4th week compared with FbTC alone.[33] Recurrence in melasma patients is well-recognized during or after cessation of any treatment (lasers or oral TXA); however, tranexamic acid patients maintained their MASI score from week 12 to 24th week and also showed an improvement despite stopping treatment and the results when compared in both groups were statistically significant in the study by Minni *et al*. ($P < 0.01$).[32] Corresponding findings of recurrence in melasma were also reported by Wu *et al*., Aamir *et al*., and Lee *et al*. in their studies.[57,59,63] In a 2013 study by Shin *et al*., patients received oral tranexamic acid (750 milligrams/day) for 2 months plus two sessions of low-fluency Q-switched Nd: YAG (1064 nm) laser at a 1-month interval or the laser alone as the control. The results were similar to ours in the case of the intervention group, but not significant in the control group.[25] Sharma *et al*. conducted a clinical trial on patients with melasma, with one group being given oral tranexamic acid (250 mg twice daily) and the other group receiving 4 mg intradermal tranexamic acid every 4 weeks for a period of 12 weeks, which showed a significant reduction in MASI for oral tranexamic acid.[64] Del Rosario *et al*. also showed similar results with oral tranexamic acid as an effective drug in treating moderate to severe melisma.[30] The systematic review and meta-analysis by Kim *et al*. on tranexamic acid-only observational studies with pre- and post-treatment MASI also showed a decrease of 1.60 in MASI (95% CI 1.20–2.00; $P < 0.001$) and established the safety profile.[65]

Many studies revealed the outcomes of topical tranexamic acid in the treatment of melasma, for instance, Banihashemi *et al*. and Ebrahimi *et al*.[37,66] Kanechorn Na Ayuthaya *et al*. compared topical tranexamic acid to a placebo treatment, although no significant difference was seen, the topical medications were able to drastically decrease pigmentation as compared to baseline data.[67] An uncontrolled study conducted in 2007 by Kondou *et al*. studied the effects of 2% topical emulsion of tranexamic acid in 25 patients for 18 weeks which showed that it was effective in 80%

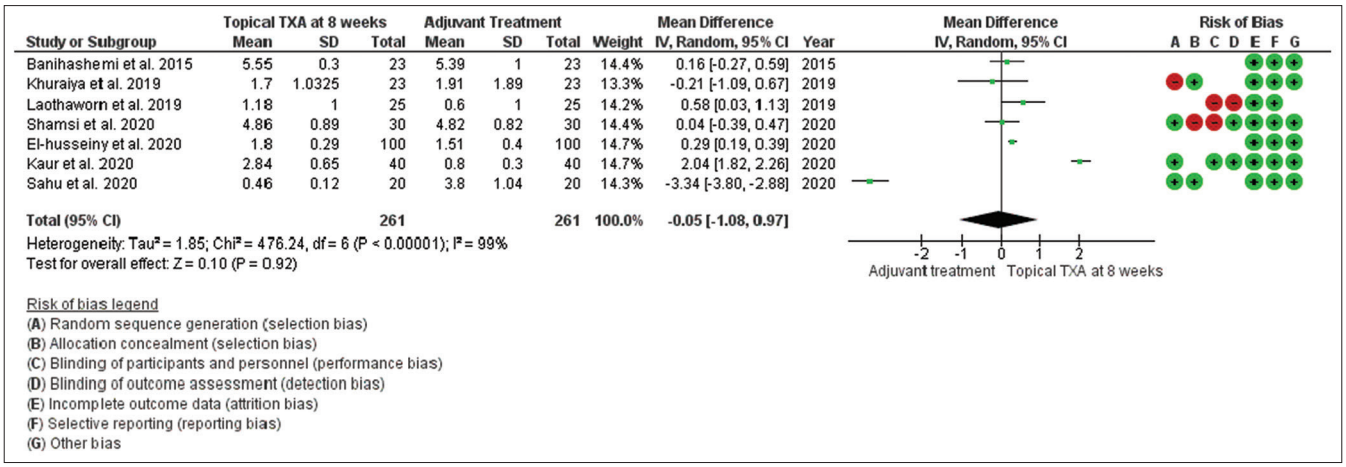

Figure 4: Funnel plot results of the efficacy of topical tranexamic acid in patients with melasma at 8 weeks

