International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
Impact Factor (RJIF): 5.67
www.dermatologypaper.com
Derma 2025; 8(2): 43-47
Received: 12-06-2025
Accepted: 15-07-2025

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Periorbital hyperpigmentation: Current treatment modalities with a spotlight on tranexamic acid

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DOI: https://www.doi.org/10.33545/26649411.2025.v8.i2a.241

Abstract
Periorbital hyperpigmentation (POH) is a frequent, multifactorial dermatological state known by discoloration of the skin around the eyes, often resulting from dermal melanin deposition, hypermelanized basal layers, and vascular or structural factors. It affects both sexes, with a higher prevalence in females, possibly due to hormonal influences. Clinically, POH presents as brown-black pigmentation of the lower eyelids, giving a fatigued appearance, and careful examination is essential to differentiate true pigmentation from shadowing effects.
A wide range of treatment modalities exists, including topically applied depigmenting agents (hydroquinone, tretinoin, kojic acid, azelaic acid, vitamin-derived agents), chemical peels, intralesional injections (fat grafting, soft tissue fillers, platelet-rich plasma, mesotherapy, botulinum toxin, tranexamic acid), and laser or microneedling therapies. The selection of treatment is determined by the underlying pathophysiology, skin type, patient tolerance, and desired outcomes. Combination therapies, targeting multiple mechanisms such as pigmentation, vascularity, and structural volume loss, often yield the most effective results.

Keywords: Microneedling, laser, chemical peels, tranexamic acid, periorbital hyperpigmentation

Introduction
Periorbital hyperpigmentation (POH) is a prevalent and multidimensional state with diverse pathogenic origins [1]. It is also referred to as Periorbital melanosis commonly referred to as periorbital or under-eye circles, dark halos, periocular pigmentation or melanosis, infraorbital melanosis, and idiopathic cutaneous hyperchromia of the orbital region encompasses the various clinical terms used to describe hyperpigmentation and discoloration surrounding the eyes. [2].
POH is a frequent state affecting both sexes, with an elevated rate observed in females. Although comprehensive epidemiological data are lacking, the increased prevalence in women is likely influenced by hormonal determinants, which are considered to play a marked role in the enhancment of the state. [3].

Clinical Features of POH
POH is clinically recognized by hyperpigmented changes around the eyelids, appearing in shades from light brown to dark brown-black. The condition imparts a fatigued appearance to the individuals. Diagnosis is mainly reliant on clinical examination. It is essential to distinguish true POH from infraorbital shadowing secondary to tear trough anatomy. This differentiation can be achieved through manual stretching in the lower eyelid skin, true pigmentation remains visible upon stretching, whereas shadowing generally intensifies or disappears entirely. An elevation in violaceous discoloration upon stretching is attributed to reduced eyelid skin thickness or increased vascularity of the lower eyelid. [4].

Treatment of POH
Topical treatment
- **Sunscreens**
  Since excessive pigmentation is often the primary or most marked contributor to dark circles, the first-line approach for management and inhibition is the application of a

- broad-spectrum (UVA/UVB) sunscreen. Physical sunscreens consisted of zinc oxide or titanium dioxide offer effective UVA/UVB protection. While older formulations can be thick and form a powdery residue, newer silicone-based formulations are better suited for the delicate eye area. For individuals with highly sensitive skin, the application of titanium-containing concealing products may serve as a favorable alternative. [5].

- **Hydroquinone** (HQ)
  HQ is a key ingredient in topical pharmacological agents and is highly effective in reducing hyperpigmentation, though it is linked with a relatively elevated occurrence of adverse effects. HQ exerts its effect by suppressing the tyrosinase enzyme, thereby preventing the transformation of L-3,4-dihydroxyphenylalanine (L-DOPA) to melanin. Management with HQ has been shown to be beneficial but tends to be gradual, typically demanding a prescription-strength concentration of 4% for optimal findings. Elevated concentrations can be compounded if necessary, but these may cause irritation; any raise beyond 4% should be implemented gradually. Potential adverse events encompass allergic contact dermatitis and subsequent post-inflammatory hyperpigmentation. Prolonged use may result in exogenous ochronosis, particularly in individuals with deeply pigmented skin, attributed to irritation-induced overstimulation of melanocytes. Patients who respond well to therapy are usually advised to maintain results using a 2% HQ maintenance regimen. [5].

- **Tretinoin**
  It is a vitamin A acid derivative, act as a potent, though slow-acting, depigmenting agent suitable for safe application to the periocular region at a 1% concentration formulated in an emollient base. As a retinoid, tretinoin functions by dispersing pigment granules within keratinocytes, disrupting pigment transfer, and promoting epidermal turnover. Common adverse events encompass erythema and peeling, and use should be monitored for marked irritation, which may worsen current hyperpigmentation. Providing individuals with clear, comprehensive guidelines can greatly enhance treatment adherence and outcomes. [6].

