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Review

THE USE OF TRANEXAMIC ACID IN DERMATOLOGY

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SUMMARY – Tranexamic acid is a synthetic derivative of the amino acid lysine, an antifibrinolytic that is primarily used to reduce bleeding in surgery, trauma, and dental procedures. Its anti-inflammatory and anti-angiogenic properties, as well as its ability to suppress melanogenesis have enabled it to be used in dermatology in the treatment of skin conditions such as melasma, acne, post-inflammatory hyperpigmentation, rosacea and angioedema. Tranexamic acid can be used by various routes of administration including oral, topical and intradermal injection, and in combination with other treatment methods. This review article presents evidence for the effectiveness of tranexamic acid in the treatment of various skin disorders.

Key words: *Tranexamic acid; Dermatology; Melasma; Acne; Rosacea; Angioedema*

Introduction

Tranexamic acid (TXA) is an antifibrinolytic agent, a synthetic derivative of the amino acid lysine, the main purpose of which is to reduce bleeding by inhibiting conversion of plasminogen to plasmin involved in fibrin degradation[1]. It is widely used in surgery, trauma, dental procedures, obstetrics and gynecology, and other conditions such as upper gastrointestinal bleeding, epistaxis and hemoptysis[2,3]. In addition to its anti-fibrinolytic effect, TXA has anti-inflammatory properties and the ability to suppress melanogenesis, which is why it has emerged in recent years as a potential treatment for various skin conditions[4].

Mechanisms of Action

Tranexamic acid inhibits ultraviolet-induced plasmin activity in keratinocytes by blocking the interaction of melanocytes and keratinocytes through inhibition of the plasminogen/plasmin system. Preventing the binding of plasminogen to keratinocytes ultimately leads to a reduction in the production of the inflammatory mediators, arachidonic acid and prostaglandin, which are melanocyte stimulators[5]. Furthermore, it has been proven that TXA inhibits protease-activated receptor 2 (PAR-2) activation by serine protease and calcium influx in keratinocytes, leading to improved permeability barrier function in rosacea patients[6]. In addition, it can suppress angiogenesis by reducing the number of CD31+ cells and down-regulating the expression level of vascular endothelial growth factor in rosacea lesion[7].

Melasma

Melasma is a common, acquired, chronic hyperpigmentation disorder presenting as light to dark brown macules on the face, usually over the forehead, nose and cheeks[8]. Although it can affect women and men, it most often affects darker-skinned women with Fitzpatrick skin type III-IV. The known etiologic factors include genetic predisposition, exposure to ultravio-

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let radiation, pregnancy, and hormonal therapy[8,9]. The high rate of relapse and ineffectiveness of the existing treatments negatively affect the quality of life of patients and often represent a challenge in treatment[10].

Wu *et al*. conducted a study on 74 women in Hangzhou, China. After 6 months of oral administration of TXA at a dose of 250 mg twice a day, gradual reduction of melasma could be observed in most patients with an overall improvement rate of 95.9%[11].

In the largest retrospective study to date performed by Lee *et al*., 561 patients were treated with oral TXA 250 mg twice a day for a median of 4 months; 89.7% of patients had visible improvement with a median time to initial response of 2 months. Melasma recurred in 27.2% of patients, with a median duration of 7 months after stopping oral TXA[12].

In their study, Sahu *et al*. studied the effect of oral and topical TXA and a modified Kligman regimen in the treatment of melasma. Sixty patients were included in the study and randomized into three groups as follows: 20 patients received oral TXA 250 mg twice daily, 20 received topical TXA, and 20 received a modified Kligman regimen (hydroquinone 2% w/w, tretinoin 0.05% w/w, fluocinolone 0.01% w/w) for 8 weeks. Reductions in the Melasma Area Severity Index (MASI) were observed in all groups with greatest reduction in MASI scores of 30% with the modified Kligman regimen, followed by oral TXA with 25% reduction, and the least reduction of 5% with topical TXA. Because adverse effects were maximal with modified Kligman, long-term administration of oral TXA may be a promising therapeutic approach for melasma[13].

