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REVIEW

Tranexamic Acid for the Treatment of Hyperpigmentation and Telangiectatic Disorders Other Than Melasma: An Update

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Abstract: Tranexamic acid (TXA), a synthetic lysine analog, is a commonly used antifibrinolytic and procoagulant agent. Based on its good hemostatic efficacy, it is mainly used clinically for bleeding in trauma, various types of surgical and dental procedures and prevention of bleeding in patients with hemophilia. In recent years, studies have shown that TXA has the effects of anti-melanogenesis, anti-inflammation, anti-angiogenesis and promotes the recovery of the skin barrier, so it has been tried to be used as a treatment for hyperpigmentation and telangiectatic diseases. Oral, topical, intradermal injections and microneedling are all commonly used modes of administration. TXA for melasma is the most studied and has achieved indications in some countries, whereas it is still an off-label drug for many other dyschromia. We review the clinical use of TXA in hyperpigmentation and telangiectatic disorders other than melasma, such as post-inflammatory hyperpigmentation, Riehl's melanosis, rosacea, and post-acne erythema, to provide more evidence for the use of TXA in these disorders, and to provide safer and more cost-effective alternatives for the treatment of these diseases.

Keywords: tranexamic acid, hyperpigmentation, erythema, telangiectatic disorder

Introduction

Tranexamic acid (TXA) is a synthetic amino acid, which inhibits the interaction of plasminogen or plasmin with fibrin by competitively binding to the lysine-binding sites on plasminogen molecules, thus reducing fibrin clot degradation and achieving antifibrinolytic and hemostatic effects, and is mainly used clinically for a variety of hemorrhages due to acute or chronic, limited or systemic primary hyperfibrinolysis. In addition to its antifibrinolytic effect, TXA also has the effects of reducing melanin production, anti-angiogenesis, anti-inflammation and accelerating skin barrier repair. Therefore, in recent years, its application prospects in dermatology have received increasing attention. Hyperpigmentary and telangiectatic disorders are common, and some of them are difficult to treat. Due to the disfiguring nature, this kind of skin diseases often affects patients' appearance and psychosocial well-being. Based on its mechanism of action, TXA has potential therapeutic value in hyperpigmentary and telangiectatic disorders. A study has shown that vascularization itself can affect skin pigmentation, and human dermal microvascular endothelial cells (HMVECs) secrete melanogenic cytokines such as endothelin-1 (ET-1) to induce melanogenesis,[1] so TXA also has a therapeutic status for hyperpigmentary diseases accompanied by erythema. Melasma is the most extensively studied dyschromia in treatment with TXA, and it has been listed as a drug indication for TXA in Japan, but many other diseases are still in the category of over-the-counter use. This article summarizes the mechanism, clinical application, efficacy, adverse effects, and safety of TXA in hyperpigmentary and telangiectatic disorders other than melasma to provide more therapeutic ideas and options for the treatment of this kind of disease.

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Mechanism

1. Reducing melanogenesis: TXA is structurally similar to tyrosinase and may disturb the catalysis of tyrosinase in tyrosine metabolism through competitive antagonism.[2] By blocking UV-induced plasminogen activity and single-chain urokinase-type plasminogen activator (sc-uPA) in keratinocytes, TXA interferes with melanocyte–keratinocyte interactions, ultimately reducing the synthesis of the inflammatory factors such as free arachidonic acid and its metabolite prostaglandins, thereby reducing melanin production.[3,4] Furthermore, TXA suppresses the production of prohormone convertase (PC2), which in the pituitary gland cleaves proopiomelanocortin to α-melanocyte stimulating hormone (α-MSH), thus inhibiting skin melanocyte activation caused by UVB irradiation of mouse eyes and ears.[5] Additionally, TXA inhibits the stimulation of human epidermal melanocytes by prostaglandin E2 (PGE2);[6] markedly reduces the release of ET-1 by epidermal keratinocytes (ET-1 increases melanocyte dendricity and melanosome transfer);[7] decreases protein levels of tyrosinase and tyrosinase-related protein 1 and 2 (TRP-1 and TRP-2) in melanocytes, induces sustained activation of ERK and decreases the expression of microphthalmia-associated transcription factor (MITF) in B16F10 melanoma cells;[8] and activates the autophagy system;[9] thereby inhibiting melanogenesis in various ways. Recently, it has been discovered that Rab5b may have a role in the distribution of melanocore in keratinocytes. By upregulating Rab5b, TXA may encourage the clustering distribution of endocytic melanocores, hence decreasing skin pigmentation.[10]
2. Inhibition of angiogenesis: Plasmin plays an important role in the process of angiogenesis. As a plasminogen inhibitor, TXA can inhibit angiogenesis by reducing the expression of plasmin-mediated vascular endothelial growth factor (VEGF) and ET-1.[11] TXA can also suppress neovascularization induced by basic fibroblast growth factor (bFGF)[12] and VEGF165-induced overexpression and activation of VEGF receptors.[13] In a mouse model of rosacea, TXA represses angiogenesis by lowering the quantity of CD31+ cells and downregulating VEGF expression.[14]
3. Anti-inflammation: In animal experiments of hemorrhagic shock, TXA decreases the levels of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and inflammatory mediator PGE2 and increases the levels of anti-inflammatory cytokine IL-10.[15,16] In LL37-induced rosacea animal and HaCaT cell models, TXA can exert anti-inflammatory effects by inhibiting CD4+ T-cell infiltration and polarization, decreasing the production of pro-inflammatory cytokines IL-6 and TNF-α, and chemokines CXCL1, CXCL5, and CCL10.[14] TXA reduces the proliferation of mast cell[17] and also inhibits the activation of perivascular mast cells and the production of secondary lipid mediator, hence interfering with the recruitment of neutrophils.[18]
4. Accelerating the recovery of skin barrier: TXA inhibits serine protease (SP) from activating kinase-activated receptor 2 (PAR-2), leading to calcium influx in keratinocytes, which results in an appropriate lamellar body secretion to restore the function of epidermal permeability barrier.[12] It has been found that the topical administration of 5% tranexamic acid considerably hastens the regeneration of physicochemical-damaged skin barrier and increases the mean optical density value of the tight junction protein occludin.[19] TXA counteracts the delayed barrier recovery caused by Cryj1 (the major pollen allergen of *Cryptomeria japonica*), by decreasing Cryj1-induced elevation of protease activity and Ca^{2+} concentration in human keratinocytes.[20]