- **Kojic acid or botanicals**
  Kojic acid and botanical agents as arbutin are advised for individuals who are unable to tolerate HQ. Kojic acid a naturally occurring, water-soluble derivative obtained from fungi, typically accessible in concentrations of 1% to 4%. It has efficacy comparable to HQ, though prolonged use may lead in contact dermatitis and erythematous reactions. Arbutin, derived from the bearberry plant, serves as a widely used depigmenting agent in Asia. As a hydroquinone-derived octyl-β-D-glucopyranoside, it exerts inhibitory effects on tyrosinase and is most often prepared in a 3% formulation. Dose escalation may improve effectiveness but pose a risk of causing or worsening hyperpigmentation. [5].

- **Azelaic acid**
  This naturally occurring nonphenolic compound exerts selective effects on abnormal melanocytes through inhibition of DNA synthesis and suppression of mitochondrial enzyme activity. It is considered as effective as, or superior to, 2% HQ, although it may cause pruritus in some patients. [5].

- **Antioxidants**
  Dermal antioxidant therapies, in combination with vitamin A, are gaining elevated attention in the management of hyperpigmentation. Vitamin E may assist in treating existing pigmentation, while vitamin C (L-ascorbic acid) may have a preventative role. When incorporating vitamin-based components into a treatment protocol, it is essential to consider potential interactions between ingredients. For instance, alpha-hydroxy acids and vitamin A can suppress vitamin C. Another critical consideration is the stability of these agents, as instability can significantly reduce their potency and therapeutic efficacy. [7].

- **Vitamin K**
  It is a vital nutrient essential for blood coagulation, from which its name—derived from the German term for coagulation—is taken. A deficiency in vitamin K can result in excessive and severe bleeding. Due to its role in promoting clotting, reducing vascular leakage, and limiting the accumulation of blood products in the periorbital region, vitamin K has for an extended period, been viewed as a possible management strategy for infraorbital dark circles. These properties may contribute to the improvement of POH [6].

- ***Glycyrrhiza glabra* derived bleaching agents**
  Glycyrrhiza glabra extracts exhibit anti-melanogenesis activity through tyrosinase inhibition. These extracts are currently incorporated into cosmetic formulations for hyperpigmentation, owing to their skin-lightening, desensitizing and anti-inflammatory activities. [6, 8].

Chemical peels

Application of chemical peels in the management of infraorbital hyperpigmentation can be applied either alone or combined with additional therapeutic modalities, as topical depigmenting agents. Multiple types of chemical peels are available for managing POH, and the selection of a specific peel depends on the patient's individual needs, the depth of pigmentation, and skin type. Careful patient selection should consider not only the Fitzpatrick skin type, ethnic background should be considered, as individuals from diverse ethnic groups may exhibit variable and often unpredictable responses to chemical peeling, regardless of their skin phenotype. [6].

Some common types of chemical peels used for treating POH

1. Superficial or light chemical peels [5]**:**

- **Glycolic acid peels**: These are mild peels that use glycolic acid to exfoliate the upper layer of the skin. They are often used for mild cases of POH.
- **Lactic acid peels**: Lactic acid peels are gentle and suitable for sensitive skin. They can improve skin texture and pigmentation.
- **Salicylic acid peels**: These peels are often used for acne-prone skin but can also improve the appearance of the periorbital area.

2. Medium chemical peels

Trichloroacetic acid peels: They are stronger and can penetrate deeper into the skin. They are effective for moderate cases of POH and can address both epidermal and dermal pigmentation [9].

3. Deep chemical peels

Phenol peels: These peels are the most potent and can penetrate the skin deeply. They are generally reserved for more severe cases of POH, but they often require a longer recovery period and are linked with an elevated probability of adverse effects. [9].

Intralesional injection

- **Autologous fat transplantation**
  In cases of POH related to attenuate and translucent lower eyelid skin overlying the orbicularis oculi, autologous fat transplantation serves as a therapeutic approach. [7].

- **Soft tissue fillers**
  The use of soft tissue fillers can effectively fill the tear trough, reducing the apparent transition zone between the dynamic contraction of the orbicularis oculi muscle and the adjacent flat contour of the cheek. [10]. Hyaluronic acid (HA) gel has been successfully utilized as a volumizing filler to achieve three-dimensional contour restoration and remodeling of the periorbital area [5]. The recommended management of violaceous periocular appearance associated with deficient subcutaneous fat involves replenishment of eyelid volume using autologous fat transplantation or injectable soft tissue fillers. [11].

