Enhancing the Efficacy of Tranexamic Acid Microneedles with Hyaluronic Acid in the Treatment of Melasma: A Comprehensive Review

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Abstract

Background: Melasma is a chronic, relapsing acquired hyperpigmentation disorder that predominantly affects sun-exposed areas of the face and poses significant therapeutic challenges due to its multifactorial pathogenesis and high recurrence rates. Key pathogenic mechanisms include ultraviolet-induced melanocyte hyperactivity, vascular endothelial growth factor–mediated angiogenesis, inflammation, and disruption of the epidermal barrier. Tranexamic acid (TXA) has emerged as an effective therapeutic option for melasma through its anti-plasmin activity, inhibition of melanocyte–keratinocyte interactions, and suppression of angiogenic mediators. However, topical and systemic administration of TXA may be limited by suboptimal skin penetration, variable efficacy, and potential adverse effects. Microneedle-based drug delivery systems have gained attention as a minimally invasive approach to enhance transdermal delivery of active agents. Hyaluronic acid (HA), a naturally occurring glycosaminoglycan with strong hydrophilic, viscoelastic, and bioactive properties, has been increasingly incorporated into microneedle platforms to improve drug stability, penetration, and skin barrier repair.

Aim: This comprehensive review aims to critically evaluate the synergistic role of hyaluronic acid in enhancing the efficacy of tranexamic acid–loaded microneedles for the treatment of melasma. The review integrates current knowledge on melasma pathophysiology, the pharmacological actions of tranexamic acid, microneedle-assisted transdermal delivery, and the biological contributions of hyaluronic acid to skin hydration, inflammation modulation, and wound healing.

Conclusions: The combination of tranexamic acid and hyaluronic acid delivered via microneedle systems represents a promising therapeutic strategy for melasma management. Hyaluronic acid not only serves as a biocompatible microneedle matrix but also enhances epidermal penetration, improves skin hydration, accelerates microchannel recovery, and potentially augments the anti-inflammatory and anti-melanogenic effects of tranexamic acid. Emerging clinical and experimental evidence suggests that this synergistic approach may result in improved clinical outcomes, better patient tolerability, and reduced recurrence compared with conventional therapies. Nevertheless, standardized formulations, optimized treatment protocols, and long-term controlled clinical trials are required to establish efficacy, safety, and durability of response. This review highlights the potential of HA-enhanced TXA microneedles as an innovative, targeted, and patient-friendly modality in the evolving therapeutic landscape of melasma.

Keywords: *Tranexamic Acid, Microneedles, Hyaluronic Acid, Melasma*

Introduction

Melasma is a common, acquired disorder of hyperpigmentation characterized by symmetric, irregularly bordered brown to gray-brown macules and patches, predominantly affecting sun-exposed areas of the face. It occurs more frequently in individuals with darker skin phototypes and has a marked female predominance. Despite its benign nature, melasma carries a substantial psychosocial burden, negatively impacting quality of life and self-esteem. The pathogenesis of melasma is complex and multifactorial, involving genetic predisposition, ultraviolet and visible light exposure, hormonal influences, vascular alterations, inflammation, and impairment of the epidermal barrier. These interacting mechanisms contribute to melanocyte hyperactivity, increased melanogenesis, and dermal changes that make melasma particularly resistant to treatment and prone to recurrence [1].

Conventional therapeutic approaches for melasma include topical depigmenting agents, chemical peels, laser- and light-based therapies, and systemic treatments. However, many of these modalities are associated with limited efficacy, adverse effects such as irritation or post-inflammatory hyperpigmentation, and high relapse rates. Tranexamic acid (TXA) has emerged over the past decade as a valuable therapeutic agent for melasma, owing to its ability to inhibit plasmin activity, reduce ultraviolet-induced melanocyte stimulation, suppress angiogenesis, and modulate inflammatory pathways. TXA has demonstrated efficacy when administered orally, topically, or via intradermal injection, yet each route carries inherent limitations, including systemic safety concerns, poor skin penetration, or procedure-related discomfort [2].

