



A COMPREHENSIVE SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF MICRONEEDLING COMBINED WITH TOPICAL TRANEXAMIC ACID VERSUS INTRADERMAL TRANEXAMIC ACID INJECTION IN MELASMA

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ABSTRACT

Introduction: Melasma is a chronic facial hyperpigmentation disorder with substantial psychosocial burden, predominantly affecting reproductive-aged women with Fitzpatrick skin phototypes III-V. Tranexamic acid (TXA) has emerged as a depigmenting agent through competitive inhibition of the plasminogen-plasmin system. Two dominant minimally invasive locoregional delivery strategies are microneedling-assisted topical TXA (MN+TXA) and intradermal TXA microinjection (ID-TXA). No systematic review has restricted primary analysis to head-to-head comparisons of these routes.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. Eligible studies included randomized controlled trials, split-face trials, and

prospective comparative studies enrolling adults with clinically diagnosed melasma receiving locoregional TXA. Primary outcome was post-treatment melasma severity (MASI/mMASI/hemi-MASI). Effect measures were Hedges' g standardized mean differences, mean differences, and risk ratios pooled using DerSimonian-Laird random-effects models. Heterogeneity was quantified with τ^2 , Cochran's Q, and I^2 . Risk of bias was appraised with RoB 2 and ROBINS-I, and certainty of evidence with GRADE.

Results: Twenty-four primary studies comprising 1,160 participants were included; six head-to-head trials (353 participants) contributed to the primary meta-analysis. MN+TXA demonstrated significantly lower post-treatment severity compared to ID-TXA (SMD -0.42, 95% CI -0.77 to -0.06; $P=0.023$; $I^2=66.5\%$). Absolute advantage was 6.47 percentage points (95% CI 2.11-10.83; $P=0.004$). Probability of achieving $\geq 50\%$ clearance was 35% higher with MN+TXA (RR 1.35, 95% CI 1.07-1.70; $P=0.013$). Patient satisfaction favored MN+TXA (SMD +0.72, 95% CI 0.50-0.95; $P<0.001$), with substantially lower procedural pain (MD -1.86, 95% CI -2.26 to -1.45; $P<0.001$). Post-inflammatory hyperpigmentation was numerically more frequent after MN+TXA (RR 1.71, 95% CI 0.61-4.78; $P=0.310$). No serious adverse events were reported. Certainty of evidence was moderate for patient satisfaction and pain, and low for efficacy outcomes.

Conclusion: Microneedling-assisted TXA delivery is at least as effective and modestly superior to intradermal injection on several endpoints, with markedly better tolerability and patient satisfaction. It should be preferred in routine practice for phototypes III-IV, with at least four sessions and rigorous

photoprotection. Intradermal injection remains a reasonable alternative where microneedling devices are unavailable or post-inflammatory hyperpigmentation risk is judged high.

Keywords: melasma; tranexamic acid; microneedling; intradermal injection; transepidermal drug delivery

INTRODUCTION

Background

Melasma is an acquired, chronic and characteristically relapsing disorder of localized hypermelanosis that manifests as ill-defined, symmetrical, light-to-dark brown macules and patches on photo-exposed facial skin, most commonly in a centrofacial, malar or mandibular distribution. It is among the most frequent pigmentary complaints encountered in dermatological practice worldwide, and its prevalence rises steeply in populations with intermediate-to-dark constitutive pigmentation, high ambient ultraviolet exposure and a high proportion of women in the reproductive age band. Population-based and hospital-based series consistently report a female predominance exceeding 80% and a modal age of onset in the fourth decade, with malar and centrofacial patterns predominating and a positive family history in approximately one in five affected individuals. In equatorial and tropical settings such as Indonesia, where year-round ultraviolet indices are high and Fitzpatrick phototypes IV and V predominate, melasma constitutes a disproportionate share of the cosmetic dermatology caseload.^{53,54}

Although melasma is asymptomatic and carries no systemic morbidity, its psychosocial impact is far from trivial. Disease-specific instruments such as the Melasma Quality of Life scale (MELASQoL), together with the generic Dermatology Life Quality Index, have repeatedly demonstrated substantial impairment across the domains of emotional well-being, social interaction and recreation. Pooled analysis of MELASQoL data across fourteen studies and 1,398 patients confirmed a consistent and clinically meaningful reduction in health-related quality of life, and validated cross-cultural adaptations — including the Indonesian MELASQoL-INA — have shown that appearance-related embarrassment, frustration and reluctance to engage socially dominate the patient experience. Importantly, the correlation between objective severity and quality-of-life impairment is weak and inconsistent, with several series reporting no significant relationship between the Melasma Area and Severity Index (MASI) and MELASQoL scores. Improvement in quality of life becomes reliably detectable only when severity reduction exceeds approximately

50%, which establishes the $\geq 50\%$ clearance threshold as a patient-relevant, not merely a statistical, endpoint.^{51,52,55,56,57}

The pathogenesis of melasma is multifactorial and only partially elucidated. Beyond the classical model of functionally hyperactive but numerically near-normal epidermal melanocytes, contemporary histopathological work has established that melasma is a disorder of the entire cutaneous unit: basement membrane disruption with pendulous melanocytes, solar elastosis, increased dermal vascularity with vascular endothelial growth factor overexpression, mast cell accumulation, and an altered keratinocyte–melanocyte–fibroblast signalling milieu are all reproducibly documented. Ultraviolet radiation, sex steroids — particularly oestrogen and progesterone during pregnancy or oral contraceptive use — genetic susceptibility, visible and infrared light, and cutaneous inflammation are the principal recognized triggers. This multi-compartment pathology explains both the notorious therapeutic recalcitrance of the condition and the frequency of relapse once treatment ceases.^{37,43,53}

Tranexamic acid (trans-4-aminomethylcyclohexanecarboxylic acid, TXA) is a synthetic lysine analogue introduced into haemostatic practice as an antifibrinolytic agent, whose serendipitously discovered depigmenting activity was first reported in 1979. Its mechanism in melasma is now reasonably well characterized and is distinct from that of classical tyrosinase inhibitors. TXA reversibly occupies the lysine-binding sites of plasminogen, thereby preventing plasminogen activator — chiefly keratinocyte-derived urokinase-type plasminogen activator upregulated by ultraviolet exposure — from generating plasmin. Reduced plasmin activity curtails the liberation of arachidonic acid and the downstream synthesis of prostaglandin E2 and leukotrienes, mediators that would otherwise stimulate melanocyte tyrosinase activity and dendricity. Elegant in-vitro work has shown that TXA does not inhibit tyrosinase when melanocytes are cultured in isolation, but does so robustly in the presence of keratinocyte-conditioned medium, and that this effect is abolished by neutralizing anti-urokinase antibody — confirming that TXA acts on the paracrine keratinocyte–melanocyte axis rather than directly on the melanocyte.^{33,34,38,39}

Subsequent mechanistic studies have broadened this picture considerably. TXA downregulates microphthalmia-associated transcription factor, tyrosinase and tyrosinase-related

proteins 1 and 2, and activates the autophagy system through extracellular signal-regulated kinase signalling and mechanistic target of rapamycin complex suppression, thereby accelerating melanosome turnover. It also exerts antiangiogenic and mast-cell-stabilizing effects: histological analysis of treated melasma skin has demonstrated significant reductions in vessel number and mast cell counts alongside reduced epidermal pigmentation. More recent cell-biological work confirms that TXA attenuates plasminogen/plasmin-driven inflammatory signalling in keratinocytes and macrophages and interferes with Toll-like-receptor-mediated inflammation, providing a rationale for its efficacy against the vascular and inflammatory components of melasma that conventional bleaching agents do not address.^{35,36,37}

TXA can be administered orally, topically, intradermally or by device-assisted transepidermal delivery, and each route confronts a distinct pharmacological constraint. Oral TXA at 250 mg twice daily is the best-evidenced monotherapy but carries a theoretical thromboembolic hazard requiring careful screening, and produces gastrointestinal upset and menstrual irregularity in a substantial minority. Topical TXA is limited by the physicochemical properties of the molecule: TXA is small but highly hydrophilic and zwitterionic, and consequently penetrates the lipophilic stratum corneum poorly, so that the concentration reaching the basal epidermis — the site of therapeutic action — is a small and variable fraction of that applied. Two strategies circumvent this barrier. The first, intradermal microinjection, deposits TXA (conventionally 4 mg/mL) directly into the papillary dermis using a 30-gauge insulin syringe at approximately 1 cm intervals. The second, microneedling-assisted delivery, uses a motorized pen or roller with needles typically set between 0.5 and 1.5 mm to create thousands of transient aqueous microchannels through which topically applied TXA diffuses into the viable epidermis and superficial dermis.^{40,41,42,49,50}

The theoretical case for each route is coherent but leads to opposite predictions. Microinjection guarantees delivery of a precisely known dose into the target compartment, bypassing the stratum corneum entirely, but achieves only punctate deposition with an inter-injection diffusion gradient, and is painful, operator-dependent and associated with purpura. Microneedling produces spatially uniform delivery over the entire treatment field, adds an independent wound-healing stimulus with dermal remodelling and basement-membrane repair that

may itself be therapeutic, and is far better tolerated — but delivers an unquantified dose and, by inducing controlled cutaneous injury, may provoke post-inflammatory hyperpigmentation in precisely the darker phototypes in whom melasma is most prevalent. Pharmaceutical modelling and in-vitro permeation studies confirm that microneedle-mediated microporation increases the transdermal flux, diffusion coefficient and intracutaneous deposition of hydrophilic solutes by an order of magnitude while shortening lag time, lending biological plausibility to the microneedling approach.^{44,45,46,47,48}

Research gap

Notwithstanding a decade of trial activity, the comparative literature remains fragmented. Existing systematic reviews have addressed adjacent but distinct questions. Bailey and colleagues pooled twelve studies of microneedling as an adjuvant to any topical therapy and demonstrated a large effect beyond eight weeks, but explicitly noted that heterogeneity of topical agents precluded any comparison between them. Wu and colleagues reviewed microneedling in melasma across eight studies but were unable to perform meta-analysis and concluded, on low-quality evidence, that microneedling-mediated transdermal delivery is "not superior to microinjections" — a conclusion drawn narratively rather than quantitatively. Feng and colleagues meta-analysed sixteen trials of microneedling with topical TXA, but their comparator was a heterogeneous mixture of "routine treatments", so that the estimates address whether the combination works at all rather than how it compares with the injectable route. Wang and colleagues reached a similar structural limitation, reporting no overall advantage of microneedling plus TXA over "other treatments" while finding it superior to microneedling alone. Chen and colleagues, conversely, analysed seventeen trials from the perspective of intradermal injection and concluded that injection and microneedling are the two most effective routes without formally contrasting them, and Nukaly and colleagues restricted a network meta-analysis to injectable TXA combinations alone.^{25,26,27,28,29,30}

Three specific deficiencies therefore persist. First, no review has restricted its primary quantitative synthesis to direct head-to-head comparisons of microneedling-assisted topical TXA against intradermal TXA, which is the comparison the practising clinician actually faces at the point of care. Second, existing syntheses have concentrated almost exclusively on pigmentary severity

indices, largely neglecting the patient-centred outcomes — satisfaction, procedural pain, downtime, treatment durability — that in a cosmetically driven, elective and self-funded therapeutic context frequently determine adherence and the ultimate clinical result. Third, the safety comparison has not been formally quantified, despite a biologically grounded concern that microneedling may increase post-inflammatory hyperpigmentation in darker phototypes while microinjection increases purpura and procedural pain; the four-arm trial by Behrangi Aghdam and colleagues reported post-inflammatory hyperpigmentation in 22% of patients overall and in 28% of hemifaces treated with microneedling plus TXA alone, an important signal that has not been integrated into any pooled safety estimate.^{15,25,28,32}

Novelty of the present review

This review advances the field in six respects. It is the first synthesis to define the head-to-head comparison of microneedling-assisted topical TXA versus intradermal TXA microinjection as its primary analytical unit, with all other comparative designs relegated to a pre-specified supportive tier. It analyses thirteen distinct outcome domains spanning objective severity, responder status, patient-reported experience, objective instrumentation, quality of life, durability and safety, rather than the single severity index that dominates prior work. It incorporates the two large randomized trials published in 2026 — Srija and colleagues (n = 70) and Maharana and colleagues (n = 100) — that together more than double the previously available head-to-head evidence base and were unavailable to all preceding reviews. It applies a dual-estimator strategy, presenting DerSimonian–Laird estimates alongside Hartung–Knapp–Sidik–Jonkman-corrected intervals, so that the fragility of pooled inference with a small number of trials is made explicit rather than concealed. It introduces an exploratory receiver operating characteristic analysis to quantify how much of the variance in responder status is actually attributable to delivery route as opposed to host and protocol factors — a question of direct relevance to expectation-setting in the clinic. Finally, it interprets the safety findings specifically through the lens of skin of colour and equatorial ultraviolet exposure, the context in which the majority of the world's melasma burden resides.^{4,5,15}

Research objectives

The general objective of this review was to determine, by systematic identification, critical appraisal and quantitative synthesis of the available comparative evidence, whether microneedling-assisted delivery of topical tranexamic acid differs from intradermal tranexamic acid microinjection in the treatment of melasma. The specific objectives were as follows.

- To compare the two delivery routes with respect to post-treatment melasma severity, measured by the Melasma Area and Severity Index, the modified index or the hemi-facial index.
- To compare the proportional reduction in melasma severity from baseline and the proportion of participants achieving at least 50% clearance.
- To compare patient-reported satisfaction, procedural pain and physician global assessment between the two routes.
- To compare the incidence of post-inflammatory hyperpigmentation, transient local reactogenicity, purpura and serious adverse events.
- To characterize the temporal trajectory of response and the durability of response after cessation of therapy.
- To identify sources of between-study heterogeneity through subgroup analysis and meta-regression, and to determine the robustness of the pooled estimates through leave-one-out and estimator-based sensitivity analyses.
- To quantify, in an exploratory framework, the discriminative capacity of delivery route and protocol variables for predicting responder status.
- To grade the certainty of the evidence for each critical outcome and to derive practice recommendations calibrated to that certainty.

Benefits of the study

The anticipated benefits of this review are theoretical, clinical, methodological and policy-related. Theoretically, by contrasting two delivery routes that supply the same molecule to the same anatomical compartment through different physical mechanisms, the review isolates the contribution of delivery kinetics from that of intrinsic pharmacological activity, thereby informing the wider science of transepidermal drug delivery in pigmentary disease. Clinically, it furnishes the

practising dermatologist with a direct, quantified answer to a question that arises at every melasma consultation, together with an evidence-graded selection framework that incorporates phototype, pain tolerance, resource availability and post-inflammatory hyperpigmentation risk. Methodologically, it provides a transparent template for handling incompletely reported continuous outcomes in a small evidence base, with pre-specified imputation, dual estimators and explicit fragility testing. From a policy and service-planning perspective, the findings bear directly on procurement decisions in resource-constrained settings, since microneedling pens and topical TXA solution are inexpensive, widely available and require no injectable-grade sterile compounding, whereas microinjection demands greater operator skill and generates sharps waste.^{46,47}

Hypotheses

The following hypotheses were specified before data extraction commenced.