- **Platelet-rich plasma** (PRP)
  PRP has been employed for the management of dark circles associated with tear trough deformity and periorbital wrinkles. Treatment typically involves six sessions of intradermal PRP injections into the tear trough deformity and lateral canthal (crow's feet) regions at one-month intervals. Significant improvement in infraorbital color uniformity has been observed, particularly when compared after three months of treatment. [7].

- **Mesotherapy**
  It involves a series of minimally invasive therapeutic approaches employing the injection of vitamins, minerals, homeopathic remedies, proteins, and other active ingredients directly into the dermis. The terms "mesolift" and "mesoglow" have been introduced to describe the toning and rejuvenating outcomes associated with mesotherapy. HA is commonly employed in this context, owing to its capacity to enhance tissue hydration and promote fibroblast activation. Specifically, HA stimulates fibroblasts to upregulate the expression of collagen type I, matrix metalloproteinase-1 (MMP-1), and tissue inhibitor of metalloproteinase-1 (TIMP-1)[12]. It has been used for the treatment of POH, with vitamin C injection. Vitamin C inhibits tyrosinase enzymes, acts as an antioxidant, promotes collagen synthesis, and reduces dermal damage. Mesotherapy showed significant enhancment in reducing POH and had elevated individuals satisfaction level [13].

- **Botulinum toxin**
  It is primarily known for its use in reducing facial wrinkles and treating certain muscular conditions can be a useful adjunctive treatment for POH by relaxing the muscles around the eyes, which might also help to reduce venous congestion in the area. This can potentially decrease the vascular component of dark circles, making them appear lighter [10].

Laser therapy

Non-invasive lasers targeting pigment and vascular structures represent an effective strategy for managing dermal melanin deposition and hypervascularity. Effective modalities include the use of intense pulsed light (IPL) and Q-switched ruby laser systems, which deliver focused light to areas of excess pigment or vascularity, resulting in selective rupture and subsequent reabsorption. Achieving optimal results generally requires multiple treatment sessions over 3-4 months. Common side effects, such as transient erythema or hyperpigmentation, can often be managed with topical depigmenting agents. Patients should also be counseled that bruising may persist for up to two weeks. Resurfacing lasers, including CO_2 and Erbium: YAG lasers, may be appropriate for certain individuals; these devices induce controlled heat-induced damage, stimulating collagen production, reducing pigmentation, and promoting skin tightening simultaneously. Treatment outcomes are highly operator-dependent but can be very effective. [5].

Microneedling

Microneedling can be used alone or with other topical biological agents such as HA, vitamin C serum, growth factors (GFs), retinol, peptides, stem cell serums, PRP, TCA, and antioxidants to enhance its therapeutic effects and address specific skin concerns [14].

Tranexamic acid (TXA)

It is a fibrinolysis inhibitor demonstrated to be effective in inhibiting bleeding adverse event across various hemostatic challenges and, in certain contexts, decreasing mortality with minimal adverse effects. [15].

TXA is currently utilized in dermatology, for its anti-pigmentary and anti-erythematous effects, attributed to its inhibitory action on melanogenesis, anti-angiogenic and anti-inflammatory properties, and its capacity to promote skin barrier repair. TXA may be administered through various routes, including oral, topical, intradermal, or microneedling delivery, either as monotherapy or in conjunction with other active agents or interventions such as laser therapy. Combination regimens have been reported to achieve superior clinical outcomes. [16].

Mechanism of action of tranexamic acid

TXA, a synthetic lysine analogue, inhibits fibrinolysis by occupying lysine-binding sites on plasminogen, thereby preventing its interaction with both plasmin and fibrin. and consequently stabilizing the fibrin mesh formed during secondary hemostasis. [15].

TXA may be administered via oral or intravenous routes, with the intravenous formulation exhibiting an elimination half-life of approximately two hours in healthy individuals, and its bioavailability is 33%-34% for both routes. The drug

is eliminated exponentially, with nearly 90% of the intravenous dose excreted renally within 24 hours. [17].
As TXA is primarily excreted via the kidneys, patients with renal dysfunction are at higher risk of complications, necessitating dose adjustments of both oral and intravenous formulations according to serum creatinine. [18]. TXA exhibits six- to ten-fold greater affinity for plasminogen and plasmin than ε-aminocaproic acid, suppressing fibrinolysis as reflected by decreased serum D-dimer levels while leaving other coagulation markers unchanged. Its efficacy is maintained in the presence of heparin, supporting its use in heparinized patients. [19].