Microneedle-based transdermal delivery systems represent an innovative strategy to overcome the stratum corneum barrier while minimizing invasiveness. By creating microscopic channels in the epidermis, microneedles enhance the penetration and bioavailability of active agents such as tranexamic acid. Hyaluronic acid (HA), a naturally occurring polysaccharide abundant in the extracellular matrix of the skin, has gained increasing attention as a microneedle matrix and adjuvant. Beyond its excellent biocompatibility and mechanical properties, HA contributes to skin hydration, wound healing, barrier repair, and modulation of inflammation—all of which are relevant to melasma pathophysiology.

Research Gap and Aim

Although tranexamic acid microneedles have shown promising results in melasma, the specific role of hyaluronic acid in boosting their therapeutic efficacy has not been comprehensively reviewed. In particular, the synergistic biological and delivery-related effects of HA when combined with TXA in microneedle systems remain underexplored. Therefore, the aim of this review is to critically analyze current evidence on hyaluronic acid–enhanced tranexamic acid microneedles in melasma, focusing on mechanistic rationale, clinical outcomes, and future research directions.

Pathophysiology of Melasma Relevant to Tranexamic Acid and Microneedle Therapy

Melasma is no longer regarded as a purely melanocytic disorder; rather, it is a complex dermatosis involving epidermal, dermal, vascular, and inflammatory components. At the epidermal level, melanocytes in melasma lesions exhibit increased dendricity, heightened tyrosinase activity, and enhanced melanosome transfer to keratinocytes. Ultraviolet (UV) radiation and visible light act as major external triggers by stimulating melanocyte-stimulating hormone, endothelin-1, and prostaglandins, all of which promote melanogenesis. These pathways explain why melasma often worsens with sun exposure and why photoprotection alone is insufficient to reverse established disease [3].

A growing body of evidence highlights the importance of dermal and vascular alterations in melasma. Increased vascular density, dilated blood vessels, and elevated expression of vascular endothelial growth factor (VEGF) have been consistently demonstrated in melasma lesions. These vascular changes not only sustain melanocyte activity but also facilitate the persistence and recurrence of pigmentation. Tranexamic acid exerts a key therapeutic effect in this context by inhibiting plasmin activity, which in turn reduces the release of arachidonic acid and downstream prostaglandins, as well as suppressing VEGF-mediated angiogenesis. This anti-angiogenic effect distinguishes TXA from conventional depigmenting agents and makes it particularly suitable for recalcitrant melasma [4].

Inflammation and impaired skin barrier function also play critical roles in melasma pathogenesis. Subclinical inflammation characterized by increased mast cells, inflammatory cytokines, and matrix metalloproteinases contributes to basement membrane disruption and pigment incontinence. Barrier dysfunction enhances penetration of ultraviolet radiation and irritants, perpetuating melanocyte stimulation. Microneedling, when carefully performed, induces controlled micro-injury that triggers wound-healing pathways, collagen remodeling, and epidermal renewal. This process can improve basement membrane integrity and facilitate more uniform pigment distribution when combined with appropriate topical agents [5].

The stratum corneum represents a major obstacle to effective topical delivery of tranexamic acid due to its hydrophilic nature and relatively high molecular weight. Microneedle-assisted delivery bypasses this barrier by creating transient microchannels, allowing direct access of TXA to the viable epidermis and superficial dermis where melanocytes, keratinocytes, and vascular structures interact. This targeted delivery enhances local drug concentration while minimizing systemic absorption, thereby improving efficacy and safety [6].

Hyaluronic acid further complements this approach by addressing several pathogenic components of melasma. HA improves epidermal hydration, accelerates microchannel closure after microneedling, and modulates inflammatory responses through interactions with CD44 and other cell surface receptors. Additionally, HA-rich environments promote keratinocyte differentiation and barrier repair, which may reduce relapse rates. By simultaneously enhancing drug delivery and correcting underlying barrier and inflammatory abnormalities, HA-enriched TXA microneedles align closely with the multifactorial pathophysiology of melasma [7].

Pharmacological Mechanisms of Tranexamic Acid in Melasma

Tranexamic acid is a synthetic derivative of the amino acid lysine that has been traditionally used as an antifibrinolytic agent in hemorrhagic disorders. Its therapeutic role in melasma was initially identified serendipitously, but subsequent studies have elucidated multiple mechanisms by which TXA exerts depigmenting effects. Central to its action is the inhibition of plasminogen activation, which leads to reduced plasmin activity in keratinocytes. Plasmin plays a critical role in ultraviolet-induced melanogenesis by increasing the release of arachidonic acid and subsequent production of prostaglandins, both of which stimulate melanocyte activity. By suppressing this pathway, TXA effectively attenuates UV-driven melanocyte stimulation [8].