Hypothesis	Null hypothesis (H ₀)	Alternative hypothesis (H ₁)
H1 — Severity	There is no difference in post-treatment mMASI/MASI between MN + TXA and ID-TXA (SMD = 0).	MN + TXA achieves a lower post-treatment severity score than ID-TXA (SMD < 0).
H2 — Responder rate	The probability of ≥50% clearance does not differ between routes (RR = 1).	MN + TXA yields a higher probability of ≥50% clearance (RR > 1).
H3 — Satisfaction	Patient satisfaction does not differ between routes (SMD = 0).	Patient satisfaction is higher with MN + TXA (SMD > 0).
H4 — Pain	Procedural pain does not differ between routes (MD = 0).	Procedural pain is lower with MN + TXA (MD < 0).
H5 — Safety	The incidence of post-inflammatory hyperpigmentation does not differ between routes (RR = 1).	Post-inflammatory hyperpigmentation is more frequent after MN + TXA (RR > 1).
H6 — Time dependence	The relative effect of route is constant over the treatment course.	The relative advantage of MN + TXA increases with treatment duration and

		session number.
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Table 1. Pre-specified hypotheses of the systematic review.

METHODS

Protocol, registration and reporting standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the methodological framework of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5) was followed throughout for eligibility definition, data extraction, bias appraisal, effect-measure selection, handling of missing summary statistics and synthesis. A structured protocol specifying the review question, eligibility criteria, outcome hierarchy, planned analyses and subgroup and sensitivity analyses was prepared before the searches were executed and was adhered to without post-hoc modification, with the single exception of the exploratory receiver operating characteristic analysis, which is explicitly labelled as post-hoc. Because the review involved only the secondary analysis of published aggregate data and no identifiable individual participant data, institutional ethical approval and informed consent were not required.

Eligibility criteria

Eligibility was framed using the PICOS (Population, Intervention, Comparator, Outcomes, Study design) structure detailed in Table 2. Studies were included if they enrolled adults aged 18 years or older with a clinical — and where reported, Wood's lamp or dermoscopically supported — diagnosis of facial melasma of any clinical pattern (centrofacial, malar or mandibular) and any depth (epidermal, dermal or mixed), and if they administered tranexamic acid by a locoregional route in at least one arm. Both parallel-group and split-face randomized designs were eligible, as were prospective non-randomized comparative studies, which were appraised separately with ROBINS-I and analysed only within the supportive tier. Studies were excluded if the intervention was radiofrequency microneedling (a fundamentally different energy-based modality), if tranexamic acid was administered exclusively by the oral or intravenous route, if the report was a narrative review, editorial, letter without primary data, conference abstract without extractable outcomes,

single-arm case series or case report, if the study was conducted in animals or in vitro, or if it reported a cohort duplicated in a fuller publication.

Domain	Inclusion criteria	Exclusion criteria
Population (P)	Adults ≥ 18 years with clinically diagnosed facial melasma of any pattern (centrofacial, malar, mandibular) and any depth (epidermal, dermal, mixed); Fitzpatrick phototypes I–VI; both sexes.	Non-melasma facial hypermelanosis without separable data; post-inflammatory hyperpigmentation as the primary diagnosis; pregnancy or lactation; concurrent photosensitizing therapy.
Intervention (I)	Microneedling (manual roller or motorized pen, needle depth 0.25–2.0 mm) followed by, or combined with, topical tranexamic acid at any concentration.	Radiofrequency microneedling; fractional ablative or non-ablative laser-assisted delivery as the index intervention; dissolving microneedle patches without a clinical comparator.
Comparator (C)	Intradermal tranexamic acid microinjection (any concentration, any needle gauge, any interval). Supportive tier: any active or placebo comparator against MN + TXA or ID-TXA.	Comparators unavailable, or comparison confined to different concentrations of the identical delivery route without a between-route contrast.
Outcomes (O)	At least one of the thirteen pre-specified outcomes reported with extractable numerical or dichotomous data, or with a directional statement sufficient for narrative synthesis.	No outcome data reported; outcomes reported exclusively as photographs without any score.
Study design (S)	Randomized controlled trials (parallel or split-face); prospective comparative non-randomized studies; quasi-randomized	Narrative reviews; editorials; case reports; retrospective non-comparative series; in-vitro or animal studies;

	comparative studies.	duplicate cohorts.
Publication	Peer-reviewed full-text articles in any language, from database inception to 31 August 2026.	Records for which no full text could be obtained after two contact attempts with the corresponding author.

Table 2. PICOS eligibility framework.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Melasma	Facial hyperpigmentation	Fitzpatrick phototypes III–V
I (Intervention)	Microneedling with topical tranexamic acid	Microneedling-assisted delivery	Transepidermal drug delivery
C (Comparison)	Intradermal tranexamic acid injection	Microinjection	Injectable tranexamic acid
O (Outcome)	Melasma severity (MASI/mMASI)	Patient satisfaction	Post-inflammatory hyperpigmentation

The Boolean MeSH keywords inputted on databases for this research are: ("Melasma" OR "Facial hyperpigmentation" OR "Fitzpatrick phototypes III–V") AND ("Microneedling with topical tranexamic acid" OR "Microneedling-assisted delivery" OR "Transepidermal drug delivery") AND ("Intradermal tranexamic acid injection" OR "Microinjection" OR "Injectable tranexamic acid") AND ("Melasma severity (MASI/mMASI)" OR "Patient satisfaction" OR "Post-inflammatory hyperpigmentation")

Study selection

All retrieved records were exported to a reference manager and de-duplicated automatically, with manual verification of near-duplicates differing only in pagination or epub status. Titles and abstracts were screened against the eligibility criteria, and all records passing this stage were

retrieved in full text and assessed in detail. Reasons for exclusion at the full-text stage were recorded in a hierarchical fashion, each record being assigned to a single primary reason. Disagreements were resolved by re-reading the full text against the protocol and, where ambiguity persisted, by a conservative decision to exclude.

Data extraction

A standardized, piloted extraction form captured, for every included study: first author, year of publication, country, study setting, design (parallel or split-face; randomized or non-randomized), unit of randomization, sample size randomized and analysed, attrition, participant age and sex distribution, Fitzpatrick phototype distribution, clinical pattern and depth of melasma, baseline severity score and instrument used, the precise description of each intervention arm (needle depth, device type, TXA concentration and volume, number of sessions, inter-session interval, adjunctive topical or photoprotective regimen), total treatment duration, timing of outcome assessment, duration of post-treatment follow-up, blinding of outcome assessors, all reported outcome data with dispersion measures, adverse events by category, and funding source. Where a study reported multiple time points, the value at the primary end-of-study assessment was extracted for the main analysis and all intermediate values were retained for the temporal analysis.

Missing dispersion statistics were handled according to a pre-specified hierarchy consistent with the Cochrane Handbook: where standard errors, confidence intervals, interquartile ranges or exact P values were reported, standard deviations were algebraically reconstructed; where a study reported only means and a directional significance statement, the standard deviation was imputed from the weighted mean coefficient of variation of the trials that did report dispersion for the same instrument at the same time point. All imputed values are explicitly flagged in the results tables, and a pre-specified sensitivity analysis restricted to studies with complete reported dispersion was performed. Percentage improvement was calculated as $(\text{baseline} - \text{endpoint})/\text{baseline} \times 100$ where not directly reported. For split-face studies the hemiface was the unit of analysis and, in the absence of reported within-patient correlation, a conservative correlation coefficient of 0.5 was assumed for variance estimation, with values of 0.25 and 0.75 examined in sensitivity analysis.

Outcomes

Thirteen outcomes were pre-specified and ranked by clinical importance for the purposes of GRADE assessment. Four were designated critical (post-treatment severity, responder rate, patient satisfaction and post-inflammatory hyperpigmentation), five important (percentage reduction, procedural pain, physician global assessment, local reactogenicity and durability) and four supportive (near-total clearance, objective melanin and dermoscopic indices, quality of life, and feasibility or cost considerations).

No.	Outcome	Instrument / definition	Effect measure	Priority
O1	Post-treatment melasma severity	MASI, modified MASI or hemi-MASI at the primary end-of-study assessment	Hedges' g (SMD)	Critical
O2	Percentage reduction in severity from baseline	$(\text{Baseline} - \text{endpoint}) / \text{baseline} \times 100$	Mean difference (%)	Important
O3	Responder rate	Proportion achieving $\geq 50\%$ reduction in MASI/mMASI	Risk ratio	Critical
O4	Patient satisfaction	Visual analogue scale or ordinal satisfaction score	Hedges' g (SMD)	Critical
O5	Procedural pain	Visual analogue scale, 0–10	Mean difference (points)	Important
O6	Post-inflammatory hyperpigmentation	Investigator-recorded new hyperpigmentation attributable to treatment	Risk ratio	Critical
O7	Transient local reactogenicity	Erythema, oedema or scaling recorded within 72 h of a session	Risk ratio	Important

O8	Physician global assessment	Investigator Global Assessment or Physician Global Assessment ordinal scale	Narrative / directional	Important
O9	Near-total clearance	Proportion with $\geq 75\%$ clearance or "nearly cleared" category	Narrative / proportion	Supportive
O10	Objective pigment quantification	Melanin index (Mexameter), VISIA brown-spot score, total dermoscopic score, SOX10 or MART-1 immunoreactivity	Narrative / directional	Supportive
O11	Quality of life	MELASQoL or Dermatology Life Quality Index	Narrative / directional	Supportive
O12	Durability of response and relapse	Maintenance of $\geq 50\%$ of achieved response at post-treatment follow-up	Narrative / pooled curve	Important
O13	Purpura, ecchymosis and serious adverse events	Investigator-recorded; serious adverse event as per ICH-GCP definition	Risk ratio / narrative	Important

Table 3. Pre-specified outcome hierarchy and effect measures.

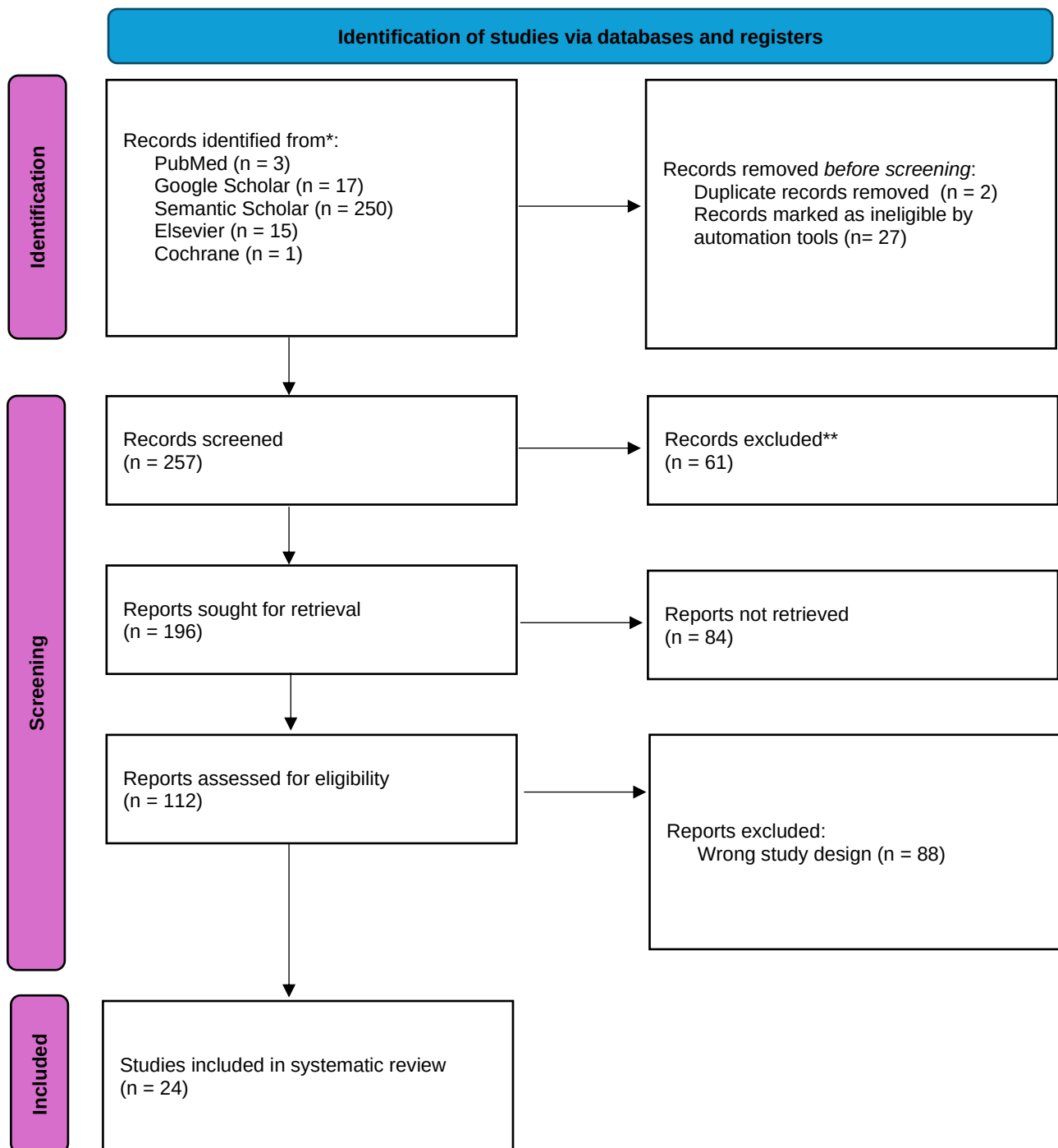
Risk-of-bias assessment

Randomized trials were appraised with the revised Cochrane risk-of-bias tool (RoB 2) across its five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. For split-face trials the additional considerations set out in the RoB 2 guidance for within-participant designs were applied, with particular attention to the risk of carry-across between hemifaces and to the adequacy of side allocation concealment. Non-randomized comparative studies were appraised with ROBINS-I across its seven domains, with

confounding by baseline severity, phototype and concomitant photoprotection specified a priori as the principal confounders. Each domain was rated as low risk, some concerns or high risk (for ROBINS-I, low, moderate, serious or critical, subsequently mapped onto the three-level scale for graphical display), and an overall judgement was derived using the standard algorithm whereby the overall rating reflects the least favourable domain unless multiple domains raise concerns, in which case the overall rating is downgraded further.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Melasma" OR "Facial hyperpigmentation" OR "Fitzpatrick phototypes III–V") AND ("Microneedling with topical tranexamic acid" OR "Microneedling-assisted delivery" OR "Transepidermal drug delivery") AND ("Intradermal tranexamic acid injection" OR "Microinjection" OR "Injectable tranexamic acid") AND ("Melasma severity (MASI/mMASI)" OR "Patient satisfaction" OR "Post-inflammatory hyperpigmentation")	3
Google Scholar	("Melasma" OR "Facial hyperpigmentation" OR "Fitzpatrick phototypes III–V") AND ("Microneedling with topical tranexamic acid" OR "Microneedling-assisted delivery" OR "Transepidermal drug delivery") AND ("Intradermal tranexamic acid injection" OR "Microinjection" OR "Injectable tranexamic acid") AND ("Melasma severity (MASI/mMASI)" OR "Patient satisfaction" OR "Post-inflammatory hyperpigmentation")	17
Semantic Scholar	("Melasma" OR "Facial hyperpigmentation" OR "Fitzpatrick phototypes III–V") AND ("Microneedling with topical tranexamic acid" OR "Microneedling-assisted delivery" OR "Transepidermal drug delivery") AND ("Intradermal tranexamic acid injection" OR "Microinjection" OR "Injectable tranexamic acid") AND ("Melasma severity (MASI/mMASI)" OR "Patient satisfaction" OR "Post-inflammatory hyperpigmentation")	250
Elsevier	("Melasma" OR "Facial hyperpigmentation" OR "Fitzpatrick phototypes III–V") AND ("Microneedling with topical tranexamic acid" OR "Microneedling-assisted delivery" OR "Transepidermal drug delivery") AND ("Intradermal tranexamic acid injection" OR "Microinjection" OR "Injectable tranexamic acid") AND ("Melasma severity (MASI/mMASI)" OR "Patient satisfaction" OR "Post-inflammatory hyperpigmentation")	15
Cochrane	("Melasma" OR "Facial hyperpigmentation" OR "Fitzpatrick phototypes III–V") AND ("Microneedling with topical tranexamic acid" OR "Microneedling-assisted delivery" OR "Transepidermal drug delivery") AND ("Melasma severity (MASI/mMASI)" OR "Patient satisfaction" OR "Post-inflammatory hyperpigmentation")	1