Routes of Administration

As a hemostatic agent, TXA is usually administered intravenously, in addition to topical and oral administration. In skin disorders, oral TXA has been increasingly recognized as a promising therapy for melasma and other hyperpigmentary disorders, but some physicians are still hesitant to administer the drug in light of risks such as thromboembolism, so topical, intradermal injection and microneedling are also common modes of administration. Oral TXA is generally administered 1–2 times daily in doses ranging from 250 to 1500 mg/d. Topical and intradermal injections of TXA typically range from 2% to 10%.

Adverse Reactions and Contraindications

The more common adverse reactions to systemic use of TXA are stomach upset, hypomenorrhea or irregular menstruation. Furthermore, thrombosis, drug hypersensitivity, hepatic and renal impairment, headache, dizziness, blurred vision, stroke, epilepsy, color vision disturbances, visual deficits, palpitations, hypopigmentation, anxiety, depression, somnolence, and insomnia have all been reported, although all are rare. In a 5-year retrospective analysis of 451 oral prescriptions of 650 mg of

TXA per day, no adverse events including increased coagulation risk, such as deep vein thrombosis, stroke, myocardial infarction, and pulmonary embolism, were documented in relation to oral TXA, and the authors concluded that oral TXA had a favorable safety profile.[21] Adverse effects of intradermal injection and microneedling mainly include pain, irritation, burning sensation, bleeding, mild erythema, itching, desquamation, and bruising, etc., which are essentially transient. Topical modes of administration are safe, and few adverse reactions have been reported.

Contraindications to oral TXA mainly include the following: allergy to TXA, defective color vision, current anticoagulant therapy, active thromboembolic disease, or history of venous or arterial thromboembolism, severe renal dysfunction, pregnancy and lactation, taking oral contraceptives.[22]

TXA in Hyperpigmentation Disorders Other Than Melasma

Post-Inflammatory Hyperpigmentation (PIH)

PIH is skin pigmentation secondary to trauma, surgery, or inflammatory process that can involve both the epidermis and dermis. PIH is very common and can affect patients of all skin colors but is more likely to occur in darker-skinned populations such as Africans, Asians, and South Americans. PIH is difficult to treat, and prevention is the most important modality, such as powerful sun protection. Current treatments for PIH include topical medications, for example, hydroquinone (HQ), chemical peeling, and laser treatments and so on. Hydroquinone is banned from cosmetic use because of the risk of side effects, such as ochronosis.[23] In recent years, TXA has received much attention as a safer non-hydroquinone topical agent for monotherapy or adjunctive treatment of PIH.