Studies have shown the effectiveness of topical TXA applied alone or in combination with other treatment methods. Kim *et al*. demonstrated the efficacy of 2% topical TXA in the treatment of melasma after 12 weeks of continuous administration[14]. Application of topical 10% TXA in combination with microneedling shows improvement in the mean modified Melasma Area Severity Index (mMASI) score, as well as in skin texture[15].

Acne and Post-Inflammatory Hyperpigmentation

Acne is a common, chronic inflammatory skin disorder which affects the pilosebaceous units of the skin. Treating acne is often challenging due to the potential side effects of conventional medications, as well as the residues that remain after the lesions have cleared[16,17]. A common pigmentary disorder that occurs as a complication of acne in patients with colored skin is known as post-inflammatory hyperpigmentation (PIH), and in patients with lighter skin color is known as acne-related post-inflammatory erythema (PIE).

In a randomized, double-blind, placebo-controlled study, Charoenwattanayothin *et al*. evaluated the efficacy of 10% TXA serum in the treatment of acne. Eighteen patients with mild to moderate acne applied 10% TXA serum on one side of the face and placebo on the other side of the face twice a day. After 8 weeks of use, acne counts in total inflammatory acne were significantly reduced on the TXA side. TXA reduced papules and pustules, but the nodule counts did not differ significantly. It was also noted that the TXA side showed reduced skin redness, as well as PIE and PIH. Side effects in the form of erythema and scaling were minor and easily resolved by applying a moisturizing cream[16].

The effect of TXA as mesotherapy on persistent post-acne erythema was studied in 15 patients. Significant improvement in acne erythema was seen after intradermal injection of TXA due to its anti-inflammatory and anti-redness effects[17].

The use of TXA in the prevention of PIH has been less well researched. A study by Rutnin *et al*. showed that oral TXA therapy started on the first day after laser treatment was not effective for the prevention of PIH after QS 532-nm Nd:YAG laser treatment. However, oral TXA accelerated clearance of PIH if continued for up to six weeks after treatment[18].

Rosacea

Rosacea is a chronic inflammatory skin disease characterized by persistent facial erythema, recurrent episodes of redness, inflammatory papules, pustules, and telangiectasias. It is classified into four main subtypes: erythematotelangiectatic, papulopustular, phymatous, ocular, and one variant, granulomatous[19]. Due to its anti-inflammatory and anti-angiogenic properties, TXA has emerged as a possible therapeutic option in the treatment of rosacea. In their study, Bageorgou *et al*. tested the effectiveness of topical TXA in the treatment of erythematotelangiectatic rosacea when applied using two different methods. Their study included 20 patients divided into two groups; the first group was treated only with TXA solution infused wet dressing for 20 minutes and the second group was treated with microneedling in conjunction with TXA solution topical application followed by TXA solution

infused dressing therapy for 20 minutes, every 15 days for four sessions. All patients showed improvement after four treatments, with the microneedling treated group showing better results[20]. The use of intradermal TXA microinjections in patients with erythematotelangiectatic rosacea also showed clinical improvement that continued after 3 months of follow-up[21].