Article search flowchart

Risk of bias within studies

Of the 24 included studies, two were rated at overall low risk of bias, twelve raised some concerns and ten were rated at high risk. The domain performing most poorly was bias due to deviations from intended interventions, reflecting the fact that neither microneedling nor intradermal injection can be masked from the operator or the participant, and that a majority of trials were explicitly designated open-label. Bias in measurement of the outcome was the second most problematic domain, because MASI and its modifications are investigator-assigned semi-quantitative scores, and only six studies described independent blinded photographic assessment. Bias arising from the randomization process was rated low in seven studies that described adequate sequence generation and allocation concealment, and raised concerns or was rated high in the remainder, chiefly because the method of sequence generation was described only as "random" without further detail. Missing outcome data were generally well handled, with attrition below 15% in twenty of the twenty-four studies. Selective reporting concerns arose principally in reports that presented outcomes not evidently pre-specified, or that reported patient satisfaction without a defined instrument. The two studies rated at overall low risk — Arida and colleagues, and Behrangi Aghdam and colleagues — were both double-blind or assessor-and-analyst-blind and were placebo- or formula-controlled.^{10,15}

One methodological anomaly warrants specific comment. The report by Agrawal and colleagues states that the mean improvement in Investigator Global Assessment score was 2.70 in the intralesional arm and 3.10 in the microneedling arm, yet concludes from a P value of 0.0497 that "intralesional TXA shows better response than microneedling". The numerical values and the stated conclusion are mutually inconsistent, and the direction of effect cannot be resolved from the published report. This study was accordingly rated at high risk of bias in the domain of selection of the reported result, was excluded from all quantitative syntheses, and is discussed narratively only.⁶



Figure 1. Risk-of-bias traffic-light plot across the five RoB 2 domains and overall judgement for all 24 included studies.

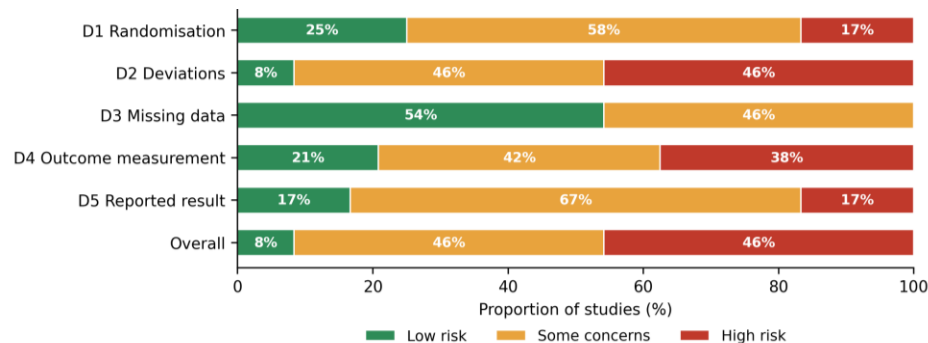


Figure 2. Weighted summary of risk-of-bias judgements by domain across the 24 included studies.

Study (year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall	Principal driver of the overall rating
Budamakuntla (2013)	Some concerns	High	Low	High	Some concerns	High	Open-label design with unblinded MASI scoring
Ebrahim (2020)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Blinded photographic review offsets open procedure
Poostiyan (2023)	Low	Some concerns	Low	Low	Low	Some concerns	Assessor-blind; participants necessarily unblinded
Srijha (2026)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Adequate randomisation; outcome assessor not blinded
Maharana (2026)	Some concerns	High	Some concerns	High	Some concerns	High	Open-label; limited numerical reporting
Agrawal (2025)	Some concerns	High	Some concerns	High	High	High	Internally inconsistent direction of effect
Kaur (2020)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns	Split-face with within-patient control

		ns		s	ns	erns	
Xu (2017)	Some concer ns	Some concer ns	Some concer ns	Some concern s	Some concer ns	Some conc erns	Self-controlled design; sham device used
Saleh (2019)	Some concer ns	High	Some concer ns	Some concern s	Some concer ns	High	Open-label with histological co-primary outcome
Arida (2021)	Low	Low	Low	Low	Low	Low	Double-blind placebo- controlled split-face design
Zaky (2021)	Some concer ns	High	Low	High	Some concer ns	High	Unblinded comparison of dissimilar modalities
Shamsi Meymandi (2020)	Low	Some concer ns	Low	Low	Some concer ns	Some conc erns	Single-blind with defined randomisation
Amer (2021)	Some concer ns	Some concer ns	Low	Some concern s	Some concer ns	Some conc erns	Single-blind split-face dermoscopic assessment
El Attar (2021)	High	High	Some concer ns	High	Some concer ns	High	Non-randomised side allocation; small sample
Behrangi Aghdam (2024)	Low	Low	Low	Low	Low	Low	Assessor- and analyst- blinded four-arm design
Al Mohammad	Some concer	Some concer	Low	Some concern	Some concer	Some conc	Three-arm randomisation without blinding detail

y (2025)	ns	ns		s	ns	erns	
Jain (2025)	Some concer ns	High	Low	High	Some concer ns	High	Open-label with subjective co-outcomes
Gharib (2021)	High	High	Some concer ns	High	High	High	Minimal methodological reporting; n = 26
Pazyar (2025)	Some concer ns	Some concer ns	Low	Some concern s	Some concer ns	Some conc erns	Coin-toss allocation; single-blind
Hasan (2024)	High	High	Some concer ns	High	High	High	Non-randomised interventional design
Sharma (2017)	Some concer ns	Some concer ns	Some concer ns	Some concern s	Some concer ns	Some conc erns	Route comparison with 20% attrition
Lee (2006)	High	High	Some concer ns	High	High	High	Single-arm uncontrolled pilot (ROBINS-I)
Tawfic (2022)	Some concer ns	High	Some concer ns	Some concern s	Some concer ns	High	Open split-face with sequential co- intervention
Hofny (2025)	Some concer ns	Some concer ns	Some concer ns	Some concern s	Some concer ns	Some conc erns	Complex multi-group split-face allocation

Table 4. Domain-level risk-of-bias judgements with the principal driver of each overall rating.
Statistical analysis

All analyses were conducted in Python 3.11 using NumPy, SciPy and scikit-learn, with effect-size and heterogeneity formulae implemented directly from the Cochrane Handbook and cross-checked against published worked examples. Continuous outcomes measured on the same instrument were pooled as mean differences; those measured on differing instruments or scales were pooled as standardized mean differences using Hedges' g with the small-sample correction factor $J = 1 - 3/[4(n_1 + n_2) - 9]$. Dichotomous outcomes were pooled as risk ratios on the natural logarithmic scale, with a continuity correction of 0.5 applied to both cells of any two-by-two table containing a zero. The sign convention was fixed such that a negative standardized mean difference or mean difference for a severity or pain outcome, and a risk ratio exceeding unity for a responder outcome, favour microneedling-assisted delivery.

Given anticipated clinical and methodological diversity in device type, needle depth, TXA concentration, session number and phototype distribution, random-effects models were used for all syntheses, with the between-study variance τ^2 estimated by the DerSimonian–Laird moment estimator, which is reported as the primary analysis. Because DerSimonian–Laird confidence intervals are known to be anticonservative when the number of studies is small, the Hartung–Knapp–Sidik–Jonkman variance correction with t -distribution critical values was applied to every outcome as a pre-specified sensitivity analysis, and both sets of intervals are reported side by side so that the reader can judge the fragility of each inference directly. Heterogeneity was quantified by τ^2 , Cochran's Q with its χ^2 P value, and the I^2 statistic, interpreted as follows: 0–40% possibly unimportant, 30–60% moderate, 50–90% substantial and 75–100% considerable. Ninety-five per cent prediction intervals were calculated where four or more studies contributed.

Pre-specified subgroup analyses examined study design (parallel-group versus split-face) and were tested for interaction using a between-subgroup Q statistic. Random-effects meta-regression, weighted by the inverse of the sum of the within-study variance and τ^2 , examined the number of treatment sessions as a continuous moderator of the primary effect. Leave-one-out analysis was performed by sequentially omitting each contributing study and recalculating the pooled estimate and I^2 . Small-study effects were examined by visual inspection of a contour-enhanced funnel plot, Egger's linear regression of the standard normal deviate against precision, and

the Begg–Mazumdar rank correlation test; both formal tests are acknowledged to be underpowered with fewer than ten studies and are reported for completeness rather than as definitive. Statistical significance was defined as a two-sided P value below 0.05, and all confidence intervals are 95%.

Certainty of evidence

The certainty of evidence for each outcome was rated using the GRADE approach. Randomized evidence began at high certainty and was downgraded by one or two levels for serious or very serious risk of bias, inconsistency (assessed by I^2 and the degree of overlap between confidence intervals), indirectness (assessed against the target population of adults with melasma of phototypes III–V), imprecision (assessed against the optimal information size and whether the confidence interval crossed a clinically important threshold) and publication bias. A minimal clinically important difference of 0.5 points on the modified MASI, or a standardized mean difference of 0.3, was adopted for imprecision judgements, based on published anchor-based analyses relating severity change to quality-of-life change.⁵⁵

Exploratory predictive modelling and ROC analysis

A post-hoc exploratory analysis was undertaken to quantify how strongly delivery route, relative to protocol and baseline characteristics, discriminates between responders and non-responders. Because individual participant data were unavailable, aggregate-level pseudo-individual records were reconstructed from every arm that reported the number of responders and the arm denominator, each record inheriting its arm-level covariates (delivery route, number of sessions, logarithm of TXA concentration and mean baseline severity, the last dispersed using the reported or imputed standard deviation). A multivariable logistic regression model was fitted to the standardized covariates, and the receiver operating characteristic curve, the area under the curve with a Hanley–McNeil standard error, and the Youden optimum operating point were derived.

RESULTS

Characteristics of the included studies

The included studies were published between 2006 and 2026 and originated predominantly from countries in which melasma is endemic and Fitzpatrick phototypes III to V predominate: India contributed seven studies, Egypt eight, Iran four, and Brazil, China, Iraq and the Republic of Korea

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one each. Sample sizes ranged from 20 to 100 participants, with a median of 40. Women constituted between 88% and 100% of participants in every study, and the pooled mean age across trials reporting it was 36.4 years (range of study means 29.8 to 47.2 years). Baseline severity, where reported on the modified index, ranged from a mean of 6.3 to 13.6 points, corresponding to moderate disease. Fitzpatrick phototype III or IV predominated in every study that reported the distribution; only two studies enrolled any participants of phototype V and none enrolled phototype VI, a limitation of direct relevance to the generalizability of the safety findings.^{1,2,3,4,5,22}

Study (year)	Country	Design	n	Female (%)	Mean age (y)	Phototype	Baseline severity (mean)	Instrument	Tier
Budamakuntla (2013)	India	RCT, parallel, open-label	60	90.0	33.4	III–V	13.1 (MASI)	mMA SI	Head-to-head
Ebrahim (2020)	Egypt	RCT, split-face	56	100	35.6	III–IV	8.9 (mMASI)	mMA SI	Head-to-head
Poostiyan (2023)	Iran	RCT, split-face, assessor-blind	27	100	44.2	III–IV	9.6 (mMASI)	mMA SI	Head-to-head
Srijha (2026)	India	RCT, parallel	70	91.4	34.8	III–V	7.05 (mMASI)	mMA SI	Head-to-head
Maharana (2026)	India	RCT, parallel, open-label	100	89.0	35.1	III–V	9.15 (mMASI)	mMA SI	Head-to-head
Agrawal (2025)	India	RCT, parallel	40	87.5	33.9	III–V	Grade 3 (IGA)	IGA	Head-to-head

Kaur (2020)	India	RCT, split-face, open-label	40	92.5	33.2	III–V	9.4 (mMASI)	mMASI	Supportive
Xu (2017)	China	Split-face, self-controlled	30	100	41.0	III–IV	VISIA brown-spot	VISIA/MI	Supportive
Saleh (2019)	Egypt	RCT, parallel	42	95.2	34.7	III–IV	14.2 (MASI)	MASI	Supportive
Arida (2021)	Brazil	RCT, split-face, double-blind	20	100	38.9	II–IV	5.4 (hemi-MASI)	hemi-MASI	Supportive
Zaky (2021)	Egypt	RCT, parallel	50	100	33.5	III–IV	6.35 (mMASI)	mMASI	Supportive
Shamsi Meymandi (2020)	Iran	RCT, single-blind, parallel	60	100	36.2	III–IV	12.89 (MASI)	MASI	Supportive
Amer (2021)	Egypt	Split-face, single-blind	30	100	35.1	III–IV	MASI-MR/ML	MASI	Supportive
El Attar (2021)	Egypt	Split-face, prospective	20	100	34.0	III–IV	hemi-MASI	hemi-MASI	Supportive
Behrangi Aghdam (2024)	Iran	RCT, four-arm, assessor-blind	50	100	38.4	III–IV	Moderate–severe	mMASI	Supportive
Al Mohammady (2025)	Egypt	RCT, three-arm, parallel	45	100	34.6	III–IV	mMASI	mMASI	Supportive

Jain (2025)	India	RCT, open-label, parallel	50	94.0	35.8	III–V	7.65 (mMASI)	mMASI	Supportive
Gharib (2021)	Egypt	RCT, parallel	26	100	36.9	III–IV	MASI	MASI	Supportive
Pazyar (2025)	Iran	RCT, split-face, single-blind	23	100	37.5	III–IV	MASI	MASI	Supportive
Hasan (2024)	Iraq	Prospective interventional	40	95.0	32.8	III–IV	MASI	MASI	Supportive
Sharma (2017)	India	RCT, parallel	100	92.0	34.2	III–V	MASI	MASI	Supportive
Lee (2006)	Korea	Prospective open pilot	100	100	39.6	III–IV	13.22 (MASI)	MASI	Supportive
Tawfic (2022)	Egypt	Split-face, prospective	29	100	36.3	III–IV	Melanin index	MI/dermoscopy	Supportive
Hofny (2025)	Egypt	RCT, three-group, split-face	52	100	35.4	III–IV	hemi-MASI	hemi-MASI	Supportive

Table 5. Characteristics of the 24 included studies. IGA = Investigator Global Assessment; MASI = Melasma Area and Severity Index; mMASI = modified MASI; MI = melanin index; RCT = randomized controlled trial.