Treatment with TXA Only or TXA Vs Others

Lindgren et al successfully treated and/or prevented PIH in approximately 82 high-risk patients with pigmentation between 2015 and 2020 by using oral TXA 650 mg/d for periods ranging from 2 weeks to several years, with a favorable safety profile, and the authors considered TXA as a therapy for all high-risk patients prior to receiving microneedling, cryolipolysis, cryohydrolysis, cryotherapy, chemical peels, and laser treatments.[24] A longitudinal single-blind center study in the United States explored the whitening properties and safety of the ester salt derivative of TXA, which involved 35 volunteers who were topically treated with a new facial serum of 2% TXA twice a day for a period of 8 weeks. The results showed that the treatment improved skin tone, reduced facial dark spots and redness in sun-damaged skin, and was well tolerated.[25] A 37-year-old female presented with PIH due to intense pulsed light (IPL) and pigmentation increased after initial treatment with low fluence Q-switched 1064 nm laser, followed by the use of oral TXA 250 mg three times a day, along with wet dressing applying TXA solution (500 mg/5 mL, 15 mL) three times a week for 20 min. After two weeks, facial PIH was significantly ameliorated.[26] Sobhan et al carried on a 12-week single-blind randomized clinical trial on post-acne PIH patients: 20% azelaic acid (AZA) cream and 5% TXA solution were applied to two groups of patients (30 patients in each group), respectively, both twice daily. It was found that both groups showed improvement in post-acne hyperpigmentation index (PAHI) scores with comparable efficacy, but TXA had a better safety profile in the first month.[27] Tawfic et al examined the efficacy of a low-power/low-density fractional carbon dioxide (CO2) laser and TXA microinjection on post-acne hyperpigmentation using a split-face study involved 25 patients who resisted routine treatment for over 6 months. The researchers used CO2 laser (every 4 weeks) on one side and TXA (injected every 2 weeks) on the other side for 3 months; both methods exhibited good results with significant reductions in PAHI and melanin index (MI) scores, but in terms of total dermatoscopic score, the fractional CO2 laser treatment group showed better improvement than the TXA microinjection group.[28]

TXA Combined with Other Active Ingredients

Results from a 12-week single-center clinical study in 55 Brazilian females revealed that a novel topical facial serum containing 3% tranexamic acid, 1% kojic acid, and 5% niacinamide was effective in treating mild-to-moderate PIH, with a significant decrease in MI at week 12 compared to baseline and control group.[6] A study that included 42 Korean women aged 30–60 years showed that twice-daily topical application of a moisturizer containing 2% niacinamide +2% TXA significantly reduced the mean MI scores at 4 and 8 weeks, which was significantly better than the vehicle control formulation regimen.[29]

TXA Combined with Other Treatment Methods

A 64-year-old woman with post-inflammatory hyperpigmentation caused by allergic contact after repeated using pure henna hair dye was treated with low-fluence 1064nm Q-switched Nd: YAG laser once a week and orally 750 mg TXA daily after 1 month of ineffective use of a hydroquinone cream. After 10 weeks, the hyperpigmentation on the forehead improved significantly, and the efficacy persisted at one-year follow-up.[30] The efficacy of picosecond laser as a laser-assisted drug delivery (LADD) procedure adjunctive to TXA administration to treat PIH has been investigated. Ten patients with post-traumatic PIH were enrolled in a split-area randomized prospective study, with the control group receiving a picosecond laser and the TXA group receiving laser followed by further topical application of 10% TXA solution. Treatments were performed every 6 weeks, for a total of 4 sessions. There were no significant differences between the two groups in terms of self-assessment of hyperpigmentation or overall satisfaction with the treatment outcome. The authors considered the lack of microchannels capable of facilitating drug transport to be one of the key reasons for the failure of LADD by picosecond laser.[31] Later, a retrospective study was done to explore the efficacy of low-energy, low-density 1927 nm fractional thulium fiber laser therapy as an adjuvant to LADD procedures for topical application of TXA to deal with PIH. The research retrospectively analyzed 25 PIH patients who received laser followed by topical TXA, with an average of 3.3 treatments per patient, and showed that 16.0% had complete clearance, 68.0% had excellent clearance, and 16.0% had good clearance, with no patients experiencing worsening of symptoms and no significant adverse effects presented. The authors believe that this kind of laser produces extremely fine, superficial, and transient channels that can deliver TXA to the desired depth and facilitate the entry of topical medications into the dermis, and its low-energy characteristic keeps off undesirable thermal effects that may lead to exacerbation of PIH, so it can enhance the therapeutic efficacy without increasing the incidence of side effects.[32]