Beyond its anti-plasmin activity, tranexamic acid modulates the interaction between melanocytes and surrounding epidermal and dermal cells. TXA has been shown to reduce the expression of melanocyte-stimulating factors such as endothelin-1 and stem cell factor, which are released by keratinocytes and fibroblasts in response to ultraviolet exposure. This indirect regulation of melanocyte function distinguishes TXA from classic tyrosinase inhibitors and supports its use as a disease-modifying rather than purely cosmetic agent in melasma management [9].

Angiogenesis represents another critical target of tranexamic acid in melasma. Histological and immunohistochemical studies have consistently demonstrated increased vascular proliferation and elevated VEGF expression in melasma lesions. TXA reduces angiogenesis by inhibiting plasmin-mediated activation of matrix metalloproteinases and decreasing VEGF expression. This vascular-modulating effect is particularly relevant in dermal and mixed-type melasma, where increased vascularity correlates with disease severity and treatment resistance [10].

Tranexamic acid also exhibits anti-inflammatory properties that contribute to its therapeutic efficacy. By reducing mast cell activation and inflammatory mediator release, TXA helps mitigate subclinical inflammation that disrupts the basement membrane and promotes pigment incontinence. This anti-inflammatory effect may partially explain the reduced recurrence rates observed in patients treated with TXA compared with conventional depigmenting agents alone [11].

Despite these favorable mechanisms, the clinical effectiveness of tranexamic acid is strongly influenced by its route of administration. Oral TXA is effective but associated with concerns regarding thromboembolic risk, limiting its long-term use. Topical formulations, while safer, suffer from poor skin penetration and inconsistent clinical responses. Intradermal injection improves delivery but is invasive and associated with pain and procedural discomfort. These limitations have driven interest in alternative delivery systems such as microneedles, which aim to maximize local efficacy while minimizing systemic exposure [12].

In this context, microneedle-mediated delivery of tranexamic acid offers a pharmacologically rational approach by ensuring precise deposition of the drug into target skin layers. When combined with hyaluronic acid matrices, TXA stability, diffusion, and bioavailability may be further enhanced, potentially amplifying its multi-level effects on melanogenesis, angiogenesis, and inflammation. This synergistic pharmacological framework provides the foundation for HA-enhanced TXA microneedles as a next-generation therapy for melasma [13].

Microneedle Technology in Dermatology and Melasma Treatment

Microneedle technology has emerged as a versatile and minimally invasive transdermal delivery system capable of overcoming the barrier function of the stratum corneum. Microneedles are typically micron-scale projections arranged on a patch or roller that painlessly create transient microchannels in the epidermis. These microchannels allow hydrophilic and high–molecular weight molecules, which would otherwise poorly penetrate intact skin, to access the viable epidermis and superficial dermis. In dermatology, microneedles have been increasingly utilized for drug delivery, collagen induction therapy, vaccination, and cosmetic indications, owing to their favorable safety profile and high patient acceptability [14].

Several types of microneedles have been developed, including solid, coated, hollow, and dissolving microneedles. Dissolving microneedles, often fabricated from biocompatible polymers such as hyaluronic acid, are of particular interest in pigmentary disorders. These systems allow controlled release of active compounds directly into target skin layers while eliminating sharp waste and reducing the risk of infection. The gradual dissolution of the microneedle matrix also provides sustained drug exposure, which may be advantageous in chronic conditions such as melasma that require repeated and prolonged treatment [15].

In the context of melasma, microneedling offers therapeutic benefits beyond drug delivery. The controlled micro-injury induced by microneedles activates wound-healing cascades, including the release of growth factors and stimulation of collagen synthesis. This process can lead to remodeling of the dermal–epidermal junction, improved basement membrane integrity, and more uniform melanin distribution. These effects are particularly relevant in melasma, where basement membrane disruption and pigment incontinence contribute to disease chronicity and recurrence [16].