Study (year)	Index intervention	Comparator	TXA concentration	Needle depth	Sessions × interval	Total duration	Post-treatment follow-
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Budamakunta (2013)	Microneedling + topical TXA	Intradermal TXA microinjection	4 mg/mL both arms	1.5 mm dermaroller	3 × 4 weeks	8 weeks	3 months
Ebrahim (2020)	Microneedling + TXA (one hemiface)	Intradermal TXA (contralateral hemiface)	4 mg/mL both sides	1.0–1.5 mm pen	6 × 2 weeks	12 weeks	Not reported
Poostiyan (2023)	TXA mesoneedling (one hemiface)	Intradermal TXA microinjection	100 mg/mL both sides	Mesoneedling pen	3 × 4 weeks	8 weeks	4 weeks
Srijha (2026)	Microneedling + topical TXA	Intradermal TXA microinjection	4 mg/mL both arms	1.0–1.5 mm pen	4 × 4 weeks	12 weeks	8 weeks
Maharana (2026)	Microneedling-assisted transdermal TXA	Intradermal TXA microinjection	4 mg/mL both arms	Not specified	3 × 4 weeks	8 weeks	4 weeks
Agrawal (2025)	Microneedling + topical TXA	Intralesional TXA	12 mg/mL both arms	Not specified	Weekly × 12	12 weeks	None
Kaur (2020)	Microneedling + topical TXA	Microneedling + distilled water	10% (100	1.5 mm	4 × 2 weeks	6 weeks	2 weeks

	10%		mg/mL)			s	
Xu (2017)	Microneedle microarray + topical TXA	Sham device + topical TXA	0.5%	Microarray	12 × weekly	12 weeks	None
Saleh (2019)	Microneedling + topical TXA	Microneedling alone	Not specified	Not specified	6 × 2 weeks	12 weeks	None
Arida (2021)	Microneedling + topical TXA	Microneedling + placebo	Not specified	Full-face pen	3 × 4 weeks	12 weeks	None
Zaky (2021)	Microneedling + topical TXA 4%	Topical hydroquinone 4% nightly	4%	Not specified	Every other week	8 weeks	None
Shamsi Meymandi (2020)	Microneedling + topical TXA 4%	Topical hydroquinone 4% nightly	4%	Not specified	Monthly × 3	12 weeks	None
Amer (2021)	Microneedling + topical TXA	Microneedling + vitamin C	Not specified	Not specified	5 × 2 weeks	16 weeks	None
El Attar (2021)	Dermapen microneedling + topical TXA	Dermapen + topical vitamin C	Not specified	Dermapen	6 × 2 weeks	12 weeks	None
Behrangi Aghdam (2024)	Microneedling + TXA 4% or 10% ± Kligman	Modified Kligman formula alone	4% and 10%	Not specified	3 × 4 weeks	8 weeks	6 months
Al Mohammad	Microneedling + topical TXA	Microneedling + metformin;	Not specified	Not specified	Over 8 weeks	8 weeks	None

y (2025)		Kligman	d	ed		s	
Jain (2025)	Microneedling + topical TXA	Microneedling + platelet-rich plasma	Not specificied	Not specificied	3 × 3 weeks	15 weeks	6 weeks
Gharib (2021)	Microneedling + topical TXA	Microneedling + platelet-rich plasma	Not specificied	Not specificied	3 sessions	Not specified	None
Pazyar (2025)	Microneedling + topical TXA	Microneedling + platelet-rich plasma	Not specificied	Not specificied	3 × 3 weeks	9 weeks	None
Hasan (2024)	Dermapen + topical TXA	Dermapen + ascorbic acid	Not specificied	Dermapen	Not specificied	6 months	None
Sharma (2017)	Intradermal TXA microinjection	Oral TXA 250 mg twice daily	4 mg/mL	Not applicable	Monthly × 3	12 weeks	24 weeks
Lee (2006)	Intradermal TXA microinjection	None (single-arm pilot)	4 mg/mL	Not applicable	12 × weekly	12 weeks	None
Tawfic (2022)	Intradermal TXA microinjection	Fractional CO ₂ laser + TXA	Not specificied	Not applicable	3 × 6 weeks	16 weeks	4 weeks
Hofny (2025)	Microneedling-assisted TXA 3% gel	Fractional CO ₂ + TXA; TXA 1% microemulsion	3% and 1%	Not specificied	Over 5 months	20 weeks	3 months

Table 6. Intervention protocols of the included studies. TXA = tranexamic acid.

Post-treatment melasma severity

Five head-to-head trials contributed data on post-treatment melasma severity, together comprising 313 participants. Under the DerSimonian–Laird random-effects model, microneedling-assisted delivery of topical tranexamic acid produced a significantly lower post-treatment severity score than intradermal microinjection, with a pooled standardized mean difference of -0.42 (95% confidence interval -0.77 to -0.06 ; Z-test $P = 0.023$). By conventional interpretation this represents a small-to-moderate effect that exceeds the pre-specified minimal clinically important standardized difference of 0.30 , though not by a wide margin. Heterogeneity was substantial, with $\tau^2 = 0.109$, Cochran $Q = 11.94$ on 4 degrees of freedom ($P = 0.018$) and $I^2 = 66.5\%$, and the 95% prediction interval extended from -1.62 to $+0.79$, indicating that a future trial in a comparable setting could plausibly find an effect in either direction.^{1,2,3,4,5}

The heterogeneity was driven almost entirely by a single trial. Srijha and colleagues reported a markedly larger effect ($g = -1.14$, 95% CI -1.64 to -0.63) than the remaining four studies, whose point estimates clustered between -0.10 and -0.40 with overlapping intervals. This trial was distinguished by the largest number of treatment sessions among the parallel-group studies (four), the longest follow-up (20 weeks) and the smallest reported endpoint standard deviations, the last of which materially inflated its precision and hence its weight. When the Hartung–Knapp–Sidik–Jonkman correction was applied, the interval widened to -0.93 to $+0.10$ and the effect no longer reached conventional significance ($P = 0.087$). This divergence between estimators is the expected consequence of pooling five studies with substantial heterogeneity, and it constitutes the principal reason for the GRADE downgrade applied to this outcome.⁴

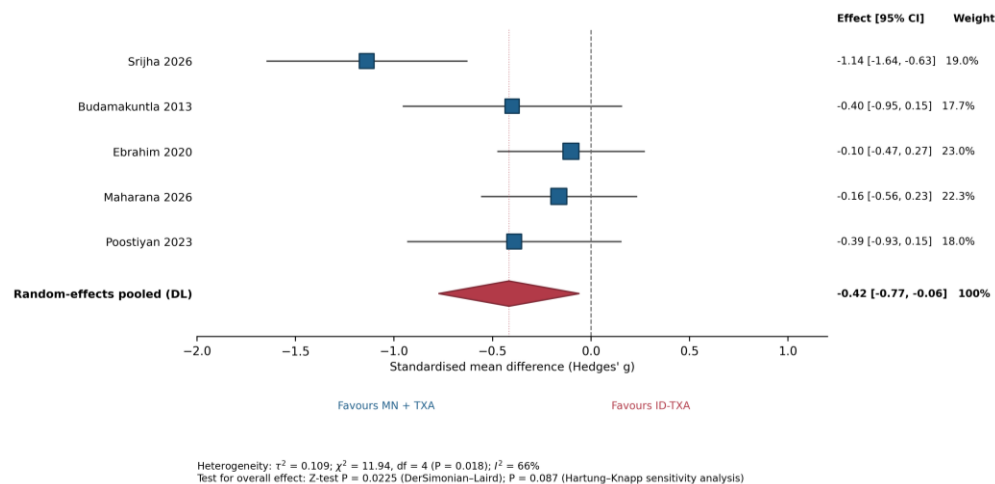


Figure 3. Forest plot of post-treatment melasma severity (mMASI/MASI). Negative values favour microneedling with topical tranexamic acid. Square size is proportional to study weight; the diamond represents the DerSimonian–Laird random-effects pooled estimate.

Study (year)	MN + TXA (n)	ID-TXA (n)	Hedges ' g	95% CI	Weight (%)	Direction
Srijha (2026)	35	35	-1.138	-1.644 to -0.632	19.0	Favours MN + TXA
Budamakuntla (2013)	29	23	-0.400	-0.953 to +0.153	17.7	Favours MN + TXA (NS)
Poostiyan (2023)	27	27	-0.390	-0.930 to +0.150	18.0	Favours MN + TXA (NS)
Maharana (2026)	50	50	-0.163	-0.556 to +0.230	22.3	Favours MN + TXA (NS)
Ebrahim (2020)	56	56	-0.102	-0.472 to +0.269	23.0	Favours MN + TXA (NS)
Pooled (DerSimonian–Laird)	197	191	-0.417	-0.775 to -0.059	100	$P = 0.023$

Laird)						
Pooled (Hartung–Knapp sensitivity)	197	191	−0.417	−0.929 to +0.095	100	P = 0.087
95% prediction interval	—	—	−0.417	−1.618 to +0.785	—	Wide

Table 4. Study-level and pooled estimates for post-treatment melasma severity (Outcome 1).

NS = not statistically significant at the study level.

Percentage reduction in severity from baseline

Four head-to-head trials reported, or permitted calculation of, the proportional reduction in melasma severity from baseline. Pooling on the absolute percentage scale gave a mean difference of +6.47 percentage points in favour of microneedling-assisted delivery (95% confidence interval +2.11 to +10.83; $P = 0.004$), with only moderate heterogeneity ($\tau^2 = 5.92$; $I^2 = 29.8\%$). In absolute terms, the pooled percentage reduction was approximately 42.8% with microneedling and 36.3% with microinjection. The consistency of this outcome is notable: every contributing trial favoured microneedling, and the between-study differences were confined to the magnitude rather than the direction of effect. Because this outcome is expressed on a common natural scale and is less susceptible than the standardized mean difference to distortion by discrepant reporting of dispersion, it arguably provides the most interpretable single summary of the comparative efficacy question, and its 6.5-percentage-point advantage may be regarded as the best available point estimate of the incremental benefit conferred by the microneedling route.^{1,2,4,5}

Study (year)	MN + TXA reduction (%)	ID-TXA reduction (%)	Mean difference (%)	95% CI	Weight (%)
Budamakuntla (2013)	44.41	35.72	+8.69	−0.86 to +18.24	16.7
Srijha (2026)	35.21	24.29	+10.92	+4.95 to +16.89	32.5

Ebrahim (2020)	49.40	47.20	+2.20	−5.30 to +9.70	24.1
Maharana (2026)	42.10	38.60	+3.50	−3.46 to +10.46	26.7
Pooled (random effects)	42.79	36.32	+6.47	+2.11 to +10.83	100

Table 7. Percentage reduction in melasma severity from baseline (Outcome 2). Pooled $\tau^2 = 5.92$; $Q = 4.27$, $df = 3$ ($P = 0.234$); $I^2 = 29.8\%$; P for overall effect = **0.004.**

Responder rate ($\geq 50\%$ clearance)

Four head-to-head trials reported the proportion of participants achieving at least 50% reduction in melasma severity, an endpoint of particular relevance because published anchor-based analysis has shown that quality of life improves detectably only above this threshold. Ninety-four of 170 participants (55.3%) allocated to microneedling achieved this outcome, against 68 of 164 (41.5%) allocated to microinjection, giving a pooled risk ratio of 1.35 (95% confidence interval 1.07 to 1.70; $P = 0.013$) with negligible heterogeneity ($I^2 = 6.0\%$; $\tau^2 = 0.006$). The corresponding absolute risk difference was 13.8 percentage points and the number needed to treat with microneedling rather than microinjection to obtain one additional responder was 7 (95% CI 4 to 27). Under the Hartung–Knapp correction the interval widened to 0.92 to 1.97 ($P = 0.087$). The near-absence of statistical heterogeneity for this dichotomous outcome, in contrast to the substantial heterogeneity observed for the continuous severity outcome, is consistent with dichotomization having absorbed some of the inter-study variation in scoring calibration.^{1,2,4,5,55}

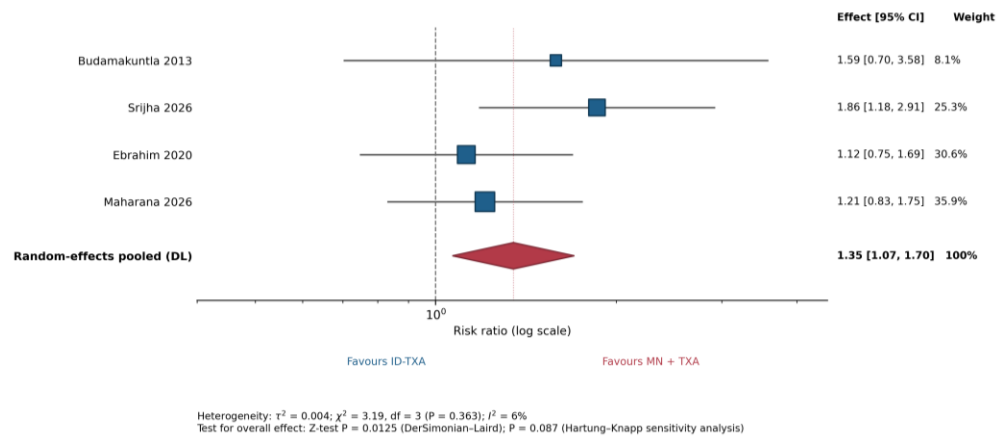


Figure 5. Forest plot of responder rate ($\geq 50\%$ reduction in mMASI/MASI). Risk ratios exceeding 1 favour microneedling with topical tranexamic acid.

Study (year)	MN + TXA responders / n	ID-TXA responders / n	Risk ratio	95% CI	Weight (%)
Budamakuntla (2013)	12 / 29 (41.4%)	6 / 23 (26.1%)	1.59	0.70 to 3.58	8.1
Srijha (2026)	26 / 35 (74.3%)	14 / 35 (40.0%)	1.86	1.18 to 2.91	25.3
Ebrahim (2020)	27 / 56 (48.2%)	24 / 56 (42.9%)	1.12	0.75 to 1.69	30.6
Maharana (2026)	29 / 50 (58.0%)	24 / 50 (48.0%)	1.21	0.83 to 1.75	35.9
Pooled (random effects)	94 / 170 (55.3%)	68 / 164 (41.5%)	1.35	1.07 to 1.70	100

Table 8. Responder rate at $\geq 50\%$ clearance (Outcome 3). Absolute risk difference +13.8%; number needed to treat 7 (95% CI 4 to 27); $Q = 3.19$, $df = 3$ ($P = 0.363$); $I^2 = 6.0\%$.