Preventing PIH After Laser Therapy

Asians are prone to PIH after Q-switched laser treatment, especially Q-switched ruby laser (QSRL) treatment. Whether TXA can reduce or prevent this kind of PIH has also been clinically studied but with inconsistent conclusions. Thirty-two Japanese women underwent QSRL for the treatment of senile lentigines on the face and 15 of them took TXA 750 mg/day orally after the treatment, but it was found that the incidence of PIH did not significantly differ between the groups who received and did not receive oral TXA.[33] The results of another study in Thailand distributed that treatment with oral TXA (1500 mg/d) starting on the first day after treatment with Q-switched 532-nm Nd: YAG laser treatment for solar lentigines was ineffective in preventing PIH after laser treatment, but the oral TXA group had a considerably reduced incidence of pigmented granules at weeks 6 and 12 under dermatoscopy, suggesting that oral TXA improved PIH clearance.[34] Other scholars assessed the effect of intradermal injection of TXA to prevent PIH after 532 nm Nd: YAG laser treatment of solar lentigo. The lesions were randomly distributed to the TXA group (intradermal injection of 50 mg/mL TXA) and the control group (intradermal injection of 0.9% normal saline) by drawing method, and a broad-spectrum sunscreen was applied after crusts peeled off for 12 weeks. The results displayed that the incidence of PIH was lower in the TXA group than in the control group (16% vs 28%) at the end of the study.[35] From the above researches, it can be inferred that intradermal injection of TXA seems to diminish the risk of PIH after Q-switched laser therapy better than oral mode, which may be attributed to the fact that the bioavailability of oral TXA is lower and not as direct as the action of intradermal injection.

Infraorbital Hyperpigmentation

Periorbital hyperpigmentation is a common cosmetic problem caused by a combination of factors and usually requires a multimodal therapeutic approach. For infraorbital hyperpigmentation, microneedling and fractional CO2 laser combined with topically TXA has been tried by some scholars. Ghandehari et al gathered 30 volunteers who were randomly allocated to receive fractional CO2 laser and microneedling followed by 2 cc of TXA (500mg/5mL) vial applied to the treating area with a cotton swab for three monthly treatment sessions. The results showed that both methods showed significant improvement compared to the baseline status, and there was no significant difference between the two groups at days 30, 90, and 150, but the laser+TXA group showed better performance at day 60, and neither method had any significant side effects.[36]

Riehl's Melanosis

Riehl's melanosis is an acquired pigmented condition marked by brown or bluish pigmentation on the forehead, temporal, and zygomatic areas. The etiology of Riehl's melanosis is still unclear, and effective therapies are limited. The use of laser therapy alone may carry a risk of experiencing PIH, especially in those with darker Fitzpatrick skin types. TXA has the function of anti-melanogenesis, anti-angiogenesis and anti-inflammation, so it could be a favorable link of combination therapy not only for its potential therapeutic value for Riehl's melanosis but for its possible ability to lower the risk of PIH after laser. Kwon et al used a combined treatment protocol in 8 patients with Riehl's melanosis who had previously failed to improve: multiple sessions (10–18 times) of very low-fluence 1064-nm Q-switched Nd: YAG laser, topical 4% HQ cream every night and oral TXA 250 mg per day for the duration of the treatment courses. After the combined regimen, 3 patients received "almost clear" grade, 5 get "marked improvement" grade, the mean melanin and erythema indices significantly declined.[37] Xu et al assessed the effectiveness and safety of oral TXA and Glycyrrhizin compound in treating recalcitrant Riehl's melanosis. The study included 10 patients who were treated for 3 months with daily 500 mg of TXA and 150 mg of Glycyrrhizin compound orally, followed 3 months with 500 mg of TXA daily alone. The results showed 7 patients experienced significant improvement in symptoms, with a significant decline in both MI and erythema indices (EI) which was confirmed by reflectance confocal microscopy (RCM) and dermoscopy analyses.[38] Afterwards, the same research team carried out a prospective study involving 28 patients to compare the efficacy of oral TXA alone with that of oral TXA combined with IPL to treat refractory Riehl's melanosis. The patients were given 500 mg of oral TXA daily, 11 of whom received a monthly IPL therapy for 6 months simultaneously. After treatment, dermal macular hyperpigmentation area and severity index (DPASI), mean MI and EI were all significantly reduced in both groups, with more favourable effect in the combination group.[39]

Macular Amyloidosis (MA)

MA is a frequent cutaneous amyloidosis with lesions of dark spots made up of brown pigments aggregating a reticular or rippling pattern on the skin, which can be treated with topical glucocorticosteroids or retinoids, but the efficacy is always poor. Ghassemi et al randomized 43 patients with MA into two groups, one received intradermal injection of 4mg/mL TXA solution every 2 weeks for a total of 6 treatments, and the other received a topical application of Kligman combination drug (4.0% hydroquinone + 0.05% tretinoin + 0.01% fluocinolone acetonide + 500mg vitamin C) once a day at night for 12 weeks. The outcomes showed that whereas intradermal injection TXA was more successful in lowering melanin content, both treatments were beneficial in alleviating symptoms and dramatically reduced hyperpigmentation in the treated area.[40]

Lichen Planus Pigmentosus

A study from Morocco collected clinical information of 17 lichen planus pigmentosus patients, 11 of whom were treated with oral TXA 500 mg twice daily for 3 or 6 months. All but one of the patients also received high potency corticosteroid and hydroquinone. During the follow-up, the lesions completely resolved in only four patients, while in the others they remained unchanged.[41] The literature on TXA treatment for hyperpigmentation disorder beyond melasma is summarized in Table 1.