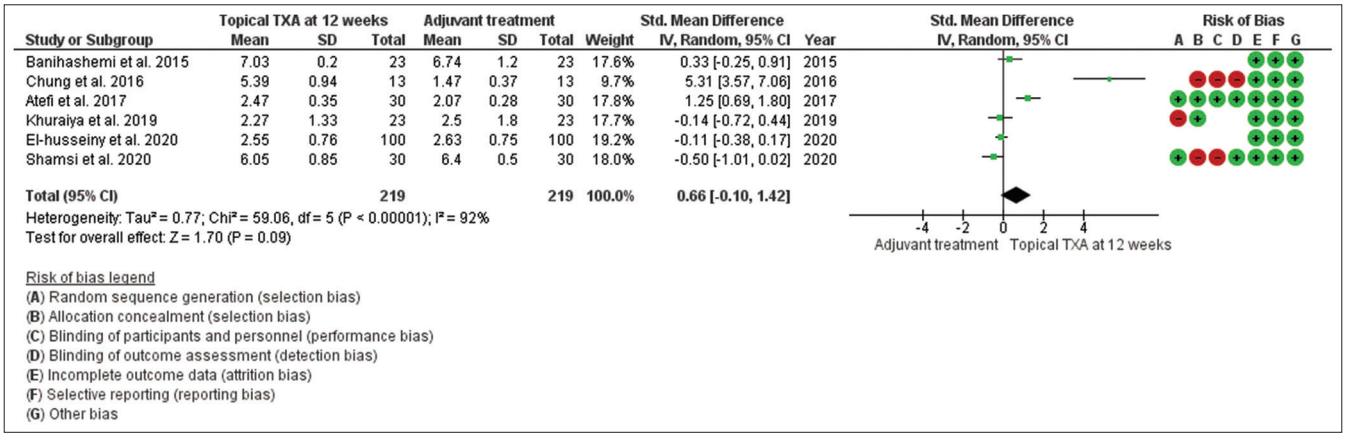

Figure 5: Funnel plot results of the efficacy of topical tranexamic acid in patients with melasma at 12 weeks

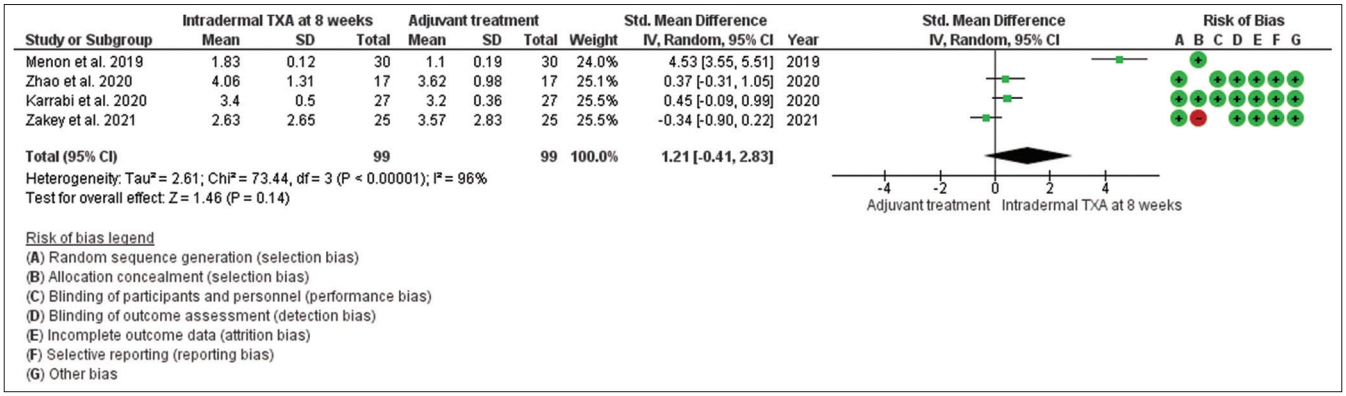

Figure 6: Funnel plot results of the efficacy of intradermal tranexamic acid in patients with melasma at 8 weeks

of patients within 8 weeks with no side effects.[68] A recent study by Chung JY *et al*. in which only IPL was compared with topical tranexamic acid in combination with IPL given randomly to any of the assigned cheeks showed a marked decrease in pigmentation and prevented rebound hyperpigmentation in topical TXA side.[38] Moreover, a pilot study by Laothaworn *et al*. showed similar results.[40] Ebrahimi *et al*. also showed significant decrease in MASI score in both groups of topical tranexamic acid and topical HQ plus dexamethasone with no significant difference between the groups.[66]

Lee *et al*. showed a significant improvement in MASI at the end of treatment following weekly intradermal injection of tranexamic acid.[59] In a study conducted by Budamakuntla *et al*. in India that evaluated the efficacy of topical TXA with micro-needling in comparison with microinjections of tranexamic acid, there was more reduction in MASI score