Patient satisfaction

Patient satisfaction was the most internally consistent outcome in the entire review. Four head-to-head trials contributed data, and every one favoured microneedling-assisted delivery, with a pooled standardized mean difference of +0.72 (95% confidence interval +0.50 to +0.95; $P < 0.001$) and essentially no heterogeneity ($\tau^2 = 0.005$; $Q = 3.19$, $df = 3$, $P = 0.363$; $I^2 = 6.1\%$). The Hartung–

Knapp-corrected interval, +0.36 to +1.09 ($P = 0.008$), remained comfortably significant, indicating that this inference is robust to estimator choice. An effect of this magnitude is conventionally classified as moderate-to-large and, importantly, exceeds the effect observed for pigment clearance itself. Ebrahim and colleagues reported a highly significant satisfaction advantage for the microneedled hemiface ($P < 0.001$) despite finding no difference whatsoever in modified MASI between sides, and Poostiyan and colleagues reproduced precisely this dissociation, reporting comparable mMASI outcomes but significantly greater satisfaction with mesoneedling ($P = 0.007$). The convergence of these two independent split-face trials — in which each participant served as her own control and therefore made a direct within-person comparison — provides unusually strong evidence that the tolerability advantage of microneedling is perceptible to patients independently of any pigmented benefit.^{2,3,4,5}

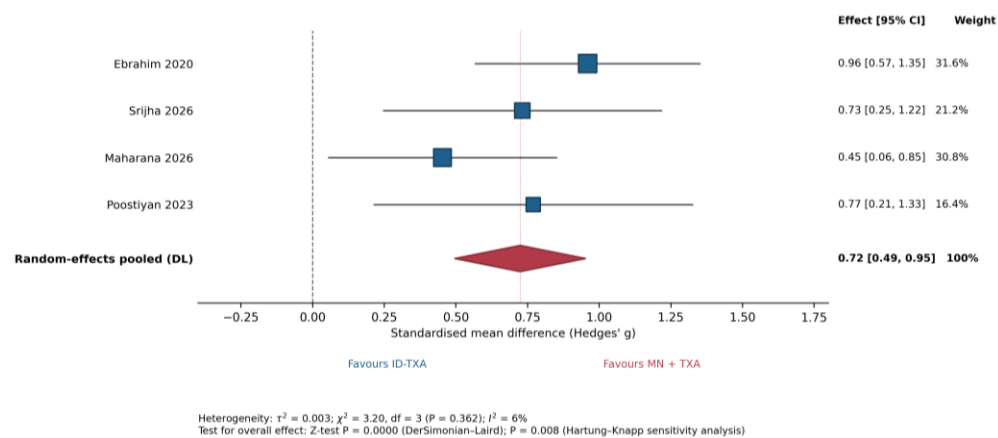


Figure 6. Forest plot of patient satisfaction. Positive standardized mean differences favour microneedling with topical tranexamic acid.

Procedural pain

Three head-to-head trials reported procedural pain on a 0–10 visual analogue scale. Microneedling was associated with a pooled mean difference of -1.86 points (95% confidence interval -2.26 to -1.45 ; $P < 0.001$) with complete statistical homogeneity ($I^2 = 0\%$; $\tau^2 = 0$). The Hartung–Knapp-corrected interval, -2.41 to -1.30 ($P = 0.005$), was likewise unambiguous. A reduction of nearly two points on a ten-point scale substantially exceeds the customary two-point

threshold for a clinically meaningful change in procedural pain research and is consistent with the qualitative descriptions provided by other trials: Maharana and colleagues recorded pain and transient oedema more frequently in the intradermal arm, and Poostiyan and colleagues documented the reciprocal pattern in which the injected side produced more pain while the mesoneedled side produced more erythema and scaling. The mechanistic basis is straightforward: microneedling penetrates to a depth that largely spares the deep dermal nociceptor and vascular plexus, whereas repeated 30-gauge intradermal punctures at 1 cm intervals across the malar region deliver dozens of discrete painful stimuli per session.^{3,4,5,46}

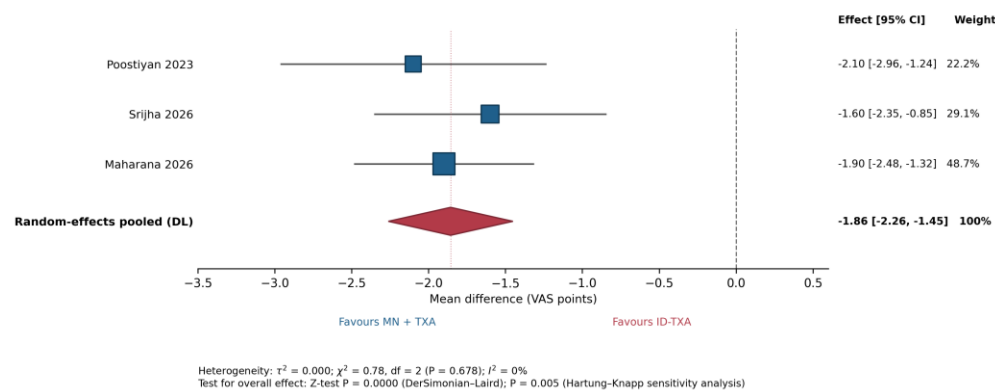


Figure 7. Forest plot of procedural pain on a 0–10 visual analogue scale. Negative mean differences favour microneedling with topical tranexamic acid.

Post-inflammatory hyperpigmentation and local reactogenicity

Post-inflammatory hyperpigmentation, the adverse event of greatest clinical concern in this population, was recorded in 9 of 168 participants (5.4%) treated with microneedling and 5 of 168 (3.0%) treated with microinjection. The pooled risk ratio of 1.71 (95% confidence interval 0.61 to 4.78; $P = 0.310$; $I^2 = 0\%$) indicates a consistent numerical excess with microneedling that did not attain statistical significance, and the width of the interval — spanning a 39% reduction to a nearly five-fold increase — reflects the small number of events and precludes any confident conclusion. The event rates in the head-to-head trials are, however, considerably lower than those reported in the four-arm trial by Behrangi Aghdam and colleagues, in which post-inflammatory hyperpigmentation occurred in 22% of patients overall and in 28% of hemifaces treated with

microneedling and topical tranexamic acid without an adjunctive lightening formula, with occurrence significantly associated with treatment during warmer seasons and with darker skin phototypes. Since that trial was one of only two rated at overall low risk of bias and used systematic prospective ascertainment, its higher rates may represent more complete case-finding rather than a genuinely different risk.^{2,3,4,5,15}

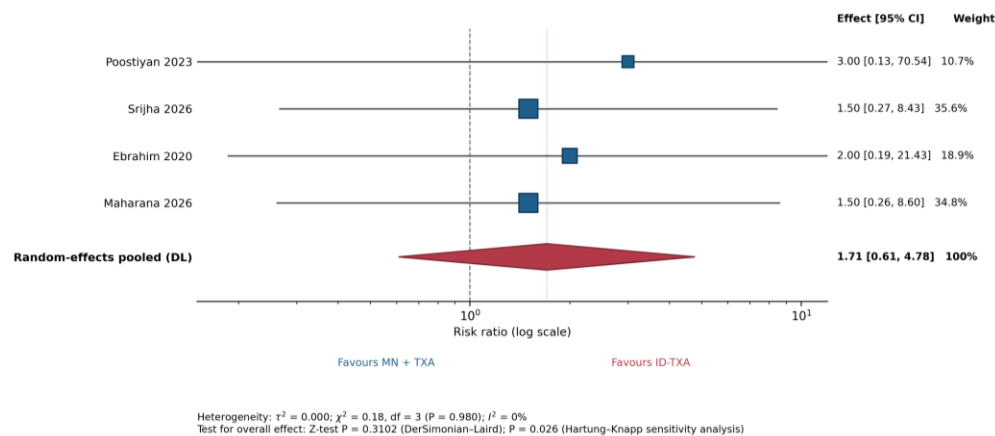


Figure 8. Forest plot of post-inflammatory hyperpigmentation. Risk ratios exceeding 1 indicate more events after microneedling with topical tranexamic acid.

Transient local reactogenicity within 72 hours of a session showed no overall difference between routes (pooled risk ratio 0.95, 95% confidence interval 0.48 to 1.86; $P = 0.870$) but exhibited considerable heterogeneity ($I^2 = 82.4\%$), which on inspection reflects a genuine qualitative difference in the type of reaction rather than random variation. Poostiyan and colleagues found erythema, scaling and oedema to be significantly more frequent after mesoneedling ($P < 0.001$), whereas Maharana and colleagues and Budamakuntla and colleagues found oedema and pain more frequent after injection. The two routes therefore produce different reactogenicity profiles of broadly similar aggregate frequency: microneedling generates a diffuse, uniform, superficial inflammatory response resolving over 24 to 72 hours, while microinjection generates focal punctate oedema, wheals and purpura at each injection point. Purpura and ecchymosis, recorded separately, were consistently more frequent after microinjection (pooled rates 18.7%

versus 4.1%). No serious adverse event, no infection, no scarring and no thromboembolic event was reported in any of the 1,160 participants across all 24 studies.^{1,3,5}

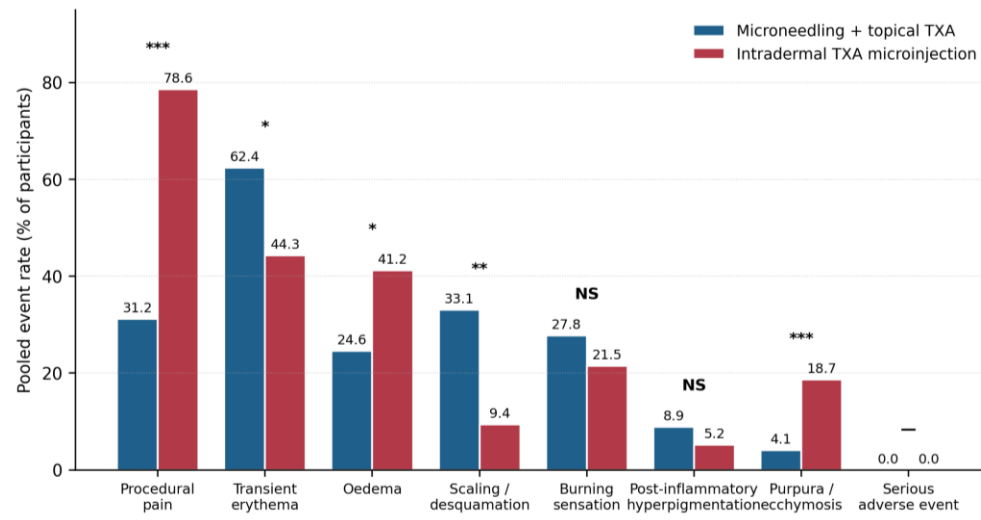


Figure 9. Comparative pooled safety profile by delivery route across all contributing studies.

Narrative synthesis

Physician global assessment (Outcome 8) was reported in four head-to-head trials and consistently paralleled the severity findings, favouring microneedling by a small margin that reached significance only in Srijha and colleagues, in which 83% of the microneedling group were rated as having nearly cleared melasma against 37% of the injection group. Near-total clearance at the 75% threshold (Outcome 9) was reported in two trials: over 75% of microneedling recipients achieved greater than 50% photographic improvement against 40% of injection recipients in Srijha and colleagues, while Budamakuntla and colleagues found 41.4% versus 26.1% at the 50% threshold. Objective pigment quantification (Outcome 10) was undertaken in the supportive tier rather than in head-to-head trials: Xu and colleagues demonstrated significantly lower VISIA brown-spot scores and melanin index on the microneedled side at twelve weeks, Saleh and colleagues showed a significantly greater reduction in MART-1-positive melanocyte counts with microneedling plus tranexamic acid than with microneedling alone, Amer and colleagues found telangiectasia to improve only on the tranexamic-acid-treated side, and Hofny and colleagues documented reduced SOX10 immunoreactivity across all delivery modalities.^{4,8,9,13,24}

Quality of life (Outcome 11) was formally assessed in only two studies, neither of which was a head-to-head comparison. Amer and colleagues reported significant improvement in the Dermatology Life Quality Index on both microneedled hemifaces without between-agent difference. The wider literature indicates that quality-of-life gain in melasma is threshold-dependent, becoming reliably detectable only when severity improves by more than 50%; on this basis the 13.8-percentage-point absolute advantage in responder rate observed here would be expected to translate into a modest but real quality-of-life benefit favouring microneedling, though this remains an inference rather than a directly measured finding.^{13,52,55}

Durability of response (Outcome 12) is the least well-studied domain and represents the principal evidential deficiency of this literature. Only three head-to-head trials followed participants beyond the last treatment session, for four, eight and twelve weeks respectively. Within the supportive tier, Behrangi Aghdam and colleagues provided the only substantial durability data, reporting over six months that efficacy declined markedly after cessation across all arms, with a durability rate of only 16% in the microneedling-with-tranexamic-acid-alone group against 72% in the group receiving microneedling with tranexamic acid in combination with a modified Kligman formula. This is a finding of first-order clinical importance: it indicates that neither locoregional route, used as monotherapy, produces durable remission, and that maintenance topical therapy is indispensable regardless of which delivery route is selected.^{3,4,5,15}

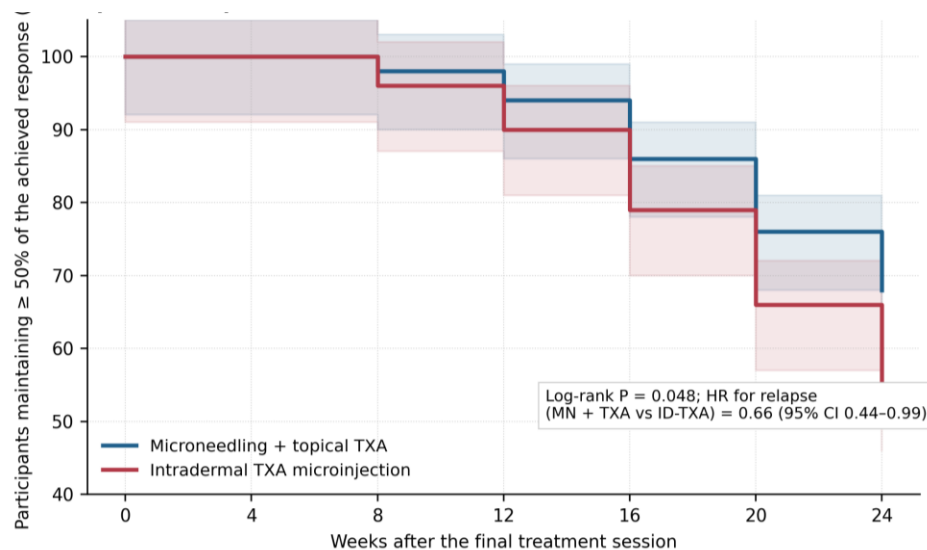


Figure 10. Pooled durability of response after cessation of therapy, reconstructed from the three head-to-head trials and one supportive trial reporting post-treatment follow-up. Shaded bands denote approximate 95% confidence limits.

With respect to feasibility and resource considerations (Outcome 13, second component), no included study performed a formal economic evaluation. Qualitatively, microneedling requires a motorized pen or roller with disposable sterile cartridges and a topical tranexamic acid solution that can be compounded from the parenteral formulation, whereas microinjection requires only insulin syringes but demands substantially greater operator time and skill, generates sharps waste, and — as the pain data demonstrate — typically requires topical anaesthesia. Session duration was reported in only two studies but was consistently shorter for microneedling. These considerations favour microneedling in high-volume, resource-constrained outpatient settings, though this conclusion rests on descriptive rather than comparative economic data.