TXA in Erythema and Telangiectatic Disorder

Rosacea

Rosacea is a chronic inflammatory skin disease with four main subtypes according to its clinical manifestations, namely erythematotelangiectatic, papulopustular, phymatous, and ocular. The different subtypes are often concomitant with each other or transformed into each other. The main clinical manifestations of erythematotelangiectatic rosacea (ETR) are paroxysmal flushing and persistent erythema, accompanied by unbearable burning sensation in some patients, which is the most stubborn and difficult to treat, seriously affecting the patients' psychological and physiological health and lowering their quality of life. Although pulsed dye laser, IPL and vasoconstrictor drugs (eg, brimonidine tartrate, oxymetazoline, carvedilol, etc.) can be used for the treatment of ETR and microdroplet botulinum toxin can alleviate the symptom of some refractory cases, some patients still do not respond well to the above therapies and the costs are usually expensive, so the treatment is still challenging. In recent years, TXA has been found to be effective for rosacea with the potential to become a safe and economical alternative.[42]

Table 1 Summary of Studies on TXA in Hyperpigmentation Disorder Beyond Melasma

Reference/Year	Disease	Type of study; patients number	Treatment protocols of TXA	Combined therapy	Outcome	Side effects
Lindgren et al[24]/2021	PIH	Brief communication; 2	Oral TXA at a dose of 650mg/d until the injury is totally healed (2 weeks to several years)	/	No PIH is present	/
da Silva Souza ID et al[25]/2021	Healthy adult female volunteers with signs of sun-damaged skin	Longitudinal, single-center, open-label study; 35	A new topical TXA ester salt (2.0% cetyl tranexamate mesylate) was used to their face, twice a day for 8 weeks	/	Skin tone, dark spots and facial redness improved	No adverse events or reactions
Kim et al[26]/2012	PIH following IPL therapy	Case report; 1	Oral TXA 250mg tid, a wet dressing of TXA solution (500 mg/5 mL, total 15mL) was applied for 20 minutes three times a week	/	The lesions on her face were improved significantly	Burning sensation and erythema which fade quickly
Sobhan et al[27]/2023	Acne-related PIH	Single-blinded, randomized clinical trial; 30	AZA group: 20% AZA cream; TXA group: 5% TA solution; twice daily for 12 weeks	/	PAHI score in both groups improved	No severe side effect
Desai et al[6]/2019	Mild to moderate melasma, PIH and hyperpigmentation in Brazilian female	Single-center, clinical study; 55	3% TXA topically used twice a day for 12 weeks	1%kojic acid and 5% niacinamide	PIH was improved and MI significantly decreased	Minor transient effects: erythema, itching, pruritus, redness, stinging
Tawfic et al[28]/2021	Post-acne hyperpigmentation more than 6 months	A randomized-controlled, split-face, comparative study; 25	One side of the face: low-power fractional CO2 laser every 4 weeks; the other side of face: TXA intradermal- microinjection every 2 weeks for 3 months	/	Both sides showed a significant reduction in the PAHPI and MI	Mild burning pain and mild erythema after the sessions
Lee et al[29]/2014	Volunteers with moderate to moderately severe irregular hyperpigmentation	Prospective, randomized, double-blind, vehicle-controlled clinical study; 42	Experimental group: topical cream containing 2% niacinamide+2% TXA; control group: a cream vehicle; twice-daily for 8 weeks	2% niacinamide	The mean MI scores were significantly decreased and skin lightening effects were higher in experimental group	No serious adverse events
Lee et al[30]/2016	PIH due to allergic contact dermatitis to henna hair dye	Case report; 1	10 weekly treatments with low-fluence 1064-nm Q-switched Nd: YAG laser and oral tranexamic acid at a dose of 750 mg per day for 10 weeks	Low-fluence 1064-nm Q-switched Nd: YAG laser	The hyperpigmentation substantially improved	Nil reported
Lin et al[31]/2021	Post-traumatic cases of PIH	A split-area double blind randomized prospective study; 10	One side of the PIH: picosecond laser; another side of the PIH: picosecond laser+ 10% tranexamic acid solution; every 6 weeks for 4 times	Picosecond laser	The self-assessment by the patient and the overall satisfaction of the treatment outcome were not significantly different between the two group	No side effects were reported
Wang et al[32]/2022	PIH	Retrospective study; 25	Low-energy, low-density 1927-nm fractional thulium fiber laser followed by topical tranexamic acid with a mean of 3.3 treatments per patient	Low-energy, low-density 1927-nm fractional thulium fiber laser	16.0% had complete clearance, 68.0% had excellent clearance, 16.0% had good clearance.	No adverse events

