Review Article

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Tranexamic acid: an important adjuvant in the treatment of melasma

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Summary

This article reviews an old drug tranexamic acid to its new use in the treatment of melasma. Its mechanism of preventing the activation of melanocyte from UV light, hormone and injured kerationcyte through the inhibition of the plasminogen activator system will be explored. The detail usage for such indication and its safety profile will also be thoroughly evaluated.

Keywords: tranexamic acid, melasma, hydroquinone, postinflammatory hyperpigmentation

Background

Publication in 1979 first revealed that tranexamic acid (TA) has a role in the treatment of melasma.[1]

Throughout the decades, there has been greater understanding regarding the relationship among the melanocyte/keratinocyte unit, the inflammatory mediator and cytokines on human melanocyte function, and the mechanism of how TA influences those pathways.

Melasma is a highly prevalent, chronic pigmentary disorder. This article will review the rationale, use, and safety profile of TA as an adjuvant treatment in melasma.

In 1979, Nijo Sadako had tried to use TA to treat a patient with chronic urticaria (that effect of TA had been reported in similar period[2,3]). Incidentally, he found that the melasma severity of that patient was significantly reduced after 2–3 weeks. Then, he put on the first trial of TA on melasma patients and showed that 1.5 g of daily oral TA together with vitamin B, C, and E supplements for 5 months has an obvious response in 11/12 patients aged 30–69. Most of the effect was noticed within 4 weeks of therapy.[1] In that time period, the mechanism of TA affecting the severity of melasma remained unknown.

Tranexamic acid (Trans-4-Aminomethylcyclohexanecarboxylic acid) (Fig. 1), is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss.[4–8] It is a synthetic derivative of the amino acid lysine and exerts its effect by reversibly blocking lysine binding sites on plasminogen molecules, thus inhibiting plasminogen activator (PA) from converting plasminogen to plasmin.[9,10]

As plasminogen also exists in human epidermal basal cells[11] and cultured human keratinocyte are known to produce PA,[12] there is basic rationale that TA will affect keratinocyte function and interaction.

Etiological factors of melasma related to PA system

The exact pathogenesis of melasma is likely multifactorial. Genetic predisposition, UV light exposure,[13,14] and hormonal influences,[15,16] are generally considered the major components.

Histopathology studies of melasma[14,17,18] showed the epidermal melanocytes are more active than in normal skin. They are enlarged, with prominent dendrites and increased synthesis of eumelanin.[18] They are also filled with more mitochondria, Golgi appara-

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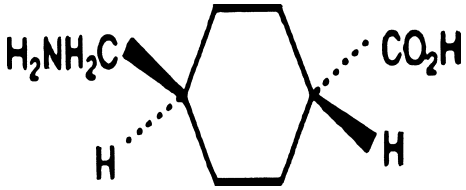

Figure 1 Chemical structure of tranexamic acid.

tus, and rough endoplasmic reticulum and ribosomes in electron microscopy, which reflect increased melanocytic activity.[17] This hyperactive melanocyte may be related to the genetic/ethnic predisposition of melasma.

Although so far no specific gene has been identified in the pathogenesis of melasma, this can be a multigenic interaction involving variations in melanocyte or keratinocyte responses to different stimulation factors, e.g., UV, hormones, AA, PG etc., which may explain the wide clinical spectrum of different patterns of melasma and responsiveness to treatment.

UV light exposure plays a key role in the pathogenesis of melasma. From the evidence of the below experiments, it is now understood that the UV-induced keratinocyte-PA system leading to melanogenesis can explain its role in melasma.

Melasma induced by hormonal replacement therapy and oral contraceptive pills has been well documented.[15,16] Actually, oral contraceptive pills and pregnancy have been shown to increase serum PA,[19] which we now know can activate the melanogenesis process.

Hence, melasma may be actually the consequence of genetically predisposed hyperactive melanocytes, which can be stimulated by UV light and by the hormone influence of keratinocyte PA system. This evidence is supported by the TA, which has been shown to reduce melasma severity in the following clinical studies.