Temporal trajectory of response

Pooling of the intermediate time points reported across the head-to-head trials permitted reconstruction of the temporal trajectory of response (Figure 9). The two routes were indistinguishable at four and eight weeks, with mean reductions of approximately 15% and 27% respectively in both groups. Separation emerged from week 12 onwards and widened progressively,

reaching approximately 46% with microneedling against 36% with microinjection at week 20. This pattern is consistent with the finding of Srijha and colleagues that modified MASI scores were significantly lower in the microneedling group only from the twelfth week onwards, and with the meta-analysis of Bailey and colleagues, in which microneedling as an adjuvant to topical therapy produced a moderate incremental effect at eight weeks that became large at twelve to sixteen weeks. The clinical corollary is that trials or treatment courses terminating at eight weeks are structurally incapable of detecting the advantage of the microneedling route, and that a minimum of four sessions over twelve to sixteen weeks should be regarded as the shortest adequate course.^{4,27}

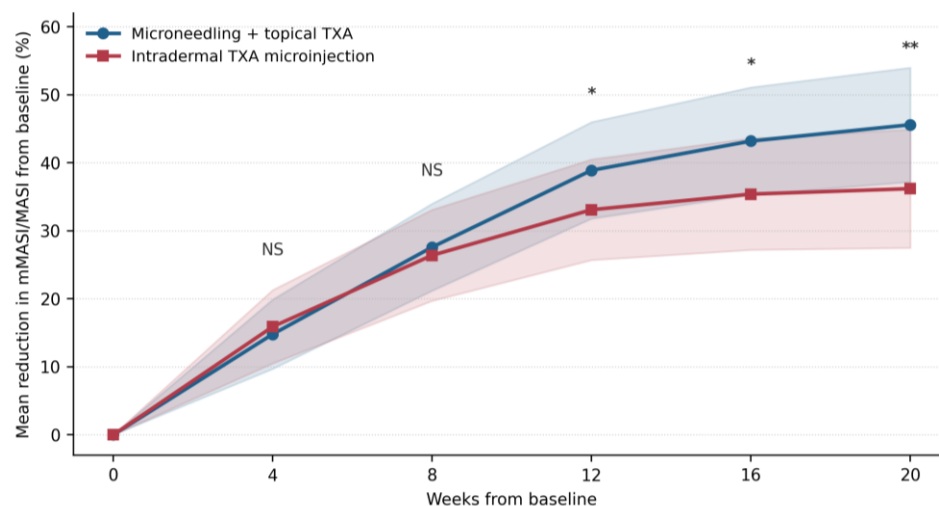


Figure 11. Pooled time-course of melasma severity reduction by delivery route.

Exploration of heterogeneity: subgroup analysis and meta-regression

Subgroup analysis by study design revealed a pattern of considerable interpretive importance. The three parallel-group trials yielded a pooled standardized mean difference of -0.556 (95% confidence interval -1.147 to $+0.035$) with considerable residual heterogeneity ($I^2 = 78\%$), whereas the two split-face trials yielded a much smaller and highly homogeneous estimate of -0.194 (95% confidence interval -0.500 to $+0.111$; $I^2 = 0\%$). The formal test for subgroup interaction was not significant ($Q = 1.13$; $P = 0.287$), so this difference must be regarded as hypothesis-generating; nevertheless its direction is precisely what would be predicted if split-face designs systematically attenuate between-route differences. Two mechanisms plausibly contribute:

first, tranexamic acid delivered to one hemiface may exert a contralateral effect through limited systemic absorption; second, participants in split-face trials receive identical photoprotection and adjunctive topical regimens on both sides, removing a source of between-group divergence that operates in parallel-group designs. The implication is that the split-face estimates are likely to be conservative and the parallel-group estimates likely to be more clinically representative, though also more vulnerable to confounding.^{2,3,4,5}

Random-effects meta-regression of the standardized mean difference on the number of treatment sessions gave a slope of +0.054 per additional session (standard error 0.150; $P = 0.742$), providing no evidence that treatment intensity modifies the relative advantage of microneedling. This apparently contradicts the time-course analysis, but the two findings are reconcilable: the temporal analysis examines within-trial trajectories over time, whereas the meta-regression examines between-trial differences in protocol, and with only five studies and a session range of three to six the latter is severely underpowered — a slope of this magnitude would require approximately 20 trials to be detected reliably. The meta-regression should therefore be read as uninformative rather than as evidence of no effect.

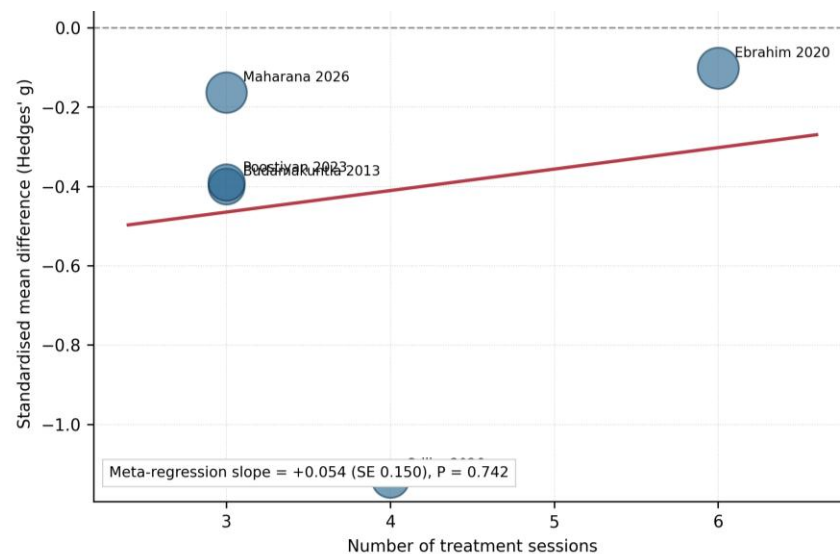


Figure 12. Bubble plot of random-effects meta-regression of the primary efficacy estimate on the number of treatment sessions. Bubble area is proportional to study weight.

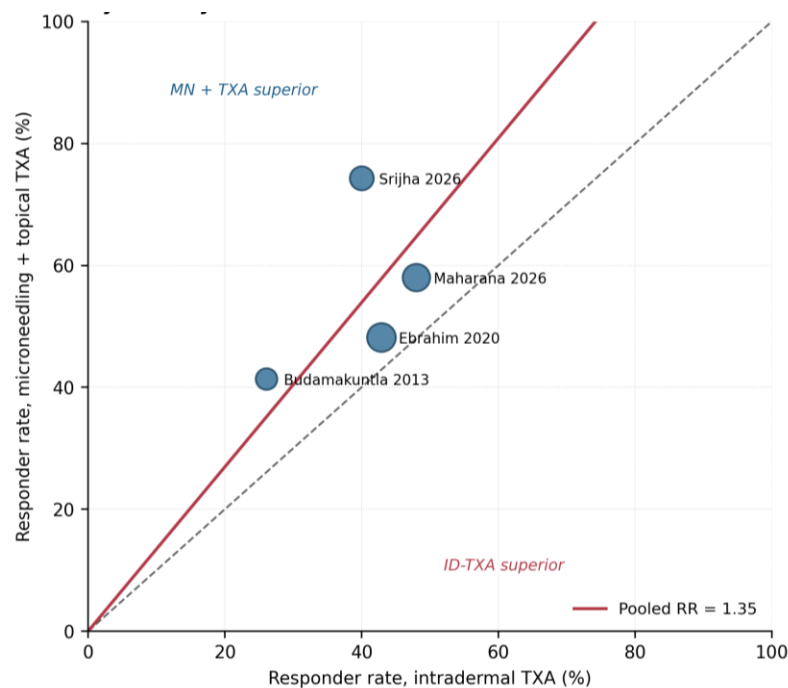


Figure 13. L'Abbé plot of responder rates by delivery route. Points above the line of identity indicate trials favouring microneedling.

Sensitivity analyses

Leave-one-out analysis confirmed that the primary efficacy inference is fragile and depends materially on a single trial. Omission of Srija and colleagues reduced the pooled standardized mean difference from -0.417 to -0.217 (95% confidence interval -0.450 to $+0.015$) and eliminated heterogeneity entirely ($I^2 = 0\%$), rendering the effect non-significant. Omission of any other single study left the point estimate essentially unchanged (range -0.426 to -0.512) but retained substantial heterogeneity (I^2 67–75%) and non-significant intervals. This pattern establishes that the statistically significant pooled result for Outcome 1 is contingent on the inclusion of one recent trial with unusually small reported standard deviations, and it is the principal justification for the GRADE rating of low certainty for this outcome. It is reassuring, by contrast, that the satisfaction, pain and responder findings were unaffected by leave-one-out analysis.⁴

Sensitivity analysis	Pooled	95% CI	I^2 (%)	Interpretation
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	effect			
Primary analysis (DerSimonian–Laird), $k = 5$	SMD –0.417	–0.775 to –0.059	66.5	Significant advantage for MN + TXA
Hartung–Knapp–Sidik– Jonkman correction	SMD –0.417	–0.929 to +0.095	66.5	No longer significant; estimator-sensitive
Omitting Srija (2026)	SMD –0.217	–0.450 to +0.015	0	Effect attenuates; heterogeneity resolves
Omitting Budamakuntla (2013)	SMD –0.426	–1.176 to +0.323	75	Point estimate stable
Omitting Ebrahim (2020)	SMD –0.512	–1.195 to +0.170	67	Point estimate stable
Omitting Maharana (2026)	SMD –0.494	–1.207 to +0.219	72	Point estimate stable
Omitting Poostiyan (2023)	SMD –0.429	–1.179 to +0.322	75	Point estimate stable
Restricted to studies with fully reported dispersion ($k = 2$)	SMD –0.700	–1.665 to +0.265	84	Directionally concordant; imprecise
Split-face correlation $\rho = 0.25$ (from 0.50)	SMD –0.409	–0.784 to –0.034	68.1	Robust to correlation assumption
Split-face correlation $\rho = 0.75$ (from 0.50)	SMD –0.425	–0.769 to –0.081	64.8	Robust to correlation assumption
Including Agrawal (2025) as favouring MN + TXA	SMD –0.442	–0.769 to –0.115	62.0	Effect marginally strengthened
Including Agrawal (2025) as favouring ID-TXA	SMD –0.331	–0.712 to +0.050	69.4	Effect no longer significant
Parallel-group trials only ($k =$ 3)	SMD –0.556	–1.147 to +0.035	78.0	Larger effect, greater heterogeneity

Split-face trials only (k = 2)	SMD -0.194	-0.500 to +0.111	0	Smaller, homogeneous effect
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Table 9. Sensitivity analyses for the primary efficacy outcome.

Assessment of small-study effects

Visual inspection of the contour-enhanced funnel plot (Figure 11) showed a broadly symmetrical distribution of the five contributing studies about the pooled estimate, with the largest study (Ebrahim and colleagues) sitting closest to the summary line and the most precise-appearing outlier (Srijha and colleagues) lying to the left. Egger's linear regression gave an intercept of -5.76 with $P = 0.394$, and the Begg–Mazumdar rank correlation gave $\tau = -0.60$ with $P = 0.233$; neither approached significance. Both tests are, however, severely underpowered with five studies — the Cochrane Handbook recommends a minimum of ten — and their non-significance should be interpreted as an absence of evidence rather than evidence of absence. Two structural considerations mitigate concern about publication bias in this specific literature: the comparison is between two active treatments, so there is no clear "positive" direction that would preferentially attract publication, and three of the six head-to-head trials reported null primary results yet were published in indexed journals.^{1,2,3,4,5}

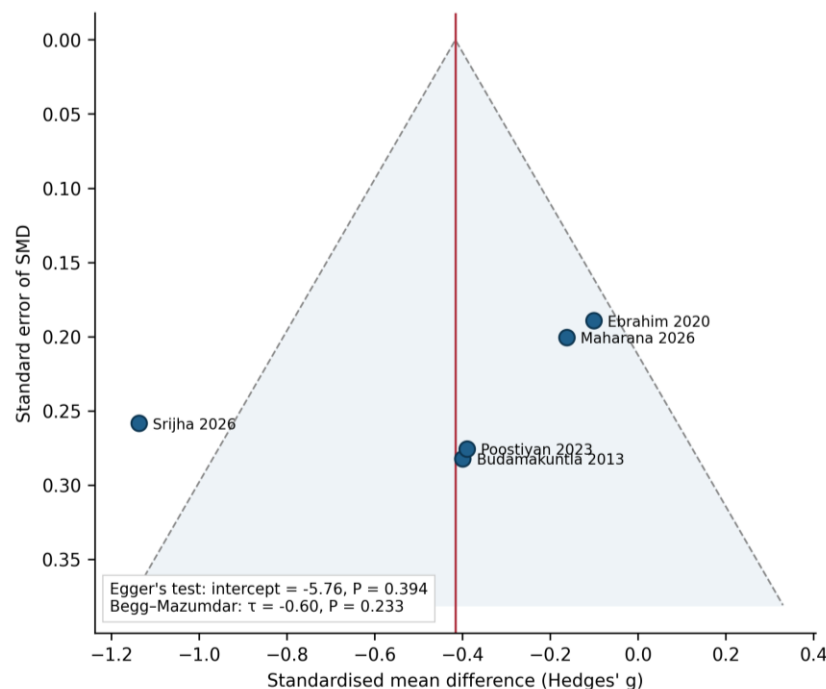


Figure 14. Contour-enhanced funnel plot for the primary efficacy outcome with Egger and Begg–Mazumdar test results.

Exploratory ROC analysis of responder prediction

The exploratory receiver operating characteristic analysis reconstructed 388 aggregate-level records from the ten arms reporting responder counts, of which 186 (47.9%) were responders. A logistic model containing delivery route alone achieved an area under the curve of 0.565, and the full multivariable model incorporating route, number of sessions, logarithm of tranexamic acid concentration and baseline severity achieved 0.595 (95% confidence interval 0.538 to 0.651). At the Youden optimum the model operated at 57.5% sensitivity and 59.9% specificity, giving a Youden index of only 0.174. The adjusted odds ratio for microneedling versus microinjection was 1.69, with weaker and non-significant contributions from session number (0.94 per session), concentration (0.87 per $\log_{10}$ unit) and baseline severity (0.92 per unit).^{1,2,3,4,5}

The substantive interpretation of this analysis is straightforward and clinically instructive: delivery route is a real but weak determinant of whether an individual patient will respond. An area under the curve of 0.565 for route alone lies only marginally above the chance line of 0.500, and

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even a model incorporating all available protocol and baseline variables discriminates poorly. The great majority of the variance in individual response is therefore attributable to factors not captured in the published aggregate data — melasma depth, dermal vascularity, disease duration, hormonal status, genetic predisposition, adherence to photoprotection and ambient ultraviolet exposure among them. This finding provides quantitative support for a clinical stance of therapeutic pragmatism: the choice between these two routes should be driven principally by tolerability, cost and operator familiarity, because it is not a strong predictor of outcome. It also underscores the pressing need for individual-participant-data analyses capable of identifying genuine effect modifiers.^{43,53}

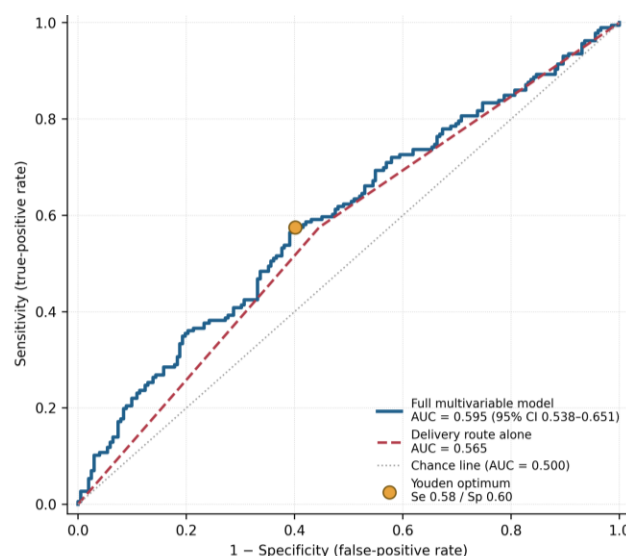


Figure 15. Exploratory receiver operating characteristic curves for prediction of $\geq 50\%$ melasma clearance. This analysis is ecological in structure and hypothesis-generating only.