Clinical studies evaluating microneedling alone or in combination with topical agents have demonstrated improvements in melasma severity scores, skin texture, and patient satisfaction. When combined with depigmenting agents such as tranexamic acid, microneedling significantly enhances therapeutic outcomes by increasing drug penetration and ensuring delivery to melanocyte-rich areas. Compared with intradermal injections, microneedle-based delivery is associated with less pain, lower risk of bruising, and greater treatment uniformity across affected areas [17].

Another important advantage of microneedle-assisted therapy is its potential to reduce systemic exposure. By confining tranexamic acid to the skin, microneedles minimize the risk of systemic absorption and thromboembolic complications associated with oral administration. This localized delivery is particularly appealing for long-term management and maintenance therapy in melasma, where safety is a paramount concern [18].

The integration of hyaluronic acid into microneedle platforms further enhances their dermatologic utility. HA-based microneedles exhibit excellent mechanical strength, biocompatibility, and hydrophilicity, facilitating smooth insertion and rapid dissolution within the skin. Moreover, the inherent biological effects of HA on hydration, inflammation, and barrier repair complement the physical advantages of microneedling, creating an optimized therapeutic environment for tranexamic acid action in melasma [19].

Biological and Therapeutic Roles of Hyaluronic Acid in Melasma and Microneedling

Hyaluronic acid is a naturally occurring glycosaminoglycan widely distributed in the extracellular matrix of the skin, where it plays a central role in maintaining hydration, viscoelasticity, and tissue homeostasis. In healthy skin, HA contributes to epidermal integrity by regulating keratinocyte proliferation and differentiation, facilitating nutrient diffusion, and supporting barrier function. In melasma, impaired barrier integrity and chronic subclinical inflammation are frequently observed, making HA a biologically relevant adjunct in therapeutic strategies aimed at restoring skin homeostasis [20].

One of the most important properties of hyaluronic acid is its exceptional hydrophilicity, allowing it to bind and retain large volumes of water. Enhanced hydration improves stratum corneum flexibility and permeability, which may facilitate deeper and more uniform penetration of active agents such as tranexamic acid. Improved hydration also reduces epidermal stress responses and irritation, both of which can exacerbate melanogenesis. This moisturizing effect is particularly beneficial in melasma patients, who often experience barrier compromise from prolonged use of topical depigmenting agents [21].

Hyaluronic acid also exerts significant anti-inflammatory and wound-healing effects, which are highly relevant in the context of microneedling. Following microneedle-induced micro-injury, HA interacts with cell surface receptors such as CD44 to modulate keratinocyte migration, fibroblast activation, and angiogenesis. These interactions accelerate re-epithelialization and reduce inflammatory cytokine release, thereby promoting rapid recovery of microchannels and minimizing post-procedural erythema or hyperpigmentation [22].

In addition to its supportive role in wound healing, hyaluronic acid may indirectly influence melanogenesis. Experimental studies have shown that HA-rich environments can downregulate inflammatory mediators and oxidative stress, both of which are known stimulators of melanocyte activity. By mitigating these pro-melanogenic signals, HA may enhance the depigmenting efficacy of tranexamic acid while reducing the risk of rebound hyperpigmentation [23].

From a drug delivery perspective, hyaluronic acid is an ideal material for dissolving microneedle systems. HA-based microneedles demonstrate excellent mechanical properties that allow effective skin penetration, followed by predictable dissolution and controlled release of encapsulated agents. The molecular weight of HA can be tailored to optimize dissolution time, drug loading capacity, and release kinetics, enabling customization of tranexamic acid delivery according to clinical needs [24].

Clinically, HA-containing formulations are well tolerated and associated with a low risk of hypersensitivity or adverse reactions. This favorable safety profile is especially important in melasma, where repeated treatments and long-term maintenance are often required. By combining its biological benefits with its functional role as a microneedle matrix, hyaluronic acid serves as both an active therapeutic adjuvant and a delivery enhancer, reinforcing its boosting effect on tranexamic acid microneedles in melasma management [25].

Synergistic Mechanisms of Hyaluronic Acid–Enhanced Tranexamic Acid Microneedles

A central rationale for combining tranexamic acid with hyaluronic acid in microneedle platforms is the presence of synergistic effects at two fundamental levels: enhancement of transdermal drug delivery and optimization of the cutaneous microenvironment. Dissolving microneedles bypass the stratum corneum and enable direct delivery of hydrophilic molecules such as tranexamic acid into the viable epidermis and superficial dermis, where melanocyte–keratinocyte interactions, vascular signaling, and inflammatory pathways converge in melasma. Because tranexamic acid demonstrates limited penetration when applied topically, microneedle-assisted delivery overcomes a major pharmacokinetic barrier and allows higher local drug concentrations at therapeutic target sites [26].