How TA affects melanogenesis

In 1998, Maeda *et al.*[20] found that on UV-exposed skin, topical TA can have a dose-dependent preventative effect on post UV induced pigmentation from 7 days onward. It has no effect on nonexposed healthy skin. They also showed that topical TA causes a dose-dependent decrease in arachidonic acid-induced pigmentation.

It is known that UV irradiation induces PA synthesis and plasmin activity in cultured keratinocyte.[21,22] Plasmin activated precursors of secretory phospholipase A2,[23] which participates in the production of AA from membrane phospholipids, is a precursor to prostaglandins E2 and leukotrienes (LK), which can subsequently lead to melanogenesis.[24–30] Plasmin also participates in the release of basic fibroblast growth factor (FGF), which is again a potent melanocyte growth factor.[31]

Hence, the authors suggested that TA inhibits UV induced plasmin activity in keratinocyte by preventing the binding of plasminogen to keratinocyte, which results in a less free AA and diminished ability to produce PGs and subsequently reduces melanogenesis in melanocyte.

In 2007, Seong *et al.*,[32] used neonatal foreskin cultured melanocytes showing a significant decrease multiplying in number, decreased in tyrosinase activity, tyrosinase-related protein TRP1/2, and melanin content in 48 h with increased concentration of TA in the culture medium after UVB irradiation. However, there was no change in number and length of melanocyte dendrites.

Same year, Maeda *et al.*[33] found that tyrosinase activity was significantly increased when melanocytes were cultured with keratinocytes conditioned medium (KCM). They proved that it was the single chain urokinase PA (Sc-uPA) in keratinocyte that induced tyrosinase activity, increased cell perimeter, area, and increased dendrites in dose depending manner.

As uPA mRNA levels are increased in quiescent cultured keratinocyte upon growth stimulation,[34] this is consistent with their experiment KCM from growth phase induce tyrosinase activity more strongly than from the confluent phase in human melanocytes culture. Maeda *et al.* suggested that the growth of keratinocytes (e.g., after inflammation, injury, UV) surrounding melanocytes may play an important role in melanin synthesis.

Actually, in the KCM with sub-confluent keratinocytes, they found that plasmin can significantly increase the amount of sc-uPA (which is already known to secreted by human keratinocyte).[12,35] This can further induce keratinocyte growth, differentiation, and migration.[36]

Furthermore, they showed that TA can inhibit the tyrosinase inducing activity of KCM in human melanocytes (which are not inhibited without KCM) without affecting viability. Hence, TA can only stop the keratinocyte-activate-melanocyte pathway.

Thus, the authors concluded that sc-uPA generated by keratinocytes increases the activity of melanocytes *in vitro*, and the blocking of this pathway may be the mechanism through which TA reduces hyperpigmentation.

In 2010, Li *et al.*[37] used intradermal TA on guinea pigs, which had been exposed to UVB for 1 month. Injection was performed every day for another month. The authors found that at the basal layer of exposed epidermis, the number of melanocytes was not reduced, but the melanin content was significantly

Table 1 Studies showing possible relationship between keratinocyte-activate-melanocyte mechanism and the effects of TA

Experiment specimen/Medium	Research agent/Molecule	Results/Findings/Effects
UV exposed skin[20]	Topical TA	Dose dependent decreased in AA and pigmentation
UV-irradiated cultured keratinocyte[21,22]	Plasminogen activator synthesis, plasmin activity both increases	Plasmin activate release of FGF and AA leads to increase in PGE2, LK, which enhance melanogenesis[23–31]
UVB irradiated neonatal foreskin cultured melanocyte[32]	Cultured with increased concentration of TA	Melanocyte decrease multiplying, tyrosinase activity, TRP1/2, and melanin content, but no change in dendrites no. and length
Melanocytes cultured in Keratinocyte conditioned medium (KCM)[33]	Single chain urokinase PA (Sc-uPA) from keratinocyte	Dose dependent increase in melanocytes, tyrosinase activity, cell perimeter, area, and no. of dentrites
Growing phase of KCM (e.g., inflammation, injury, UV light)[33]	uPA mRNA levels are increased[34] Plasmin increased amount of sc-uPA from keratinocyte[12,35]	Stronger tyrosinase activity of melanocytes further induces keratinocyte growth, differentiation, and migration[36]
Melanocytes cultured in KCM[33]	TA solution	Inhibit tyrosinase inducing activity of KCM in melanocytes; no change in cell viability
UVB exposed guinea pig skin[37]	Intradermal TA	Basal epidermis reduced in melanin, but not in melanocyte number

TA, tranexamic acid.