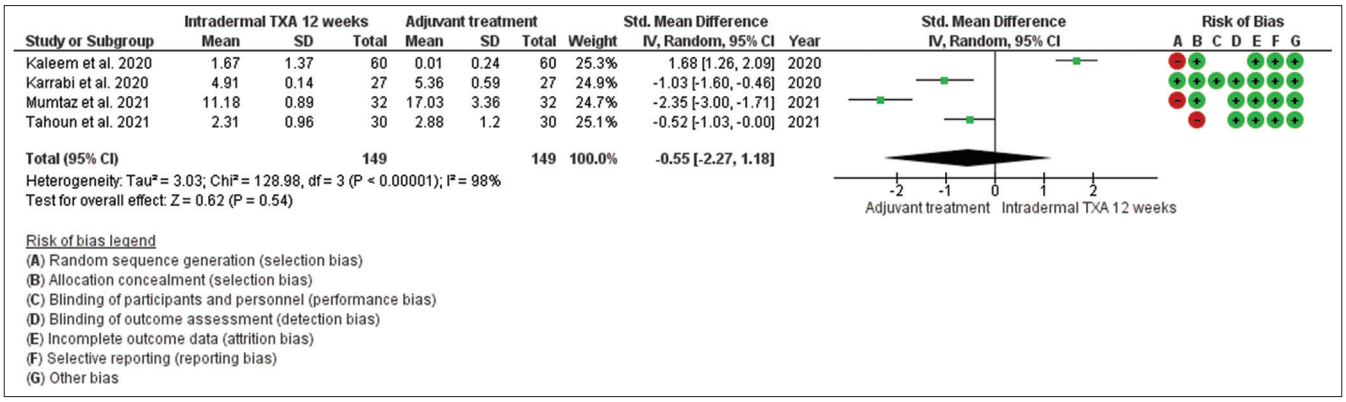

Figure 7: Funnel plot results of the efficacy of intradermal tranexamic acid in patients with melasma at 12 weeks

in micro-needling group than in microinjection group, but the difference was not significant.[69] Studies conducted by Menon *et al*.[45] and Kaleem *et al*.[46] showed a significant reduction in the mean MASI score with tranexamic acid. Similar results were also seen with Zaky *et al*.[51] Another study by Tahoun *et al*. exhibited significant diminution in dark fine granules, homogeneous pigmentation, and pseudo-reticular brown network with intradermally treated tranexamic acid.[49]

There were a few limitations to the study; we addressed the clinical efficacy of tranexamic acid in melasma and not the adverse events associated with it, and did not address the role of variation in skin color that may have played a role. Furthermore, carrying out a meta-analysis inherently brings bias in terms of heterogeneity of the included studies, which was also seen in our analysis. Further research is needed to compare the clinical efficacy as well as the safety profile of tranexamic acid in melasma through large randomized controlled trials focusing on its clinical implications.

Conclusion

Oral tranexamic acid is superior to the other standard treatments of melasma; it can be used either alone or combined with other standard treatments. Topical and intradermal routes of tranexamic acid were not found superior to the standard treatment. However, a multicentric, larger-scale study is required to support our observation.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table: Baseline characteristics of the included studies for meta-analysis