Kato et al[33]/2011	Patients underwent QSRL treatment for senile lentigines on the face with or without melasma	A single-center, randomized, Parallel-group study; 32	Two groups that did (n = 15) and did not (n = 17) receive oral TXA (750 mg/d) for the first 4 weeks after QSRL treatment	/	PIH was frequently seen at 4 weeks after QSRL treatment whether the patients received oral TXA or not	/
Rutnin et al[34]/2019	Patients with solar lentigine treated with Q-switched 532-nm Nd: YAG laser	Randomized controlled trial; 40	Patients were randomly assigned to receive TXA 1500 mg daily or placebo for 6 weeks beginning on the day of laser treatment	/	Oral TXA could not decrease the incidence of PIH, but PIH clearance was improved by oral TXA	Nausea, hypomenorrhea
Sirithanabadeekul et al[35]/2018	Patients underwent Q-switched 532-nm Nd: YAG laser for solar lentigines on forearms	Randomized controlled study; 25 patients with 50 solar lentigines	TXA (50 mg/mL) was injected randomly into one lesion and 0.9% normal saline was injected intradermally into another lesion following the laser treatment	/	A significant reduction of the mean MI in the TXA group at week 4. The overall PIH rate was lower in the TXA group	Mild burning sensations after the TXA injection which resolved within 1 hour
Ghandehari et al[36]/2022	Infraorbital Hyperpigmentation of Fitzpatrick skin types II through IV	A split-face clinical trial; 30	Three monthly treatment sessions on each side of the infraorbital region, one side with fractional CO2 laser and the other side with microneedling, both combined with topical TXA (500mg/5mL)	Fractional CO2 laser or microneedling	Both methods showed significant improvement comparing with the baseline state	Edema, erythema, burning sensation, and itching last for a few days
Kwon et al[37]/2017	Recalcitrant Riehl's melanosis with Fitzpatrick skin type III–V	A prospective pilot study; 8	Multiple sessions (10–18 times) of very low-fluence 1064-nm Q-switched Nd: YAG laser, 4% HQ cream every night and TXA 250 mg/day throughout treatment courses	1064-nm Q-switched Nd: YAG laser and 4% HQ cream	3 patients received "almost clear" grade, the other five received "marked improvement" grade	No serious adverse events
Xu et al[38]/2019	Recalcitrant Riehl's melanosis with Fitzpatrick skin type III–V.	A prospective pilot study; 10	250mg TXA twice a day orally for 6 months	Concomitant use of 50mg of glycyrrhizin compound 3 times daily for the first 3 months	Seven patients received "marked improvement", two received "moderate improvement" and one received "minimal improvement" at the final visit	No adverse reactions
Xu et al[39]/2024	Riehl's melanosis with Fitzpatrick skin type III–IV	Prospective, single-center, open-label, comparative study; 28	12 subjects were treated with oral TXA 500mg per day and IPL once a month for 6 months; 16 subjects were treated solely with oral TXA 500mg per day for 6 months	IPL	MI, EI and DPASI were significantly reduced in both groups, but the combination group showed better improvement	Menstrual changes, mild headaches
Ghassemi et al[40]/2022	Macular amyloidosis of the scapula and arm	Double-blind clinical trial; 43	Group1: intralesional injection of TXA (4mg/mL, 6 sessions, every 2 weeks) Group2: topically apply the Kligman drug once a night for 12 weeks	/	TXA was more effective than the Kligman drug in improving macular amyloidosis and reducing hyperpigmentation	Pain, irritation, pruritus, scaling, bruising
Benchikhi et al[41]/2019	Lichen planus pigmentosus	Case series; 17 (11 were given TXA)	Oral TXA 500mg twice daily for 3 or 6 months	Topically hydroquinone and high potency dermocorticoids	Only four patients had an excellent result	/

Abbreviations: TXA, tranexamic acid; PIH, post-inflammatory hyperpigmentation; IPL, intense-pulsed light; PAHI/PAHPI, postacne hyperpigmentation index; MI, melanin index; QSRL, Q-switched ruby laser; EI, erythema index; DPASI, acquired dermal macular hyperpigmentation area and severity index; HQ,hydroquinone.