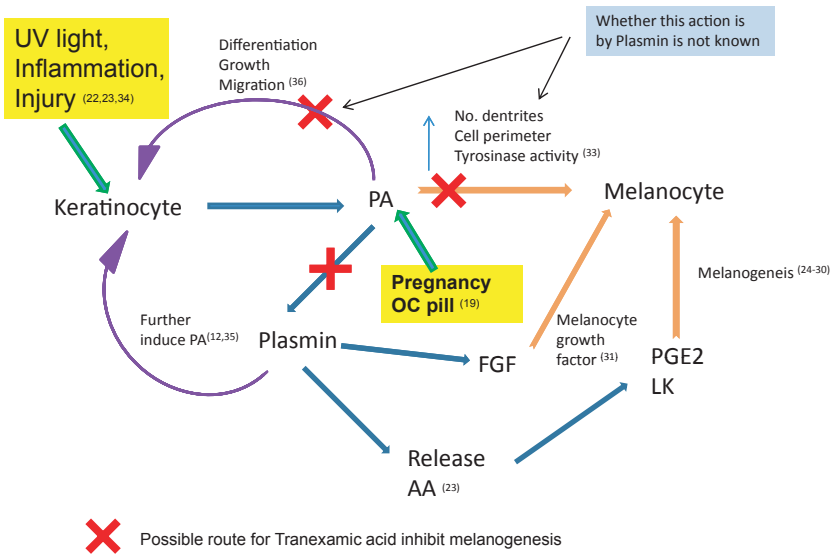

Figure 2 Summarizes the potential mechanism of TA affecting the process of melanogensis. TA, tranexamic acid.

lowered. Hence, they suggest TA has no effect on the number of melanocytes, but on the expression of melanin. (See Table 1 and Fig. 2 for overall summary).

Clinical studies of using TA on patients with melasma

After the first study in 1979, Japanese scientists had also shown in two other uncontrolled trials the effect of TA in the reduction in melasma. In 1985, Hajime *et al.*[38] showed 33/40 patients aged 24–60 had their melasma reduced in severity with 1–1.5 g daily oral TA in 10 weeks' time.

In 1988, 11 patients with melasma were treated with oral TA 0.75–1.5 g/day. All of them had decreased severity in a few months without adverse reaction. However, pigmentation recurred after few months cessation of the medication.[39]

Then, further similar studies have been performed in Asia after the millennium.

In 2001, Zhu *et al.*[40] used 250 mg TA, 0.2 g vitamin C, and 0.02 g vitamin E orally three times daily

to treat 128 melasma patients, compared to 30 control cases taking vitamins C and E only. A duration of 6–8 weeks is considered one course of treatment.

In the treatment group, 20% of patients showed more than 95%, 30% more than 60%, and 33% between 20% and 60% reduction in pigmentation (*P*-value < 0.01).

Authors also found that increasing the treatment duration (or the number of course) was more effective than increasing the dose of TA. Overall, there was no change in the coagulation parameter and only a few cases of reported GI upset during the study.

In 2005, Liu *et al.*[41] gave 250 mg TA three times daily, vitamin C 0.3 g, and vitamin E 0.1 g orally per day for melasma patients for 2 months, compared to a control group with vitamins C and E only. The treatment group (176) showed more improvement than the control group (70), with around 24% showing 90% improvement and 40% with 60% clinical improvement (*P*-values < 0.001 both in area reduction and improvement index).

Both the treatment and control groups had around 5% with mild tolerable GI symptoms. Of 61 (around 30%) cases in the treatment group checking the coagulation parameter, there was no significant abnormality detected.