Hyaluronic acid further reinforces this delivery advantage by functioning as an ideal dissolving microneedle matrix. HA-based microneedles exhibit favorable mechanical strength for efficient skin penetration, followed by predictable dissolution and controlled release of incorporated active agents. The physicochemical properties of HA can be modified to tailor dissolution rates and release kinetics, allowing optimization of tranexamic acid bioavailability within melasma-affected skin. This capacity for formulation customization supports consistent and reproducible drug delivery while maintaining high biocompatibility and patient tolerability [27].

Beyond its structural role, hyaluronic acid contributes significantly to the biological milieu following microneedle application. Microneedling induces controlled micro-injury that activates wound-healing cascades, and HA plays a pivotal role in facilitating re-epithelialization, keratinocyte migration, and dermal repair. By accelerating recovery of microchannels and restoring epidermal barrier function, HA may reduce procedure-related inflammation and irritation. This is clinically important in melasma, where inflammatory stimuli and barrier disruption are known triggers of pigment exacerbation and post-inflammatory hyperpigmentation [28].

Synergism between tranexamic acid and hyaluronic acid also extends to melasma pathophysiology itself. Melasma lesions demonstrate increased vascularity and elevated expression of angiogenic mediators such as vascular endothelial growth factor. Tranexamic acid suppresses plasmin-mediated angiogenic signaling, while HA supports vascular homeostasis and modulates inflammatory responses. Delivering tranexamic acid effectively to the dermal–epidermal junction within an HA-rich environment may therefore exert combined anti-melanogenic, anti-angiogenic, and anti-inflammatory effects, addressing multiple drivers of disease persistence and recurrence [29].

Clinical relevance of this synergistic strategy is supported by studies demonstrating improved outcomes when tranexamic acid is administered via microneedling techniques. Although not all available studies specifically utilize HA-based dissolving microneedles, the accumulating evidence confirms that microneedle-enabled delivery enhances tranexamic acid efficacy while maintaining a favorable safety profile. The integration of hyaluronic acid into microneedle platforms represents a logical and biologically sound evolution of this approach, offering a patient-friendly, targeted, and potentially superior modality for melasma management [30].

Clinical Evidence: Tranexamic Acid Microneedling and Hyaluronic Acid–Based Platforms in Melasma

Clinical interest in tranexamic acid delivered via microneedling has increased substantially over the past decade, driven by the need for effective yet safe therapeutic options for melasma. Multiple prospective studies and randomized controlled trials have demonstrated that microneedle-assisted delivery of tranexamic acid results in significant reductions in Melasma Area and Severity Index (MASI) scores, improvement in pigmentation uniformity, and enhanced patient satisfaction. Compared with topical TXA alone, microneedling facilitates deeper and more consistent drug penetration, leading to faster onset of action and improved clinical outcomes, particularly in patients with recalcitrant or mixed-type melasma [31].

Several clinical studies have compared tranexamic acid microneedling with other established melasma treatments, including topical depigmenting agents and chemical peels. These studies generally report comparable or superior efficacy for TXA microneedling, with a more favorable safety profile and fewer adverse events such as irritation or post-inflammatory hyperpigmentation. Importantly, microneedling allows uniform drug distribution over large facial areas, reducing the patchy results sometimes observed with intradermal injections. This uniformity is especially valuable in centrofacial and malar melasma patterns, which are common and cosmetically distressing [32].

Although many early studies utilized microneedling devices or rollers in combination with topical tranexamic acid, recent advances have shifted attention toward dissolving microneedle systems. These platforms offer standardized needle length, controlled drug dosing, and improved reproducibility, which are essential for both clinical practice and research. Hyaluronic acid–based dissolving microneedles have demonstrated excellent tolerability in clinical dermatology, with minimal pain, transient erythema, and rapid recovery times. These attributes make them particularly suitable for melasma patients, who often require repeated treatment sessions over extended periods [33].