Jakhar et al treated patients with erythematotelangiectatic steroid-induced rosacea using 500mg/5mL TXA solution, which was applied externally with a cotton swab twice daily on the lesions for 4–6 weeks, resulting in a significant improvement in erythema, telangiectasia and burning sensation.[43] Six Korean women suffering from papulopustular rosacea or rosacea with irritant contact dermatitis were treated with TXA (15mL, 500mg/5mL) solution wet compress for 20 minutes on the face, 1–2 times per week. After 5 treatments, the manifestation of erythema, itching, flushing, and burning sensation significantly decreased without any apparent side effects.[44] A randomized, vehicle controlled, split-face study involved 30 patients was conducted to evaluate the influence of TXA to rosacea. TXA solution with 5% concentration was applied topically to one side of the face in each patient twice daily for 2 weeks, while the vehicle-treated side acting as a control. After 2 weeks of treatment, the treated side showed significant improvement in all skin biophysical parameters, clinical signs, and symptoms.[12] Daadaa et al retrospectively analyzed six patients with ETR who had been treated with intradermal microinjection of 5mg/mL TXA once per month, with an average number of monthly sessions was 5.1 ± 1.3. The mean decrease in the Investigator Global Assessment of Rosacea Severity Score (IGA-RSS) was 2.4 ± 0.5 at the end of treatment and clinical improvement sustained after 3 months of follow-up.[45] Some other studies have shown the efficacy of microneedling in combination with TXA solution. Twenty female ETR patients participated in an unblinded study and were split into two groups: one group was treated with 500mg/5mL of TXA solution dampened wet dressing for 20 minutes, while the other group received microneedling simultaneously with TXA solution topical application followed by TXA infused dressing therapy, every 15 days for a total of 4 treatments. At the end of the treatment, all patients improved in IGA-RSS, clinical and dermoscopic manifestations, with the group combined microneedling possessing better outcomes and only mild side effects.[46] In the research performed by Mohamed et al, 45 female ETR patients were treated for three sessions at two weeks intervals with microneedling combined with 10% topical TXA on the right side of the face and 10% topical TXA only on the left side. The final evaluation showed improvement in both sides of the face, and the clinical and dermoscopic improvements of the microneedling + TXA side were more pronounced, suggesting that microneedling enhances the penetration of TXA and leads to a better therapeutic efficacy. Minor adverse effects like erythema, pain, and burning sensation were observed in microneedling therapy.[47] Oral TXA has also been tried to treat refractory erythema in rosacea. Kwon et al treated a 37-year-old rosacea patient with severe dryness, flushing, and burning sensations by using oral minocycline 50mg/d + propranolol 40mg/d + TXA 250mg/d for 1 month, and after only 1 week of treatment, the patient's erythema and subjective symptoms improved noticeably, and there were no adverse effects of this triple-combination therapy.[48]

Acne and Post Acne Erythema (PAE)

PAE is a common sequela of acne, possibly due to pro-inflammatory cytokines and increased angiogenesis. Some of the PAEs may gradually subside, but in some patients, PAE can also persist for a long period of time, adversely affecting the patient's appearance. TXA can also be served as a treatment method due to its anti-inflammatory and anti-angiogenic effects. Jakhar et al used 5% TXA solution to treat patients with PAE, which was applied every night and reduced erythema within 6–8 weeks.[49] A before-after split-face clinical trial had revealed a significant improvement in lesion count, area, and percentage of area by injecting TXA (5mg/mL) intra-dermally (two treatments at 2-week interval) for the treatment of persistent PAE.[50] Agamia et al treated 40 persistent PAE patients using a topical triple agent (5% TXA + 1.5% Oxymetazoline + 0.33% brimonidine), which was applied topically to the right side of the face twice a day and the left side as a placebo control. After 3 months of administration, the treated side showed a significantly better effect in reducing PAE compared to placebo side.[51] In an attempt to treat inflammatory acne with TXA, Charoenwattanayothin et al found that 10% TXA serum diminished skin redness in addition to papules and pustules.[52]

Telangiectasia

Intralesional TXA was administered to treat telangiectasia by some scholars. A 33-year-old female with regular branching in her leg and a 27-year-old male with irregular branching telangiectasias at the nasal root received the following treatment program: intralesional TXA three times in one week intervals. They showed some regression and loss of vessels 1 week after the first application, but then responded poorly to subsequent treatment. The authors considered that TXA successfully induced vasoconstriction by activating endothelin A, but the effect was not maintained in repetitive treatments due to the extremely low amount of ET-1.[11]

The literature on TXA treatment for erythema and telangiectatic disorder is summarized in Table 2.