In 2008, Wu *et al.*[42] used 250 mg two times daily oral TA as a single modality in treating 256 melasma patients (no control group). Thirty-three percent of the patients started to have clinical response in the first month, and 33% more showed improvement after the second month. After 6 months treatment, 10.5% patients showed 90% pigmentation reduction, 18.8% showed 60% improvement, and 51.6% had 30% reduction.

During treatment, 4.3% of patients showed GI upset and 3.5% had a decrease in the amount of mensus. The author had checked the first 100 patients' clotting parameter, which was all essentially normal.

Another trial in the same year by Mafune *et al.*[43] used 750 mg oral TA 2 tabs three times daily compared with a placebo for 8 weeks. In a comparison of clinical photos, 76/99 (76.8%) of the TA group showed improvement, whereas only 27/100 (27%) had an effect in the placebo group ($P < 0.001$). In the treatment group, there was one case of transient chest discomfort, but the patient's details were not mentioned.

In 2011, Cho *et al.*[44] carried the first controlled trial to use 500 mg/day of TA as an adjuvant therapy to 24 clients treated with intense pulse light or Nd:Yag laser for melasma compared to 27 clients who received the same treatment without TA. The modified MASA score was statistically significantly lower in the TA adjuvant group ($P < 0.005$). Up to 6 months of TA treatment did not lead to any significant systemic side effect.

Hence, from the above clinical studies, the usual effective dose of TA can be 250 mg 2–3 times daily, much lower than the usual dose to reduce excessive bleeding, and it should take at least 1 month to see a clinical response. It is the duration of the therapy, not the higher dose, that makes the treatment regime more effective (Table 2).

Other forms of TA administration for melasma

In 2006, Lee *et al.*[45] showed that 85 patients who completed weekly intradermal injections of TA for 12 weeks had significant decreases in the MASI melasma area and severity index from 8 weeks onward (eight rated good, 65 rated fair results). No significant side effect has been noted. However, it is not a double-blinded placebo control trial.

Topical TA in liposome formulation was developed in 2002,[46] and different patent topical TA products are already available in the cosmetic market.[47] Kondou *et al.* published an uncontrolled study in 2007 exploring the effects of a topical 2% TA emulsion applied to 25 melasma patients for 5–18 weeks. They showed that the TA emulsion improved the pigmentation in 20 subjects (80%). No side effect was recognized, and improvement was observed within 8 weeks.[48]

However, in 2012, a split face study in Thailand[49] was carried out with topical 5% TA in 23 women for a 12-week period. The result did not show any extra benefit from the topical TA, but caused more irritation to the applied area.

Topical TA is not commonly available, but it seems to be a potential modality if the pharmcokinetic infiltration of TA through the epidermis is thoroughly studied with different vehicles and if the issue of irritation can be resolved.

Ionotophoresis of TA using chemical enhancer and constant electric current has been reported.[50] This modality and machine are also available in the market, although clinical study is yet pending to prove its efficacy.[51]

Intravenous TA has also been advocated for the "whitening of skin" in Taiwan since 2007 and spread across some Asian countries. The usual recommended dose would be 500 mg TA every 2–4 weeks together with ascorbic acid, sometimes through direct intravenous injection or with normal saline infusion.[52] There is no clinical study to justify this use. Authors of this article would like to comment that this would be a highly underdose to have its