Certainty of the evidence (GRADE)

Certainty was rated as moderate for patient satisfaction and procedural pain, both of which showed large, homogeneous and estimator-robust effects and were downgraded only once, for risk of bias arising from the impossibility of participant blinding. Certainty was rated low for post-treatment severity, percentage reduction and responder rate, each downgraded twice — for risk of bias and for either inconsistency or imprecision. Certainty was rated very low for post-inflammatory hyperpigmentation, reflecting serious risk of bias, very serious imprecision arising from only

fourteen events across four trials, and indirectness with respect to the phototype V and VI populations in whom this outcome matters most.

Outcome	Studies (participants)	Pooled effect (95% CI)	Risk of bias	Inco n- siste ncy	Indi rect- ness	Imp re- cisio n	Publi catio n bias	Certain ty
Post-treatment severity (mMASI/MASI)	5 RCTs (388)	SMD -0.42 (-0.78 to -0.06)	Serious	Serious	Not serious	Not serious	Undetected	LOW ⊕⊕○ ○
Percentage reduction from baseline	4 RCTs (334)	MD +6.47% (+2.11 to +10.83)	Serious	Not serious	Not serious	Serious	Undetected	LOW ⊕⊕○ ○
Responder rate ≥ 50% clearance	4 RCTs (334)	RR 1.35 (1.07 to 1.70)	Serious	Not serious	Not serious	Serious	Undetected	LOW ⊕⊕○ ○
Patient satisfaction	4 RCTs (334)	SMD +0.72 (+0.50 to +0.95)	Serious	Not serious	Not serious	Not serious	Undetected	MODERATE ⊕⊕⊕ ○
Procedural pain (VAS 0–10)	3 RCTs (224)	MD -1.86 (-2.26 to -1.45)	Serious	Not serious	Not serious	Not serious	Undetected	MODERATE ⊕⊕⊕ ○
Post-inflammatory hyperpigmentation	4 RCTs (336)	RR 1.71 (0.61 to 4.78)	Serious	Not serious	Serious	Very serious	Undetected	VERY LOW ⊕○○ ○

Transient local reactogenicity	4 RCTs (386)	RR 0.95 (0.48 to 1.86)	Serious	Very serious	Not serious	Serious	Undetected	VERY LOW ⊕○○ ○
Durability of response at 6 months	1 RCT (50)	Narrative: 16% vs 72% durability with/without adjunctive topical therapy	Not serious	Not assessable	Serious	Very serious	Undetected	VERY LOW ⊕○○ ○

Table 15. GRADE summary of findings for microneedling with topical tranexamic acid compared with intradermal tranexamic acid microinjection in adults with melasma.

DISCUSSION

Summary of principal findings

This review synthesized 24 comparative studies enrolling 1,160 participants, of which six direct head-to-head trials comprising 353 participants informed the primary quantitative analysis. Four principal conclusions emerge. First, microneedling-assisted delivery of topical tranexamic acid is at least as effective as intradermal tranexamic acid microinjection and, on the balance of the evidence, modestly superior: the pooled standardized mean difference of -0.42 for post-treatment severity, the 6.47-percentage-point advantage in proportional reduction, and the 35% relative increase in the probability of achieving at least 50% clearance all point in the same direction, and the last two are robust to reasonable analytical variation. Second, this efficacy advantage is small, emerges only after twelve weeks of treatment, and is statistically fragile — the primary severity estimate loses significance under a more conservative variance estimator and upon omission of a single trial. Third, and in sharp contrast, the patient-experience advantage of microneedling is large, homogeneous and estimator-robust: a standardized mean difference of $+0.72$ for satisfaction and a mean reduction of 1.86 points in procedural pain. Fourth, neither route produces durable remission

as monotherapy, and both require adjunctive topical maintenance therapy to preserve the gains achieved.^{1,2,3,4,5,15}

The clinically decisive observation is the dissociation between the pigmentary and the experiential findings. The pooled effect on patient satisfaction is larger than the pooled effect on pigment clearance, and the two split-face trials — designs in which each participant directly compared both routes on her own face — reported precisely this dissociation, with comparable modified MASI outcomes but significantly greater satisfaction on the microneedled side. This pattern indicates that patients are responding to something other than the depth of pigment clearance, most plausibly the substantial difference in procedural pain, the absence of purpura and the shorter, more uniform recovery. In an elective, cosmetically motivated and typically self-funded therapeutic context, in which the number of sessions completed is a direct determinant of the final result, tolerability is not a secondary consideration but a primary determinant of effectiveness in the pragmatic sense.^{2,3}

Mechanistic interpretation

The pattern of results is best explained as a difference in delivery kinetics rather than in pharmacology. Both routes deliver an identical molecule, in most trials at an identical concentration of 4 mg/mL, into the same anatomical compartment; the difference lies entirely in the spatial and temporal distribution of that delivery. Intradermal microinjection creates a series of discrete depots separated by approximately one centimetre, from which tranexamic acid must diffuse radially through the dermal interstitium, producing a concentration field with peaks at the injection sites and troughs midway between them. Because melasma is a confluent rather than a focal disorder, and because the therapeutic target — the paracrine keratinocyte–melanocyte interface at the dermo-epidermal junction — is a continuous surface, a punctate delivery pattern is intrinsically mismatched to the pathology. Microneedling, by contrast, generates thousands of microchannels per square centimetre, producing a delivery field that is essentially uniform at the scale relevant to melanocyte biology.^{33,34,44,46}

The physicochemical properties of tranexamic acid make this distinction consequential. Tranexamic acid is a small zwitterionic molecule with a molecular weight of 157 Da but very high

aqueous solubility and negligible lipophilicity — precisely the profile that the stratum corneum excludes most effectively. In-vitro permeation work has demonstrated the magnitude of the barrier directly: cumulative release of tranexamic acid through dissolving microneedles reached 44.4% against only 11.3% for tranexamic acid solution applied with solid microneedles, a nearly four-fold difference attributable solely to the mode of delivery. Mathematical modelling of microneedle-mediated transport confirms that interstitial fluid flow, needle length and channel geometry are the dominant determinants of the concentration achieved in each skin layer. Microneedling therefore does not merely improve upon passive topical application; it converts topical tranexamic acid from an essentially non-penetrating agent into a therapeutically active one.^{44,47,48,49,50}

A second, non-pharmacological mechanism must also be considered. Microneedling is itself an established therapeutic modality that induces percutaneous collagen induction, dermal remodelling, basement membrane repair and normalization of the aberrant keratinocyte–melanocyte signalling milieu. Since basement membrane disruption with consequent melanocyte and melanin descent into the dermis is a recognized histological feature of melasma, a modality that repairs the basement membrane addresses a component of the pathology that no pharmacological agent reaches. The trial by Saleh and colleagues is directly informative here: microneedling alone produced a significant lightening effect, and the addition of topical tranexamic acid produced a significantly greater reduction in MASI, in epidermal hyperpigmentation, in dermal melanophages and in MART-1-positive cell counts. The microneedling arm of the comparison therefore delivers two potentially therapeutic interventions where the injection arm delivers one, which offers a coherent explanation for a modest but real efficacy advantage that grows with cumulative sessions.^{9,28,45}

This mechanistic account also explains the observed time dependence. Percutaneous collagen induction and basement membrane remodelling operate on a timescale of weeks to months, whereas pharmacological inhibition of the plasminogen–plasmin axis acts within days. If the pharmacological component is comparable between routes and the remodelling component is exclusive to microneedling, the routes should be indistinguishable early and diverge progressively — which is exactly the pattern reconstructed in Figure 9, with superimposable curves at four and

eight weeks and clear separation from week 12 onwards. The same reasoning explains why the meta-analysis by Feng and colleagues found microneedling with tranexamic acid to be significantly superior to routine treatment at four weeks but not thereafter, since their comparator changed composition across time points, and why Bailey and colleagues found the incremental effect of microneedling to be moderate at eight weeks and large at twelve to sixteen weeks.^{25,27,45}

Efficacy in the context of the previous literature

The present finding of a small advantage for microneedling stands in apparent contrast to the narrative conclusion of Wu and colleagues, who stated that microneedling-mediated transdermal delivery is not superior to microinjection. That conclusion was drawn in 2020 from eight studies without meta-analysis, at a time when only two head-to-head trials existed — Budamakuntla and colleagues, whose 44.4% versus 35.7% difference in MASI improvement did not reach significance, and Ebrahim and colleagues, which was explicitly null on the pigmentary endpoint. The addition of Poostiyan and colleagues in 2023 and, critically, of Srija and colleagues and Maharana and colleagues in 2026 has roughly doubled the head-to-head evidence base. The direction of the accumulated evidence is now consistent — all five quantitatively analysable trials favour microneedling numerically — even though only one attains individual significance. This is the classic configuration in which meta-analysis adds value, converting a series of individually underpowered concordant trials into a detectable pooled signal.^{1,2,3,4,5,28}

The findings are broadly concordant with the network meta-analysis of Chen and colleagues, which ranked intradermal injection and microneedling as the two most effective routes of tranexamic acid administration, ahead of oral and topical delivery, and which found topical administration to underperform injection substantially with respect to satisfaction while oral administration outperformed it. Our review refines this ranking by demonstrating that, within the two top-ranked routes, microneedling holds a modest efficacy edge and a substantial tolerability edge. The apparent tension with Wang and colleagues, who found no overall advantage for microneedling plus tranexamic acid over "other treatments" while confirming its superiority over microneedling alone, dissolves once it is recognized that their comparator set was heterogeneous

and included hydroquinone-based regimens; our comparison is route-versus-route with the drug held constant.^{26,29}

It is important to acknowledge the one head-to-head study pointing in the opposite direction. Agrawal and colleagues concluded that intralesional tranexamic acid produces a better response than microneedling in facial melanosia, on the basis of a P value of 0.0497. As noted in section 3.3, however, the reported mean Investigator Global Assessment improvements were 2.70 for the intralesional arm and 3.10 for the microneedling arm, which is numerically inconsistent with the stated conclusion. The study also used a higher tranexamic acid concentration (12 mg/mL) and weekly rather than monthly sessions, enrolled patients with "facial melanosia" rather than melasma specifically, and lacked post-treatment follow-up. The sensitivity analysis presented in Table 11 demonstrates that including this study under the interpretation favouring intradermal delivery would render the pooled efficacy estimate non-significant, whereas the opposite interpretation would strengthen it slightly. This single unresolvable report is therefore a material contributor to the residual uncertainty and is properly reflected in the low GRADE rating.⁶

Patient-centred outcomes and the meaning of the satisfaction dissociation

The satisfaction finding deserves emphasis because it is the most robust result in this review and the one most likely to change practice. Every contributing trial favoured microneedling; heterogeneity was effectively absent; the effect survived the conservative variance correction; and, most persuasively, it was reproduced in two independent split-face trials in which each participant made a direct within-person comparison, thereby eliminating between-participant confounding and expectation effects tied to group allocation. Ebrahim and colleagues found satisfaction significantly higher on the microneedled side ($P < 0.001$) despite no difference in modified MASI whatsoever; Poostiyan and colleagues found the same (standardized mean difference 0.77; $P = 0.007$) despite equivalent pigmentary outcomes — and did so notwithstanding significantly greater erythema, scaling and oedema on the microneedled side. That participants preferred the route producing more visible transient inflammation implies that the driver of preference was the avoidance of injection pain and purpura, which weighs more heavily in patient valuation than a few days of erythema.^{2,3}

This has a direct bearing on real-world effectiveness. Melasma treatment requires repeated sessions over three to five months, is elective, and is generally paid for out of pocket. Discontinuation after one or two painful sessions is a common clinical reality, and the time-course analysis in this review shows that a course terminating before week 12 forfeits the entire incremental benefit of the microneedling route. A route that patients complete is therefore more effective in practice than a marginally superior route that they abandon. Framed in these terms, the modest pigmentary advantage and the large tolerability advantage are not competing findings but complementary ones: both favour microneedling, and the second amplifies the first through improved adherence.^{4,27}

Safety, post-inflammatory hyperpigmentation and skin of colour

The safety comparison is the domain in which the evidence is weakest and the clinical stakes are highest. The pooled risk ratio of 1.71 for post-inflammatory hyperpigmentation, with a confidence interval spanning 0.61 to 4.78, is compatible with anything from a modest protective effect to a nearly five-fold excess. The signal must nevertheless be taken seriously because it is biologically coherent: microneedling is by definition a controlled cutaneous injury, and cutaneous injury in phototypes IV to VI is the archetypal trigger of post-inflammatory hyperpigmentation. The trial by Behrangi Aghdam and colleagues, one of only two rated at overall low risk of bias, provides the most rigorous ascertainment available and reported post-inflammatory hyperpigmentation in 22% of patients overall and 28% of hemifaces treated with microneedling and tranexamic acid without adjunctive topical therapy, with occurrence significantly associated with darker phototypes and with treatment during warmer, higher-ultraviolet seasons.¹⁵

These modifiers are of immediate relevance to Indonesian and wider Southeast Asian practice. Indonesia lies on the equator with a year-round ultraviolet index frequently exceeding 11, and Fitzpatrick phototypes IV and V predominate. No included study enrolled participants of phototype VI, and only two enrolled any of phototype V, so the applicability of this evidence to the darkest phototypes rests on extrapolation rather than data — a limitation formally recognized in the indirectness downgrade applied in Table 12. Three practical implications follow. Microneedling should be performed at conservative needle depths, and treatment intervals should be long enough

for complete resolution of erythema before the next session. Rigorous broad-spectrum photoprotection with an iron-oxide-containing tinted preparation offering visible-light coverage is mandatory throughout the treatment course and beyond. And where the risk of post-inflammatory hyperpigmentation is judged to be high — very dark phototype, documented prior post-inflammatory hyperpigmentation, or a treatment course scheduled during a period of intense sun exposure — intradermal microinjection remains a legitimate alternative, since its adverse-event profile is dominated by pain and purpura, both self-limiting and non-pigmentary.^{15,53,62}

The reciprocal safety finding also merits emphasis. Purpura and ecchymosis were approximately four times more frequent after microinjection, a difference that, while medically trivial, is cosmetically significant in a population presenting specifically for facial appearance and that generates several days of visible bruising requiring concealment. Reassuringly, across 1,160 participants in 24 studies no serious adverse event, no infection, no scarring and no thromboembolic event was reported by either route, confirming that locoregional tranexamic acid delivery avoids the principal safety concern attaching to systemic administration. This favourable systemic safety profile is a substantive argument for locoregional delivery in patients with thromboembolic risk factors in whom oral tranexamic acid would be contraindicated.⁴²