Study	Country	Sample size (*n*)	Study design	Intervention and other treatment	Mean or Median age (in years)
Karn *et al*. 2012[24]	Nepal	260	Prospective, interventional, randomized controlled trial	Oral TXA 250 mg bid and topical HQ and sunscreen versus HQ+sunscreen	17-55
Shin *et al*. 2013[25]	Korea	44	Randomized prospective trial	Oral TXA 750 mg per day plus QSNY laser versus QSNY laser	18-55
Padhi *et al*. 2015[26]	India	40	Prospective, parallel, randomized open-label comparative clinical study	Oral TXA 250 mg bid and FbTC cream versus FbTC cream	24-55
Lajervadi *et al*. 2017[27]	Iran	88	Single center, parallel group, assessor and analyst blinded randomized control trial	Oral TXA 250 mg bid and 4% HQ versus 4% HQ	18-65
Rafi *et al*. 2017[28]	Pakistan	140	Randomized controlled trial	Topical 2% HQ and oral TXA 500 mg daily versus topical 2% HQ	15-45
Colferai *et al*. 2018[29]	Brazil	37	Mono centric, randomized, double-blind, controlled trial	Oral TXA 250 mg bid and sunscreen versus sunscreen	43.97
Del Rosario *et al*. 2018[30]	USA	44	Single center, randomized study	Oral TXA 250 mg bid and sunscreen versus sunscreen	>18
Malik *et al*. 2019[31]	Pakistan	100	Interventional comparative study	Oral TXA 250 mg bid and 3% topical TXA bid versus oral TXA 250 mg bid and azelaic acid	12-50
Yaghoobi *et al*. 2019[32]	Iran	69	Prospective randomized clinical trial	Oral TXA 250 mg versus 4% topical HQ cream	18-60
Minni *et al*. 2020[33]	India	130	Parallel designed, prospective, interventional triple blind randomized controlled study	Oral TXA 250 mg bid and topical FbTC versus topical FbTC	36
Sahu *et al*. 2020[34]	India	60	Prospective, comparative, interventional study	Oral TXA 250 mg bid versus topical TXA versus modified Kligman's regimen	18-50
Shihab *et al*. 2020[35]	Indonesia	50	Randomized trial	Oral TXA 250 mg bid and 4% HQ versus 4% HQ	21-64
Basit *et al*. 2021[36]	Pakistan	60	Randomized trial	Oral TXA 250 mg bid and topical FbTC versus topical FbTC	18-60
Banihashemi *et al*. 2015[37]	Iran	23	Double-blind clinical trial	5% liposomal TXA on one side of the face and 4% topical hydroquinone cream on the opposite side of the face once a night, for 12 weeks.	25-47
Chung *et al*. 2016[38]	Korea	13	Single center, randomized, split-face (internally controlled) study	Four monthly sessions of IPL to both sides of the face along with 2% TXA to one side of the face (topical TXA side) and vehicle without TXA to the other side	41.38±4.37 years
Atefi *et al*. 2017[39]	Tehran	60	Randomized double-blinded clinical trial	5% TXA versus 2% topical HQ	38±6.27 years in TXA group and 39.97±7.86 in HQ
Laothaworn *et al*. 2018[40]	Thailand	25	Randomized, prospective, split-face, controlled trial	Topical 3% TXA on one side of the face and the vehicle treatment on the other side of the face for 8 weeks and 1064-nm QSNY laser to the entire face at baseline and after 4 weeks.	30-63
Khuraiya *et al*. 2019[41]	India	23	Prospective comparative study	Topical TXA 5% cream and triple combination of tretinoin, hydroquinone, fluocinolone on each half of face	18-50
El-Hussiney *et al*. 2020[42]	Egypt	100	Prospective split-faced comparative study	5% TXA cream on right side face lesions versus 4% HQ cream on left side lesions	22-40
Kaur *et al*. 2020[43]	India	40	Split-face, prospective, randomized, open-label study	10% topical TXA solution application on one side of the face and distilled water on the other side of face.	26-48

Contd...

Supplementary Table: Contd...

Study	Country	Sample size (*n*)	Study design	Intervention and other treatment	Mean or Median age (in years)
Shamsi *et al*. 2020[44]	Iran	60	Single-blind randomized clinical trial	One group micro-needling plus topical 4% TXA, monthly and another group topical 4% HQ, nightly.	18-35
Menon *et al*. 2019[45]	India	30	Split-face comparative study	Micro-needling with 1 mL (4 mg/mL) TXA on left side, micro-needling with 20% vit C on right side	35-39
Kaleem *et al*. 2020[46]	Pakistan	60	Non-randomized clinical trial	Intradermal TXA (4 mg/mL) on one side of face, multiple microinjections of 0.9% NS on opposite side of face	36±7.9
Karrabi *et al*. 2020[47]	Iran	54	Single-blind, randomized, parallel-group clinical trial study	Intradermal microinjections of TXA	34.29±7.45
Zhao *et al*. 2020[48]	China	17	Split-face randomized controlled trial	Localized Myjet-assisted injection of TXA (0.5 g: 5 mL) and Vit C (1 g: 2.5 mL)	39.47±6.05
Tahoun *et al*. 2021[49]	Egypt	30	Prospective split-face comparative study	Micro-needling with 1.5 mL (100 mg/mL) of TXA on right side, micro-needling with 1.5 mL of 20% vit C on left side	40±6.11
Mumtaz *et al*. 2021[50]	Pakistan	64	Non-randomized controlled trial	Intradermal TXA (4 mg) in group B and 1 mL PRP in group A	Group A : 24.63±9.87 Group B: 23.94±8.93
Zakey *et al*. 2021[51]	Egypt	50 (27 completed the study)	Prospective, randomized study	Micro-needling with topical 4% TXA every other week in group B, topical 4% HQ cream at night in group A	31.16±19.16

TXA=tranexamic acid, HQ=hydroquinone, QSNY laser=Q-switched neodymium-doped yttrium aluminum garnet laser , FbTC=fluocinolone-based triple combination cream, IPL=intense pulsed light laser, NS=Normal saline, PRP=platelet-rich plasma