Table 2 Summarizes clinical studies using oral TA in the treatment of melasma

Studies	No. of patients/ Control	Age	Dose of oral TA	Control Tx	Duration	Results	Side effects	Remarks
Sadako *et al.*[1]	12/0	30–69	1.5 g/day + Vit B, C, E		5 months	11/12 have obvious result		Effect onset mostly in 4 weeks
Hajime *et al.*[38]	40/0	24–60	1–1.5 g/day		10 weeks	33/40 decrease in severity		
Higashi[39]	11/0	35–61	0.75–1.5 g/day		A few months	All decrease in severity	No adverse reaction	Symptoms recur after treatment stopped for few months
Zhu *et al.*[40]	128/30	30–49	750 mg/day + Vit C, E	Vit C, E	6–8 weeks	20% >95% ↓ 30% >60% ↓ 33% 20–60%↓ $P < 0.001$	Few cases GI upset	Observe increase duration of TA more effective than increased dose. No change in clotting profile
Liu *et al.*[41]	176/70	25–57	750 mg/day + Vit C, E	Vit C, E	2 months	24% >90% ↓ 40% >60% ↓ $P < 0.01$	5% GI upset in both group	No change in clotting profile
Wu *et al.*[42]	256/0	21–65	500 mg/day		6 months	10.5% >90% ↓ 18.8% >60% ↓ 51.6% 30%↓	4.3% GI upset, 3.5% mensus↓	33% response in 1st month, 33% in 2nd month. No change in clotting profile
Mafune *et al.*[43]	99/100	Above 15	2.25 g/day	Placebo	8 weeks	76.8% *vs.* 27% improved $P < 0.001$	1 transient chest discomfort	
Cho *et al.*[44]	24/27	32–50	500 mg/day + IPL/NdYag	IPL/Nd Yag	6 months	mMASA ↓ 43.8% *vs.* 23.6% $P < 0.005$	No significant side effect	

TA, tranexamic acid.

whitening effect. This also posts a potential risk of intravenous infection and cardiac overload for certain clients. Hence, the use of intravenous TA to reduce pigmentation of the skin has yet to be proven with further study.

Properties of TA and its safety profile

In 1999, Dunn and Goa[53] made a very detailed review of the pharmacodynamic and pharmacokinetic properties of TA and its clinical use.

Tranexamic acid forms a reversible complex with a high affinity lysine binding site of plasminogen such that it cannot bind to the surface of fibrin, retarding the fibrinolysis process. Suppression of fibrinolysis by TA is manifested in surgical patients by reductions in blood levels of D-dimer, but the drug has no effect on blood coagulation parameters.

The usual recommended dose of TA for clinical use is 0.5–1.5 g three times daily. Orally taken, TA will reach the peak plasma concentrations within 3 h and is not affected by food in the GI tract. For intravenous administration, 45% of the dose is recovered in urine in the first 3 h, and 90% of the drug is eliminated mostly in 1 day. TA is weakly (approximately 3%) bound to plasma protein, the plasminogen. The drug can cross the blood–brain barrier and the placenta, but excretion into breast milk is minimal. There is no available data regarding pharmacokinetics of TA applied topically on skin epidermis.

The commonly reported side effects of TA are nausea or diarrhea and, orthostatic reactions. Disturbances in color vision have also been documented. No mutagenic activity or harmful fetal effects have been reported.[54–56] Adverse events that have been reported include anaphylactic shock,[57,58] skin reaction,[59,60] and acute renal cortical necrosis.[61,62] TA has no effect on coagulation parameters. The suspected reported thrombotic incidents related to TA are summarized in Table 3 below.

In several randomized studies of patients with cardiac surgery involving cardiopulmonary bypass, no increase in incidence of thrombotic events were reported,[8,74–76] and there was also no such tendency toward bleeding disorders in 256 pregnant women.[77] In two case-control studies, the use of TA for the treatment of menorrhagia had no statistically significant association with risk of VTE.[78,79]

In the18th Expert Committee on the Selection and Use of Essential Medicines, Prof. Ian Roberts showed in his randomized studies of more than 20 000 trauma patients that a loading dose of 1 g TA followed by 1 g TA infusion over 8 h not only reduced mortality in the next 4 weeks, but it also reduced