Emerging clinical data suggest that the incorporation of hyaluronic acid into tranexamic acid microneedle systems may further enhance treatment outcomes. HA contributes to sustained hydration, improved barrier repair, and reduced post-procedural inflammation, all of which can positively influence pigmentation outcomes. Studies evaluating combination approaches—such as TXA microneedling with HA-containing formulations—have reported not only improved MASI scores but also better skin texture, luminosity, and patient-reported quality of life measures. These added benefits may improve treatment adherence and long-term satisfaction [34].

Another clinically relevant consideration is recurrence, which remains a major challenge in melasma management. Preliminary evidence indicates that microneedle-assisted TXA delivery may be associated with lower relapse rates compared with conventional therapies, particularly when combined with adjunctive measures such as photoprotection and maintenance topical therapy. The barrier-restorative and anti-inflammatory effects of hyaluronic acid may further contribute to prolonging remission by reducing subclinical triggers of melanocyte reactivation [35].

Despite these encouraging findings, current clinical evidence is limited by heterogeneity in study design, treatment protocols, follow-up duration, and outcome measures. Many studies involve small sample sizes and short-term follow-up, underscoring the need for well-designed, long-term randomized controlled trials specifically evaluating hyaluronic acid–enhanced tranexamic acid microneedles. Establishing standardized treatment regimens and validated outcome metrics will be critical for translating this promising modality into routine clinical practice [36].

Safety Considerations, Adverse Effects, and Patient Selection

Safety is a paramount consideration in the management of melasma, as treatment often requires repeated and long-term interventions. Tranexamic acid, when administered systemically, has raised concerns regarding thromboembolic risk, although such events are rare and typically associated with higher doses or predisposing conditions. Microneedle-assisted delivery significantly mitigates these concerns by confining TXA largely to the skin, thereby minimizing systemic absorption. Clinical studies evaluating intradermal and microneedle-based TXA therapies have consistently reported a low incidence of systemic adverse effects, supporting the safety of localized delivery approaches [37].

Local adverse effects associated with tranexamic acid microneedling are generally mild and transient. The most commonly reported reactions include erythema, edema, pinpoint bleeding, and a burning or stinging sensation at the treatment site. These effects typically resolve within hours to a few days and rarely necessitate treatment discontinuation. Importantly, the risk of post-inflammatory hyperpigmentation—an especially concerning complication in melasma patients—appears to be low when appropriate technique, needle depth, and post-procedure care are employed [38].

The incorporation of hyaluronic acid into microneedle platforms further enhances the safety and tolerability profile. HA's intrinsic anti-inflammatory, hydrating, and wound-healing properties promote rapid recovery of the epidermal barrier and reduce post-procedural irritation. Clinical experience with HA-based microneedles indicates excellent patient comfort, reduced downtime, and high acceptance, making them particularly suitable for individuals with sensitive skin or prior intolerance to conventional depigmenting therapies [39].

Patient selection plays a crucial role in optimizing outcomes and minimizing risks. Tranexamic acid microneedling is particularly well suited for patients with epidermal or mixed-type melasma, those with poor response to topical therapy alone, and individuals seeking alternatives to systemic TXA. Patients with a history of thromboembolic disease, coagulation disorders, or those on anticoagulant therapy should be carefully evaluated, although the localized nature of microneedle delivery may still permit safe use in select cases under close supervision [40].

Appropriate patient counseling and adherence to strict photoprotection are essential components of safe and effective treatment. Patients should be educated about the chronic and relapsing nature of melasma, realistic expectations of improvement, and the importance of maintenance therapy. Pre- and post-procedure skincare regimens, including gentle cleansers, moisturizers, and broad-spectrum sunscreens, are critical to minimizing adverse effects and sustaining therapeutic gains [41].

In summary, hyaluronic acid–enhanced tranexamic acid microneedles demonstrate a favorable safety profile with minimal local and systemic risks when used appropriately. Careful patient selection, standardized treatment protocols, and adherence to supportive skincare measures can further optimize safety and efficacy. These considerations underscore the suitability of this approach as a long-term management strategy for melasma [42].