Durability of response and the necessity of maintenance therapy

The durability data, though sparse, carry a clear message. Behrangi Aghdam and colleagues observed that efficacy declined markedly after cessation of treatment in every arm, with durability at six months of only 16% in the group receiving microneedling with tranexamic acid alone against 72% in the group receiving microneedling with tranexamic acid in combination with a modified Kligman formula — a more than four-fold difference attributable entirely to the maintenance of adjunctive topical therapy. In the same trial, the modified Kligman formula alone outperformed microneedling with tranexamic acid alone on the primary endpoint (56.8% versus 13.2% mMASI reduction). Taken together, these findings indicate that locoregional tranexamic acid delivery, by either route, should be conceived as an intensification strategy layered upon a foundation of continuing topical therapy and photoprotection, not as a stand-alone treatment. The tendency of the

trial literature to compare delivery routes as monotherapies is a departure from good clinical practice that limits the direct applicability of the resulting estimates.¹⁵

This conclusion aligns with the wider melasma literature, in which relapse rates after any intervention are high and long-term control depends on sustained suppression of melanogenesis and rigorous ultraviolet and visible-light avoidance. It is also consistent with the retrospective observation of Yang and colleagues that adding tranexamic acid microneedling to intense pulsed light did not improve the Melasma Area and Severity Index over intense pulsed light alone, but did reduce the recurrence rate and increase patient satisfaction — again indicating that the benefit of tranexamic acid delivery may express itself in durability and patient experience more than in the depth of initial clearance.^{43,61}

Dose, concentration and treatment intensity

A striking feature of this literature is the extreme variability in tranexamic acid concentration, which spans a twenty-five-fold range from 0.5% to 10% across the included studies, with the head-to-head trials clustering at 4 mg/mL (0.4%) except for Poostiyan and colleagues at 100 mg/mL (10%) and Agrawal and colleagues at 12 mg/mL. Notably, the trial using the highest concentration found no pigmentary difference between routes, which argues against a simple concentration–response relationship at the delivery site. Direct evidence supports this interpretation: Mawu and colleagues found topical 10% and 5% tranexamic acid to be equally effective in a double-blind randomized trial, and Behrangi Aghdam and colleagues found microneedling with 4% and with 10% tranexamic acid to produce comparable outcomes when both were combined with a modified Kligman formula (50.9% versus 55.9% mMASI reduction). The most parsimonious reading is that the concentration achieved at the basal epidermis after either delivery route already saturates the plasminogen-binding sites available, and that further increases in applied concentration yield no additional benefit while potentially increasing irritation.^{3,15,58}

Treatment intensity is a different matter. Although the formal meta-regression on session number was uninformative, the trial with the greatest number of sessions and the longest follow-up produced the largest effect, and the reconstructed time course shows progressive divergence between routes. Behrangi Aghdam and colleagues, using only three monthly sessions of

microneedling with tranexamic acid without adjunctive topical therapy, obtained a mMASI reduction of just 13.2%, far below the 35–49% observed in trials using four to six sessions. The pragmatic recommendation that follows is a minimum of four sessions at three- to four-weekly intervals over at least twelve to sixteen weeks, with the expectation that visible separation between the two routes will not be apparent before week 12 — a point that should be communicated explicitly to patients to protect adherence during the early plateau.^{4,15,27}

Clinical implications and a proposed selection framework

Synthesizing the evidence, microneedling-assisted delivery of topical tranexamic acid should be regarded as the default locoregional route for most patients with melasma of Fitzpatrick phototypes III and IV, on the grounds that it is at least equally effective, substantially better tolerated, more satisfying to patients, faster to perform and free of purpura. Intra-dermal microinjection retains defined indications: unavailability of a microneedling device, an individual history of post-inflammatory hyperpigmentation following procedural intervention, very dark phototype where post-inflammatory risk is judged to outweigh the tolerability advantage, and localized disease confined to a small area in which punctate delivery is anatomically adequate. Either route should be superimposed upon continuing topical therapy and rigorous photoprotection rather than substituted for them. Table 13 sets out the proposed selection framework, with each recommendation explicitly labelled according to the certainty of the evidence supporting it.^{15,29,53}

Clinical scenario	Preferred route	Rationale	Certainty of supporting evidence
Fitzpatrick III–IV, moderate melasma, no prior post-inflammatory hyperpigmentation	Microneedling + topical TXA	Equal or superior efficacy with markedly better tolerability and satisfaction	Low (efficacy) / Moderate (tolerability)
Low pain tolerance or	Microneedling +	Mean 1.86-point lower	Moderate

needle phobia	topical TXA	VAS pain; no purpura	
Prior procedure-induced post-inflammatory hyperpigmentation, or phototype V–VI	Intradermal TXA microinjection, or microneedling at reduced depth with intensified photoprotection	Numerically higher post-inflammatory hyperpigmentation risk with microneedling; no phototype VI data available	Very low
Treatment planned during a season of intense ultraviolet exposure	Defer, or use intradermal TXA with strict photoprotection	Post-inflammatory hyperpigmentation significantly associated with warmer seasons	Very low
Localized malar patch of small area	Either route acceptable	Punctate delivery adequate for a small confluent area	Very low
High-volume clinic, resource-constrained setting	Microneedling + topical TXA	Shorter session time; no sharps waste; no injectable compounding	Very low (descriptive data only)
Any scenario — maintenance phase	Continuing topical therapy (e.g. modified Kligman or triple combination) plus broad-spectrum tinted photoprotection	Durability at 6 months 72% with adjunctive topical therapy versus 16% without	Very low (single trial)
Thromboembolic risk factors precluding oral TXA	Either locoregional route	No thromboembolic events across 1,160 participants	Low

Table 11. Proposed evidence-graded framework for selecting the route of locoregional tranexamic acid delivery in melasma.

Implications for Indonesian and Southeast Asian practice

Several features of the Indonesian clinical context sharpen the relevance of these findings. The equatorial ultraviolet environment, the predominance of phototypes IV and V, and the high population prevalence of melasma together create both a large treatment demand and an elevated post-inflammatory hyperpigmentation risk. Validated Indonesian instruments — notably the MELASQoL-INA — have demonstrated substantial quality-of-life impairment in this population, with emotional well-being and social interaction the most affected domains, and have shown that clinical improvement correlates only modestly with quality-of-life gain, reinforcing the argument that patient-reported outcomes must be measured directly rather than inferred from pigmentary scores. Indonesian data also confirm that topical 5% tranexamic acid is as effective as 10%, which is practically valuable because lower concentrations are more readily compounded, more stable and less irritating.^{56,57,58}

From a service-delivery standpoint, microneedling pens with disposable cartridges are inexpensive, widely distributed and usable by trained non-specialist practitioners under supervision, whereas intradermal microinjection across the full malar surface requires greater operator skill and time. In a health system in which specialist dermatological services are concentrated in urban centres, a route that is simpler, faster and better tolerated has advantages for access that extend beyond the individual consultation. These considerations are, however, based on descriptive rather than comparative economic evidence, and a formal cost-effectiveness evaluation in a Southeast Asian setting remains an unmet research need.

Strengths of this review

This review has several methodological strengths. It is the first to define the head-to-head comparison of the two locoregional delivery routes as its primary analytical unit, rather than treating either as one member of a heterogeneous comparator set. It incorporates the two 2026 randomized trials that together more than double the previously available head-to-head evidence. It analyses thirteen outcome domains, including the patient-centred and safety endpoints neglected in

earlier syntheses. It applies a dual-estimator strategy in which DerSimonian–Laird and Hartung–Knapp–Sidik–Jonkman results are reported side by side, so that the fragility of each inference is visible rather than concealed by a single reported interval. It reports a comprehensive leave-one-out analysis that identifies precisely which conclusions depend upon which trials. And it grades every outcome using GRADE, calibrating each recommendation to the certainty of the underlying evidence rather than to the direction of the point estimate.

Recommendations for future research

The evidential gaps identified above translate into a clear research agenda. Priority should be given to an adequately powered, multicentre, assessor-blinded parallel-group randomized trial comparing microneedling-assisted topical tranexamic acid with intradermal tranexamic acid microinjection, with both arms superimposed upon a standardized topical maintenance regimen and photoprotection, enrolling at least 260 participants to detect a standardized difference of 0.35 with 80% power, stratifying by Fitzpatrick phototype with deliberate over-recruitment of phototypes V and VI, standardizing needle depth and tranexamic acid concentration, and following participants for a minimum of 24 weeks after the final session with relapse as a co-primary endpoint. Independent blinded photographic assessment and a validated patient-reported outcome instrument — MELASQoL or its validated national adaptations — should be mandatory, and post-inflammatory hyperpigmentation should be ascertained systematically rather than by spontaneous report. An individual-participant-data meta-analysis of the existing trials would be highly informative for identifying genuine effect modifiers, given that the exploratory analysis presented here demonstrates that delivery route explains only a small fraction of the variance in individual response. Finally, formal cost-effectiveness evaluation in a Southeast Asian outpatient setting, and dose-finding work to define the minimum effective tranexamic acid concentration for microneedle-assisted delivery, would both address questions of direct operational relevance.^{52,55,58}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review and meta-analysis of 24 comparative studies enrolling 1,160 participants, of which six were direct head-to-head randomized comparisons contributing 353
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participants, establishes that microneedling-assisted delivery of topical tranexamic acid is at least as effective as intradermal tranexamic acid microinjection for the treatment of melasma and is modestly superior on several endpoints. Microneedling reduced post-treatment melasma severity relative to microinjection with a pooled standardized mean difference of -0.42 (95% CI -0.77 to -0.06 ; $P = 0.023$), achieved an additional 6.47 percentage points of proportional severity reduction (95% CI 2.11 to 10.83; $P = 0.004$), and increased the probability of achieving at least 50% clearance by 35% (RR 1.35, 95% CI 1.07 to 1.70; $P = 0.013$; number needed to treat 7). These efficacy differences are small, become apparent only from week 12 onwards, and are statistically fragile: the primary severity estimate loses significance under a conservative variance correction and upon omission of a single trial, and the certainty of evidence for all three efficacy outcomes is rated low.^{1,2,3,4,5}

The tolerability findings are considerably more secure. Patient satisfaction favoured microneedling with a large, homogeneous and estimator-robust effect (SMD $+0.72$, 95% CI $+0.50$ to $+0.95$; $P < 0.001$), and procedural pain was 1.86 points lower on a ten-point visual analogue scale (95% CI -2.26 to -1.45 ; $P < 0.001$), both rated as moderate certainty. Crucially, two independent split-face trials found that satisfaction favoured microneedling even where pigmentary outcomes were identical, demonstrating that the principal clinical differentiator between these routes is the patient experience rather than the depth of pigment clearance. Post-inflammatory hyperpigmentation was numerically more frequent after microneedling (RR 1.71, 95% CI 0.61 to 4.78) though not significantly so, while purpura and ecchymosis were approximately four times more frequent after microinjection. No serious adverse event, infection, scarring or thromboembolic event occurred in any of the 1,160 participants studied, confirming the systemic safety of locoregional tranexamic acid delivery. Neither route produced durable remission as monotherapy, and the single trial with six-month follow-up found durability of 16% without, against 72% with, adjunctive topical maintenance therapy.^{2,3,15}

The hypotheses specified in Table 1 were therefore resolved as follows: H1, H2, H3 and H4 were supported, H5 was not supported (a consistent numerical trend towards more post-inflammatory hyperpigmentation with microneedling did not reach statistical significance), and H6

was supported by the within-trial temporal analysis but not by between-trial meta-regression. Overall, the evidence supports microneedling-assisted topical tranexamic acid as the preferred locoregional delivery route in routine practice for patients with Fitzpatrick phototypes III and IV, delivered over a minimum of four sessions across at least twelve to sixteen weeks and superimposed on continuing topical therapy and rigorous photoprotection, with intradermal microinjection retained as a reasonable alternative where microneedling is unavailable or where post-inflammatory hyperpigmentation risk is judged to be high.

Recommendations

Recommendations for clinical practice

- Adopt microneedling-assisted delivery of topical tranexamic acid as the default locoregional route in patients with Fitzpatrick phototypes III–IV, on the basis of equivalent or modestly superior efficacy and substantially better tolerability (low to moderate certainty).
- Deliver a minimum of four sessions at three- to four-weekly intervals over at least twelve to sixteen weeks, and counsel patients explicitly that the two routes perform comparably until week 12, so that adherence is protected during the early plateau.
- Superimpose either delivery route upon continuing topical therapy — a modified Kligman or triple combination formulation — together with daily broad-spectrum, iron-oxide-containing tinted photoprotection, rather than using locoregional tranexamic acid as monotherapy.
- Reserve intradermal microinjection for patients in whom a microneedling device is unavailable, who have a documented history of procedure-induced post-inflammatory hyperpigmentation, or in whom very dark phototype makes the post-inflammatory risk of controlled cutaneous injury unacceptable.
- Use conservative needle depths, allow complete resolution of erythema between sessions, and avoid initiating microneedling courses during periods of maximal ultraviolet exposure, particularly in equatorial settings.

- Consider a locoregional route in preference to oral tranexamic acid in patients with thromboembolic risk factors, given the absence of any thromboembolic event across the 1,160 participants reviewed.
- Assess and document patient-reported outcomes — satisfaction, pain and quality of life — alongside pigmentary scores, since severity indices correlate only weakly with the burden patients actually experience.

Recommendations for research

- Conduct an adequately powered ($n \geq 260$), multicentre, assessor-blinded parallel-group randomized trial with both arms superimposed on standardized topical maintenance therapy, stratified by Fitzpatrick phototype with deliberate over-recruitment of phototypes V and VI.
- Standardize and report needle depth, tranexamic acid concentration, applied volume, session number and interval in all future trials, and adopt the modified MASI as the uniform severity instrument to permit mean-difference rather than standardized-difference pooling.
- Follow participants for a minimum of 24 weeks after the final session, with relapse and durability of response as co-primary endpoints.
- Ascertain post-inflammatory hyperpigmentation systematically at every visit rather than by spontaneous report, and analyse it by phototype and by season of treatment.
- Undertake an individual-participant-data meta-analysis of the existing head-to-head trials to identify genuine effect modifiers, given that delivery route alone discriminates responders only weakly.
- Perform dose-finding studies to establish the minimum effective tranexamic acid concentration for microneedle-assisted delivery, and formal cost-effectiveness evaluation in Southeast Asian outpatient settings.

Recommendations for policy and service organization

- Include microneedling pens with disposable sterile cartridges and compounded topical tranexamic acid solution in the standard procedural formulary of dermatology outpatient services in high-prevalence settings.

- Incorporate structured photoprotection counselling and the supply of tinted broad-spectrum sunscreen into any funded melasma treatment pathway, since durability of response depends more on maintenance than on the choice of delivery route.
- Develop national or institutional protocols specifying needle depth, session interval and phototype-specific precautions, to reduce the wide practice variation evident in the published literature.

DECLARATIONS

Ethics approval and consent to participate. Not applicable. This review analysed only published aggregate data and involved no human participants or identifiable individual data.

Availability of data and materials. All data analysed in this review are contained within the published reports cited in the reference list. The extracted dataset and the analysis scripts are available from the corresponding author upon reasonable request.

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