Table 3 Summarized suspected thrombotic incidents related to tranexamic acid

Year	Age	Sex	Pre-exist	Indication	Dose	Duration	Adverse event
1976	31	♀	Thrombocytosis 700 × 109/L	Menorrhagia	3.0–4.5 g/day	10 days	Intracranial arterial thrombosis[63]
	32	♀	Thrombocytosis 540 × 109/L		0.5–1.0 g/d	1 year	
1977	39	♀	C1 esterase inhibitor def	Angioedema	6 g/day	1 year	Carotid artery thrombus[64]
1982	26	♀		IUCD induced menorrhagia	1.5 g/day	40 days	Right internal carotid artery thrombus[65]
1988	83	♂		Idiopathic thrombocytopenic purpura	1.5 g/day	16 months	Deep vein thrombosis right thigh[66]
1989	62	♀		Subarachnoid hemorrhage	24 g/day iv	3 days	Massive pulmonary embolism[67]
1994	49	♀	Acute promyelocytic leukemia with all-trans retinoic acid	Hemorrhagic diathesis	6 g/day iv	10 days	Suspected fatal thromboembolism[68]
2002	29	♂		Acquired. VIII deficiency	3 g/day	6 months	Pulmonary embolism[69]
2005	60	♂	Heavy smoker, massive blood transfusion	Gastrointestinal bleeding	1 g orally	1 h	Acute myocardial infarction[70]
2010	38	♀	O.C pills ? duration	Metrorrhagia Hb 7.7 g/dL	1.5 g/day	5 weeks	Left cerebral stroke[71]
2010	62	♂		Major cardiac surgery	148 mg/kg iv	Intraoperation	Ischemic seizure, brain infarction[72]
	86	♂			139 mg/kg iv		
	79	♂			125 mg/kg iv		
2011	59	♀	Bronchiectasis, lobar lung resection	Chronic hemoptysis	4 g/day	6 months	Pulmonary embolism[73]

thrombotic events in these patients (although not statistically significant).[80]

Hence, TA seems to have a very safe profile and the theoretical thrombotic risk is actually very low. The risk may be higher mainly if the patient has pre-existing morbidity, old age, has other prothrombotic drugs (e.g., oral contraceptive pills), or uses a very high dose and long duration of TA.

Some authors[42] suggest other contraindications of using TA should be: Pregnancy, breastfeeding, coronary disease, blood coagulation problems, current treatment with blood thinning drugs, e.g., aspirin, Plavix etc., and too high expectations for treatment outcome.

How TA is different from current treatment for melasma

Currently available treatments which are effective in reducing melasma include hydroquinone,[81–84] Glycolic acid peel,[85,86] Intense pulsed light,[87,88] low-fluence Q-switched Nd:YAG (1064 nm) laser,[89,90] and fractional resurfacing lasers.[91–93]

As there is no single modality to satisfactorily control melasma, topical cosmetics are also very commonly used as a complimenting agent. The most common ingredients that have been used include azelaic acid[94,95] kojic acid,[96,97] ascorbic acid,[98,99] arbutin,[100] licorice extract,[101] and soy extract.[102] Their mechanisms of actions have also been described in details.[103]

All the pre-existing treatment of melasma aim at reducing the formation of melanin from melanocyte (topical agents) and eliminating pre-existing melanin pigment (peeling, IPL, laser). However, they inevitably may activate melanocyte by different irritation, inflammation or by injuries to keratinocyte that lead to recurrence or postinflammatory hyperpigmentation (PIH).

Tranexamic acid is now the only modality that can actually prevent the activation of melanocyte by sunlight, hormonal influence, and injured keratinocyte (after UV, peeling, IPL, laser) through the inhibition of the PA activation system. It can not only reduce the formation of melasma, but also reduce the likelihood of recurrence after other treatment modalities themselves activate melanocyte.

Conclusion

With the increased evidence showing the interaction between keratinocytes and melanocytes in the process of melanogenesis through the PA activation system, there are more reasons and rationales to justify adding TA, the PA inhibitor, as an adjuvant in the treatment of melasma, to improve the efficacy of known effective treatments and reduce chance of recurrence.

Theoretically, any insult or injury to keratinocyte may induce hyperpigmentation through this PA activation system. Hence, TA may have its role in the prevention and treatment of PIH, which contributes to reduce the related risk in cosmetic laser/procedural therapy.

Its safety profile was thoroughly explored and with simple guidelines and alertness to contraindications, oral TA can be used safely and effectively in the treatment of melasma. The recommended dose would be 250 mg two times daily for at least 1 month. Prolonging prescription period should have a better effect than increasing the dosage.

However, there is no controlled trial study in other ethnic groups, e.g., Caucasians or Africans, and further data collection and risk assessment is necessary in these groups.

We hope that this review can bring more insights to the etiology of melasma related to the keratinocyte-PA-activate-melanocyte system, so that more controlled trial studies in different ethnic groups and investigations including gene exploration can be carried out to make more target therapy available in the future.

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