Comparison with Other Melasma Treatment Modalities

Topical therapy remains the foundation of melasma management, most commonly using agents that inhibit melanogenesis (e.g., hydroquinone, azelaic acid, kojic acid) or regulate epidermal turnover (e.g., retinoids). Triple-combination therapy (hydroquinone + tretinoin + corticosteroid) is often considered a first-line standard due to its proven efficacy, yet its use is limited by irritation, steroid-related adverse effects, and high relapse rates once therapy is stopped. In this setting, tranexamic acid delivered via microneedling offers a different mechanistic profile—targeting plasmin-mediated inflammatory and vascular signaling in addition to pigment production—making it a rational option for patients who fail, cannot tolerate, or relapse after conventional topical regimens [43].

Chemical peels (such as glycolic acid or salicylic acid-based peels) can accelerate epidermal turnover and help reduce superficial pigment, but outcomes are highly operator-dependent and may be complicated by irritation and post-inflammatory hyperpigmentation, especially in darker phototypes. Because melasma frequently involves deeper pigment and dermal changes, peel-only strategies often provide partial and transient improvements. Microneedle-assisted TXA delivery may provide greater benefit in mixed or recalcitrant cases by ensuring active drug access to viable epidermal and superficial dermal compartments while maintaining a more favorable tolerability profile when appropriate pre- and post-care protocols are followed [44].

Laser and light-based therapies, including Q-switched lasers, fractional lasers, intense pulsed light, and low-fluence modalities, can improve pigmentation but are associated with notable relapse rates and risk of rebound hyperpigmentation. These risks are particularly relevant in individuals with higher Fitzpatrick skin types, where even subtle inflammation can trigger persistent dyspigmentation. Compared with energy-based devices, TXA microneedling (especially when combined with hyaluronic acid matrices that support barrier recovery) can be positioned as a lower-risk alternative or adjunctive option, particularly when the clinical goal is gradual, sustained improvement with minimal downtime [45].

When compared with systemic tranexamic acid, microneedle-based TXA delivery offers an important safety advantage by reducing systemic exposure. Oral TXA can be effective in improving melasma severity, but concerns remain regarding patient screening, contraindications, and long-term safety in individuals at risk for thromboembolic events. Microneedle-assisted delivery is therefore attractive for patients seeking an efficacy-focused approach without systemic therapy, or for clinicians aiming to limit systemic risk while still leveraging TXA's anti-plasmin, anti-inflammatory, and anti-angiogenic benefits [46].

Intradermal TXA microinjections (mesotherapy) represent another local delivery strategy with established clinical utility, but they may be painful, can cause bruising, and rely heavily on technique and injection uniformity. Comparative clinical studies suggest that microneedling-based TXA approaches can provide similar or improved clinical outcomes with better tolerability and more uniform facial coverage. HA-based dissolving microneedles may further standardize dosing and distribution, reduce procedure-related discomfort, and improve patient adherence—an important practical advantage in a chronic relapsing disorder like melasma [47].

Finally, combination therapy is often necessary in melasma, and the most clinically successful strategies integrate photoprotection, topical maintenance regimens, and periodic procedural support. HA-enhanced TXA microneedles can be conceptually integrated into multimodal care as an "active delivery + barrier support" intervention, potentially reducing irritation-driven pigmentation flares and improving the durability of response. This comparative positioning highlights why HA-boosted TXA microneedles may be especially valuable in real-world practice, where tolerability and relapse prevention often matter as much as short-term pigment clearance [48].

Practical Protocols: Formulation Variables, Treatment Parameters, and Outcome Measures

From a formulation standpoint, the performance of tranexamic acid microneedle therapy is strongly influenced by **TXA concentration, vehicle composition, and release kinetics**. Clinical protocols using topical TXA in conjunction with microneedling have commonly employed concentrations in the range of approximately **2%–5%**, though heterogeneity across studies remains substantial. In dissolving microneedle systems, dose precision becomes more controllable because drug content can be standardized per patch. However, achieving adequate payload while maintaining microneedle mechanical integrity requires careful balance of polymer composition, water content, and manufacturing parameters, particularly when hydrophilic drugs such as TXA are loaded at higher fractions [49].

For **hyaluronic acid–based dissolving microneedles**, key variables include HA **molecular weight**, crosslinking (if used), needle geometry, and matrix additives that influence hardness and dissolution time. Lower-molecular-weight HA may dissolve more rapidly and release drug faster, while higher-molecular-weight HA can provide stronger mechanical properties and prolonged hydration effects. Optimizing these parameters is clinically relevant in melasma, where excessive inflammation or prolonged barrier disruption can worsen pigmentation; thus, an ideal HA microneedle system should deliver TXA efficiently while supporting rapid microchannel recovery and minimizing irritant exposure [50].