Angioedema and Urticaria

Angioedema is a sudden localized swelling of deeper skin layers caused by increased permeability of blood vessels, often accompanied by urticaria. It can affect any part of the body, but usually affects loose skin of the face and genitals. Although this process is often self-limited and lasts for several days, it can become life-threatening if it affects the upper airway. Angioedema may be mediated by bradykinin and/or mast cell mediators including histamine, and occurs either on a hereditary or acquired basis, with or without urticaria[22,23]. One of the causes of hereditary angioedema without urticaria is the C1-esterase inhibitor (C1-INH) deficiency. TXA is a possible treatment option for the prophylaxis of hereditary angioedema. Although its efficacy is lower than that of attenuated androgens and is not recommended as first-line prophylaxis, it is preferred in pediatric population because of its more favorable side effect profile[24]. Acquired angioedema can be idiopathic, caused by C1-INH deficiency or by drug intake, most often angiotensin-converting enzyme (ACE) inhibitors[25]. Beauchêne *et al.* conducted a retrospective study to evaluate the benefits of emergency use of TXA in the treatment of ACE inhibitor-induced angioedema episodes. The study included 33 patients who experienced a severe episode of angioedema, of which 27 patients showed significant improvement when treated with TXA alone, while the remaining 6 patients were treated with additional therapy due to partial improvement after TXA treatment[26].

Side Effects and Contraindications

The main concern with the use of oral TXA has been the risk of causing arterial and venous thrombosis. Although cases of thrombosis have been reported in patients receiving oral TXA, these patients usually had comorbidities associated with hypercoagulability including clotting disorders, history of pulmonary embolism, prolonged immobility, hormone therapy, drug interactions, active bleeding, cancer, and surgery[10]. The most common side effects associated with oral TXA include gastrointestinal discomfort such as bloating, nausea, diarrhea, and vomiting. Other side effects that occur are headache, numbness or facial pruritus, hair shedding, facial hypertrichosis, tremor, palpitations, back pain, dysmenorrhea, tinnitus, nasal and sinus discomfort, transient amnesia, and lip or periorbital swelling[10,27]. Topical TXA is well tolerated and rare side effects such as scaling and erythema are minimal and resolved after application of a moisturizing cream[16]. TXA administered intradermally may cause side effects such as pain, burning sensation, transient bleeding, erythema and swelling at the injection site[21].

Contraindications to oral TXA include allergy to TXA, comorbidities such as renal dysfunction, malignancy, cardiovascular and respiratory disease, known defective color vision, current anticoagulant therapy, active thromboembolic disease, or history of venous or arterial thromboembolism, including deep vein thrombosis, pulmonary embolism, arterial thrombosis, stroke, and subarachnoid hemorrhage. It is also contraindicated during pregnancy and breastfeeding, in patients who are taking hormonal contraception or replacement therapy, and in smokers[10,27]. Patients must be carefully examined through a detailed history of contraindications and risks before starting TXA therapy, and detailed instructions should be given to monitor the possible side effects.

Conclusion

In recent years, there has been an increasing use of TXA in dermatology as a therapeutic and prophylactic agent. Oral TXA has proven effective in the treatment of melasma, and although topical TXA has been shown to be less effective, it can be used in combination with other therapeutic methods such as microneedling to increase effectiveness. Although it has not shown effectiveness in the prevention of PIE, it can significantly improve post-acne erythema. It may also be effective in the treatment of mild to moderate acne and rosacea, but further research is needed.

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Sažetak

PRIMJENA TRANEKSAMIČNE KISELINE U DERMATOLOGIJI

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Traneksamična kiselina sintetski je derivat aminokiseline lizina, antifibrinolitika koji se prvenstveno rabi za smanjenje krvarenja u kirurškim zahvatima, traumi i stomatološkim zahvatima. Njegova protuupalna i antiangiogena svojstva, kao i njegova sposobnost suzbijanja melanogeneze omogućili su mu upotrebu u dermatologiji u liječenju kožnih stanja kao što su melazma, akne, poslijeupalna hiperpigmentacija, rozacea i angioedem. Traneksamičnu kiselinu moguće je primijeniti na različite načine: oralno, lokalno i intradermalno te u kombinaciji s drugim metodama liječenja. Ovaj pregledni članak prikazuje dokaze o učinkovitosti traneksamične kiseline u liječenju različitih kožnih poremećaja.

Ključne riječi: *Traneksamična kiselina; Dermatologija; Melazma; Akne; Rozacea; Angioedem*