

## CPD

## The emerging importance of tranexamic acid in dermatology

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## Summary

Tranexamic acid (TA) is an antifibrinolytic agent, increasingly recognized as being of utility for a wide variety of skin diseases. We review the evidence supporting the use of TA for a range of dermatological indications, including (among others) melasma, postinflammatory hyperpigmentation, urticaria, angio-oedema and haemostasis, in addition to practical considerations of its use by dermatologists.

## Introduction

Tranexamic acid (TA) is an antifibrinolytic agent with a long history of use in physiological bleeding. After the serendipitous discovery of TA as a treatment for urticaria and angio-oedema, interest has recently been rekindled for its efficacy in treatment of melasma. We discuss the hypothesized mechanisms of action of TA, the strongest evidence supporting the use of TA for various dermatological indications and practical suggestions of how its use may be incorporated into clinical practice. Contraindications to use of TA are outlined in Table 1, while studies using TA for dermatological indications are summarized in Table S1.

## Mechanisms of action

TA is an antifibrinolytic, reversibly binding to plasminogen, and thus preventing its conversion to plasmin and subsequent breakdown of fibrin. Additionally, TA reduces expression of vascular endothelial growth factor and endothelin-1, which also acts to minimize bleeding and hamper angiogenesis. In pigmentary disorders, TA is thought to reduce melanogenesis by inhibiting ultraviolet (UV) light-induced plasmin activity. Ordinarily, UV light enhances interaction of

plasmin with keratinocytes, resulting in prostaglandin E<sub>2</sub> release, which in turn stimulates melanocyte tyrosinase activity.<sup>1</sup> Both the anti-angiogenic and antime-lanogenetic properties are thought to contribute to the efficacy of TA in melasma. TA has been used prophylactically to prevent hereditary angio-oedema via its ability to reduce bradykinin levels through its effect on plasminogen.<sup>2</sup>

## Melasma

Melasma is a common acquired pigmentary disorder with a predilection for the face and an association with hormones, pregnancy and female sex. In melasma, various doses of TA and routes of administration have been trialled (Table S1).

Lee *et al.*<sup>3</sup> reported the largest retrospective case series to date of 561 patients treated with oral TA 250 mg twice daily for a median of 4 months, and reported a 90% improvement in melasma, with the median time of improvement being 2 months. Melasma recurred in 27.2% of patients on stopping therapy. Sharma *et al.*<sup>4</sup> reported oral TA 250 mg twice daily as showing similar efficacy to intradermal TA 4 mg/mL microinjections weekly in 100 patients for 3 months. A study in which intradermal TA was injected less frequently (4 mg/mL monthly) showed injected intradermal TA to be less efficacious with greater recurrence rate than oral TA 250 mg twice daily,<sup>5</sup> suggesting that intradermal TA injections should be administered more frequently to achieve equivalent efficacy to oral TA.

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**Table 1** Contraindications to tranexamic acid

Absolute contraindications	Relative contraindications
Active thromboembolic disease: DVT, PE, cerebral thrombosis	Concomitant use with the oral contraceptive pill
Personal or family history of thromboembolism including DVT, PE, cerebral thrombosis, cerebral retinal vein or artery occlusion	Acute promyelocytic leukaemia taking all-trans retinoic acid
Intrinsic risk of thrombosis or thromboembolism, e.g. thrombogenic valvular disease, thrombogenic cardiac rhythm disease or hypercoagulopathy	Breast-feeding
Hypersensitivity to TA or excipients	Renal/hepatic impairment: may require dose adjustment
Patients on Factor 9 complex concentrates or anti-inhibitor coagulant concentrates	
Pregnancy	
Fibrinolytic conditions due to consumption coagulopathy	
Severe renal insufficiency	
History of convulsions	
Acquired disturbances of colour vision	

DVT, deep vein thrombosis; PE, pulmonary embolism; TA, tranexamic acid.

The efficacy of topical TA for melasma is less well researched; one study with 60 patients suggested no significant difference in reduction of pigmentation in melasma between topical TA 5% twice daily vs. hydroquinone 2% twice daily for 12 weeks.<sup>6</sup>

Synergistic therapeutic effects upon melasma have been reported when combining topical TA with Q-switched neodymium:yttrium–aluminium–garnet (Nd:YAG) laser<sup>4</sup> and intradermal TA with 4% hydroquinone cream.<sup>7</sup> Application of a topical serum containing TA 3%, kojic acid 1% and nicotinamide 5% resulted in significant objective improvement in melasma, hyperpigmentation and postinflammatory hyperpigmentation (PIH) after 12 weeks.<sup>8</sup>

### Postinflammatory hyperpigmentation

Evidence supporting the use of TA as prophylaxis against PIH is not as compelling. Using higher injected doses than for melasma, one study reported that intradermal TA injections 50 mg/mL reduced PIH rates by 12% after Q-switched Nd:YAG laser on 50 solar lentigines.<sup>9</sup> However, oral TA 750 mg appeared to show no significant reduction in PIH following treatment with Q-switched ruby laser in 32 patients.<sup>10</sup> PIH secondary to allergic contact dermatitis from henna hair dye treated with a combination of low-fluence Q-switched Nd:YAG laser and oral TA was found to improve PIH in one patient.<sup>11</sup>

### Other pigmentary disorders

In a study by Xu *et al.*,<sup>12</sup> 7 of 10 patients treated with a combination of oral TA 50 mg once daily and glycyrrhizin compound (15 mg once daily) for 3 months showed marked improvement of recalcitrant Riehl melanosis as measured by melanin index. Moisturizing

cream containing 2% niacinamide and 2% TA appeared to be more effective at reducing facial pigmentation compared with moisturizing cream alone.<sup>13</sup> Of note, TA monotherapy has not been reported to successfully treat other facial dyschromias.