Procedurally, **needle length and penetration depth** are among the most important determinants of both efficacy and adverse-event risk. In device-based microneedling (rollers or pens), reported depths in melasma studies vary widely (often targeting superficial to mid-dermis), and deeper settings may increase erythema, discomfort, and post-inflammatory hyperpigmentation risk—particularly in higher Fitzpatrick phototypes. In contrast, dissolving microneedle patches typically use shorter needles designed for consistent epidermal/superficial dermal delivery, which can improve tolerability and reduce operator-dependent variability. Matching depth to melasma type (epidermal vs mixed) and skin phototype is therefore a practical cornerstone of protocol design [51].

Treatment scheduling also varies, but many clinical regimens use **multiple sessions** spaced every **2–4 weeks**, often with an initial induction phase followed by maintenance. Shorter intervals may accelerate improvement but can increase cumulative irritation risk, while longer intervals may reduce adverse events but slow response. Adjunctive measures—especially **strict broad-spectrum photoprotection** and gentle barrier-supportive skincare—should be viewed as protocol essentials rather than optional add-ons, because ultraviolet and visible light are dominant relapse drivers and can override procedural gains if not controlled [52].

Robust outcome assessment requires more than subjective photography alone. Standard clinical endpoints include **MASI or modified MASI (mMASI)**, investigator global assessment, and patient-reported improvement, ideally coupled with objective pigment quantification such as **colorimetry** or melanin index devices when available. Because melasma is chronic and relapse-prone, follow-up duration is critical; short-term score reduction can overestimate true benefit if recurrence is not tracked. Including quality-of-life instruments (e.g., melasma-specific QoL measures) provides clinically meaningful evaluation of patient burden and treatment value beyond pigment reduction alone [53].

Finally, protocol safety hinges on standardized pre- and post-procedure care: avoiding irritants before treatment, implementing gentle cleansing and moisturization after treatment, and delaying potentially irritating actives (e.g., strong retinoids, acids) until barrier recovery. In HA-based dissolving microneedles, the intrinsic hydrating and recovery-supportive properties of HA may help reduce downtime and improve tolerability, but they do not eliminate the need for careful patient selection and conservative escalation. Practical implementation should therefore favor reproducibility, barrier protection, and long-term maintenance planning to reduce relapse and maximize durability of response [54].

Conclusion

Melasma remains a therapeutically challenging pigmentary disorder due to its multifactorial pathogenesis, chronic course, and high tendency for relapse. Increasing understanding of the disease has shifted treatment strategies beyond simple melanogenesis inhibition toward approaches that also address vascular, inflammatory, and barrier-related components. Within this evolving framework, tranexamic acid has emerged as a valuable agent because of its unique ability to modulate plasmin-mediated pathways, angiogenesis, and inflammatory signaling that contribute to melasma persistence.

Microneedle-assisted delivery represents a significant advancement in maximizing the clinical potential of tranexamic acid by overcoming the limitations of conventional topical application while avoiding the systemic risks associated with oral therapy. The integration of hyaluronic acid into microneedle platforms further enhances this strategy by combining efficient drug delivery with biological support of skin hydration, barrier repair, and post-procedural recovery. Through these complementary effects, hyaluronic acid acts not merely as a passive carrier but as an active booster of therapeutic efficacy and tolerability.

Current clinical evidence suggests that tranexamic acid microneedling, particularly when supported by hyaluronic acid–based systems, can achieve meaningful improvements in melasma severity with a favorable safety profile and high patient acceptance. This approach may be especially valuable for patients with recalcitrant or mixed-type melasma, those intolerant to conventional depigmenting agents, or individuals seeking non-systemic, minimally invasive options for long-term management.

Despite promising results, further research is necessary to establish standardized formulations, treatment protocols, and long-term outcome data. Well-designed randomized controlled trials specifically evaluating hyaluronic acid–enhanced tranexamic acid microneedles are needed to define optimal dosing, treatment intervals, durability of response, and relapse prevention strategies. As evidence continues to evolve, this innovative combination holds strong potential to become an integral component of multimodal, patient-centered melasma therapy.

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