TXA as a depigmenting agent
Plasminogen binds to fibrin through its high-affinity lysine-binding site. When this site is saturated with TXA, plasminogen is displaced from the fibrin surface. [20]. Although plasmin can still be generated attributed to conformational alterations in plasminogen, its ability to bind to and degrade the fibrin network is suppressed. TXA distributes into both intracellular and extracellular compartments and is predominantly excreted unchanged in the urine [21].

Inhibition of ultraviolet-induced plasmin activity
Ultraviolet exposure stimulates epidermal keratinocytes to increase plasminogen activator production in situ. TXA, a natural plasmin inhibitor, prevents the conversion of plasminogen to plasmin by forming a reversible complex with plasminogen, thereby inhibiting plasminogen activator activity. [22]. TXA also inhibits the attachment of plasminogen to keratinocytes, thereby preventing UV-enhanced plasmin activity within these cells. Plasmin is a protease that promotes the intracellular release of arachidonic acid (AA) and alpha-melanocyte-stimulating hormone (α-MSH), both of which stimulate melanogenesis. [23]. By inhibiting plasmin activity, TXA reduces the availability of AA in keratinocytes, thereby attenuating UV-induced melanogenesis. Topical administration of TXA has demonstrated efficacy in diminishing hyperpigmentation triggered by ultraviolet exposure. [22].

Reduction in prostaglandin production
Following ultraviolet (UV) exposure, prostaglandins (PGs) initiate signaling pathways that regulate melanocyte proliferation, differentiation, and apoptosis. Among them, prostaglandin E2 (PGE2), abundantly secreted by keratinocytes in response to UV radiation (UVR), promotes dendritic extension in melanocytes and enhances tyrosinase activity. TXA suppress PG formation, thereby reducing melanocyte tyrosinase activity. This pharmacological property of tranexamic acid (TXA) has been successfully utilized in the management of melasma, UV-induced hyperpigmentation, and various types of post-inflammatory hyperpigmentation (PIH). [21].

Reduction of vascularity
Exposure to UVR induces angiogenic factors including VEGF, b-FGF, and IL-8. VEGF-mediated activation of keratinocytes results in the release of AA metabolites and plasminogen, promoting melanogenesis. TXA targets the vascular system; inhibition of plasmin decreases b-FGF availability, thereby suppressing melanocyte proliferation, angiogenesis, and neovascularization. [21].

Effects on melanogenesis
Tyrosinase-related proteins (TRP-1 and TRP-2) are key enzymes in the Raper-Mason route of melanogenesis. [24]. TXA not only decreases tyrosinase concentrations but also downregulates the expression of TRP-1 and TRP-2. Stimulation of the extracellular signal-regulated kinase (ERK) signaling route promotes degradation of microphthalmia-associated transcription factor (MITF), the main transcription factor governing melanogenic enzymes, thereby reducing melanogenesis. [21]. TXA induce the ERK route, resulting in decreased MITF protein levels and subsequent suppression of inflammation-induced melanogenesis through reduced tyrosinase expression. Furthermore, TXA can directly modulate tyrosinase transcription, enhancing its anti-melanogenic and anti-inflammatory effects. [24].

Conclusion
Periorbital hyperpigmentation (POH) remains a challenging cosmetic and dermatological concern due to its multifactorial etiology, which includes genetic, vascular, structural, and pigmentary components. Current management relies on a broad spectrum of treatment strategies, ranging from topical depigmenting agents and chemical peels to intralesional injections, laser therapy, and microneedling. While traditional depigmenting agents such as hydroquinone, tretinoin, and kojic acid have shown variable efficacy, combination therapies addressing pigmentation, vascularity, and tissue volume yield superior outcomes.
In recent years, tranexamic acid (TXA) has emerged as a promising therapeutic option. Its multimodal mechanisms—anti-melanogenic, anti-angiogenic, and anti-inflammatory—make it uniquely effective in reducing hyperpigmentation. TXA inhibits ultraviolet-induced plasmin activity, suppresses prostaglandin production, reduces vascular factors, and downregulates melanogenic enzymes. It may be delivered through oral, topical, intradermal, or microneedling routes, either as monotherapy or as part of combination regimens. Clinical evidence supports its safety and efficacy, particularly in resistant or recurrent cases of POH.
Future research should focus on large-scale clinical trials and standardized treatment protocols to validate TXA's role as a first-line or adjunct therapy. With growing evidence, TXA represents a significant advance in the individualized and effective management of periorbital hyperpigmentation.

Conflict of Interest
Not available

Financial Support
Not available

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How to Cite This Article
Raslan HE, EL-din El-Samongy MAF, Elgarhy LH, Hodeib AAEH. Periorbital hyperpigmentation: Current treatment modalities with a spotlight on tranexamic acid. International Journal of Dermatology, Venereology and Leprosy Sciences. 2025; 8(2): 43-47.