### Angio-oedema and urticaria

In 1977, preoperative patients were given oral TA 1 g four times/day prior to surgery to prevent angio-oedema episodes.<sup>14</sup> TA reduced the frequency and severity of chronic urticaria in two patients treated with TA 1 g four times/day, which was reduced according to response.<sup>15</sup>

A review of TA monotherapy in 33 French patients with angio-oedema secondary to angiotensin-converting enzyme inhibitors showed that 81% of patients had a significant improvement with TA monotherapy, but the remaining 19% required additional bradykinin inhibitor due to only partial improvement.<sup>16</sup> Wintemberger *et al.* suggested TA was efficacious as prophylaxis for angio-oedema in 64 patients, reducing attack frequency by 75% in just under 30% of patients.<sup>17</sup> The cost of injectable TA is significantly cheaper than that of bradykinin inhibitor, but C1 inhibitor concentrates and fresh frozen plasma are still first-line therapy in the USA and Europe. The use of TA is advocated for long-term reduction of frequency and severity of hereditary angio-oedema attacks.

### Reduction of bleeding

TA is frequently used as treatment for menorrhagia and by surgeons to reduce perioperative bleeding. Powell *et al.*<sup>18</sup> used topical TA to treat haemorrhaging congenital haemangiomas in two patients. The use of

gauze soaked in TA, epinephrine (adrenaline) and lidocaine in 20 patients undergoing Mohs micrographic surgery reduced the amount of bloodstain on the gauze compared with the saline control group, suggesting this could be a beneficial haemostatic aid during surgery.<sup>19</sup> A recent double-blind placebo-controlled trial in 131 patients suggested that intradermal injections of TA 100 mg/mL prior to dermatological surgery reduced bleeding, as assessed by the ratio of surgical wound size to bloodstain. Haemostasis was found to be subjectively enhanced in the TA group also ( $P = 0.043$ ), especially those on anticoagulant medications ( $P = 0.01$ ).<sup>20</sup>

### Safety profile

Although TA is not licensed for dermatological conditions, it has a long-standing safety profile.<sup>14</sup> Oral doses of TA to treat melasma are comparable to licensed monthly doses for menorrhagia. All of the studies presented in this article have demonstrated only mild adverse effects (AEs). The commonest AEs include abdominal pain, bloating, nausea and vomiting, numbness or facial pruritus, tinnitus, transient amnesia, tremor, dysmenorrhoea, hair shedding, facial hypertrichosis, lip or periorbital swelling, and palpitations. In the largest retrospective review of patients taking oral TA for melasma, one patient did develop a deep vein thrombosis, but this was due to an undisclosed coagulopathic state.<sup>3</sup>

### Practical use and conclusions

In Dermatology, the best evidence supporting the use of TA monotherapy is for melasma, but there remains a risk of relapse following cessation. Research on its long-term efficacy and safety remains limited. TA has been proven helpful as first-line treatment for and to reduce the frequency of attacks of chronic angio-oedema. More recently, the use of topical and injected TA to reduce bleeding in dermatological surgery has shown promise, and may be particularly helpful in patients undergoing protracted procedures (including Mohs micrographic surgery). Case reports have suggested that TA may also be helpful for treatment of rosacea<sup>21</sup> and rhytides.<sup>22</sup>

Interestingly, the doses of TA are variable dependent on the condition being treated. The highest dose, 100 mg/mL, is required for haemorrhage prevention, while the dose in PIH and melasma treatment is variable, ranging from 4 to 50 mg/mL.

TA in a carefully selected patient cohort has the potential to be an efficacious and cost-effective treatment; however, counselling and screening of patients, particularly for thrombophilia, before use is essential (Table 1).

### Learning points

- TA is a long-standing antifibrinolytic agent with multiple reported uses in dermatology.
- Dermatological indications for TA use remain off-licence.
- Systemic and intradermal TA have been used to effectively treat melasma.
- Systemic TA can be as prophylaxis against attacks of hereditary angio-oedema.
- AEs of TA include abdominal pain, bloating, nausea and vomiting, numbness or facial pruritus, tinnitus, transient amnesia, tremor, dysmenorrhoea, hair shedding, facial hypertrichosis, lip or periorbital swelling, and palpitations.
- Patients should be counselled about the rare risk of thromboembolic events, and underlying risk factors should be ascertained before initiation of treatment.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Studies of the use of tranexamic acid in dermatology.

## CPD questions

### Learning objective

To gain up-to-date knowledge on the dosage, indications for and adverse effects of tranexamic acid.

#### Question 1

What dose of tranexamic acid was used in the largest case series of patients to date treated for melasma?

- (a) 100 mg once daily.
- (b) 250 mg once daily.
- (c) 250 mg twice daily.
- (d) 500 mg twice daily.
- (e) 500 mg four times daily.

#### Question 2

What was the recurrence rate following discontinuation of tranexamic acid for treatment of melasma in the largest reported case series of patients to date?

- (a) 7%.
- (b) 27%.
- (c) 47%.
- (d) 67%.
- (e) 87%.

#### Question 3

When was the first reported use of tranexamic acid in hereditary angio-oedema?

- (a) 1957.
- (b) 1977.
- (c) 1987.
- (d) 1997.
- (e) 2017.

#### Question 4

Which of the following are possible adverse effects of treatment with tranexamic acid?

- (a) Abdominal pain.
- (b) Bloating.
- (c) Headache.
- (d) Hypertrichosis.
- (e) All of the above.

#### Question 5

Tranexamic acid has been reported for treatment of which of the following conditions?

- (a) Melasma.
- (b) Riehl melanosis.
- (c) Solar lentigines.
- (d) (a) and (b) only.
- (e) (a) and (c) only.

## Instructions for answering questions

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