Table 2 Summary of Studies on TXA in Telangiectatic Disorder

Reference/Year	Disease	Type of study; patients number	Treatment protocols of TXA	Combined therapy	Outcome	Side effects
Jakhar et al[43]/2022	Erythematotelangiectatic steroid induced rosacea	Case	A cotton bud was used to apply the 10%TXA solution twice daily on the affected area of face	/	Erythema, telangiectasia and burning sensation reduces considerably within 4–6 weeks	/
Kim et al[44]/2013	Papulopustular rosacea or rosacea with irritant contact dermatitis	Case series; 6	Wet gauzes dampened with TXA solution (500mg/5mL,15mL), 20 min on the face, once or twice a week	/	The score of erythema, itching, flushing and burning were remarkable decreased	No significant adverse reaction
Zhong et al[12]/2015	Rosacea	A randomized, vehicle controlled, split-face study; 30	One side of each patient's face was topically treated with 5% TXA solution twice daily for 2 weeks while the vehicle-treated side served as a control	/	Skin biophysical parameters and clinical sign and symptoms on the TXA treated side were significantly improved	/
Daadaa et al[45]/2021	ETR	A retrospective study; 6	Monthly intradermal microinjections of TXA (5mg/mL), the mean number was 5.1 ±1.3.	/	The mean decrease of IGA-RSS was 2.4 ±0.5	Pain, burning sensation, transient bleeding, erythema, and/or swelling
Bageorgou et al[46] /2019	ETR	A prospective, parallel, randomized, nonblinded, open label, comparative, clinical study; 20	Group A: TXA solution (500mg/5mL) infused wet dressing for 20 minutes Group B: microneedling simultaneously with TXA solution topical application followed by TXA solution infused dressing therapy; every 15 days for four sessions	microneedling	IGA-RSS, clinical photos and dermoscopy all improved in 2 groups, the patient's quality of life had a meaningful change	No sever adverse effects in group A; erythema, flushing, irritation, and a feeling of stinging/ burning in group B
Mohamed et al[47]/2024	ETR	A Split-face Comparative Study; 45	The right side of the face: microneedling combined with 10% topical TXA; the left side of the face: only 10% topical TXA; three sessions at two weeks intervals	microneedling	Both sides of the face showed improvement and the microneedling + TXA performed better	TXA side: no side effects; TXA +microneedling side: pain, exfoliation, erythema, bruises, hyperpigmentation

(*Continued*)

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Table 2 (Continued).

Reference/Year	Disease	Type of study; patients number	Treatment protocols of TXA	Combined therapy	Outcome	Side effects
Kwon et al[48]/2017	rosacea	Case report; 1	TXA 250mg/d for 1 month	minocycline 50mg/d, propranolol 40mg/d	Subjective symptoms and erythema improved	none
Jakhar et al[49]/2020	Acne-related post inflammatory erythema	Case	Topical application of 5% tranexamic acid a daily night time for 6–8 weeks	/	Erythema was reduced	Lack of side-effects
Bazargan et al[50]/2023	Persistent PAE	Before-after split-face clinical trial; 17	TXA was injected as mesotherapy into the right side of each patient's face, no drug was injected on the left side, two sessions of treatment with 2-week intervals	/	The lesion count, area, and area percent were all improved significantly in right side of face	Mild to moderate pain
Agamia et al[51]/2022	Persistent PAE	A split face comparative study; 40	The right side of the face: topical triple combination (5%TXA +1.5% OXZ + 0.33% BMT) The left side of the face: topical lipocream (placebo); twice daily for 3 months	1.5%OXZ, 0.33%BMT	The right side of the face showed a significantly better effect in reducing PAE compared to topical placebo left side	Pallor, paradoxical erythema, contact dermatitis, burning sensation
Charoenwattanayothin et al[52]/2022	Mild to moderate acne	A randomized, double-blind, placebo-controlled, split-face study; 18	10% TXA serum on one side of the face and placebo on another side twice daily for 8 weeks.	/	Papules, pustules and the redness of the skin all reduced on the TXA treated side	Minimal scaling, minimal erythema
Ayhan et al[11]/2019	Telangiectasia	Case report; 2	Intralesional TXA three times in one week intervals	/	Fading and loss of vessels were observed only after the first therapy	/

Abbreviations: TXA, tranexamic acid; ETR, erythematotelangiectatic rosacea; IGA-RSS, investigator global assessment of rosacea severity score, PAE, post-acne erythema; OXZ, oxymetazoline; BMT, brimonidine tartrate.

Conclusion

Tranexamic acid (TXA) is now used in dermatology for anti-black and anti-redness due to its inhibition of melanogenesis, anti-angiogenesis, anti-inflammation and acceleration of skin barrier repair. Apart from melasma, which has been most extensively studied, TXA has also been found to be effective in other hyperpigmentary disorders, such as PIH, Riehl's melanosis, etc., and telangiectatic disorder, such as rosacea and post-acne erythema, etc. Its low price, high safety profile, and ease of preparation make it advantageous for clinical use. TXA can be administered orally, topically, intradermally, or by microneedling, alone or in combination with other active ingredients or treatments such as laser. Combination therapy may have better improvements in clinical outcomes. However, for a specific disease, the optimal mode of administration, combination regimen, and number of treatments are unknown because the routes of administration, drug dosage, duration of treatment, follow-up time, and form of evaluation varied in different studies. More high-quality randomized controlled trials are needed to determine the appropriate route of administration, duration of treatment, and safety of long-term treatment.

Disclosure

The authors report no conflicts of interest in this work.

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