TRANEXAMIC ACID IN DERMATOLOGY

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ABSTRACT:

Facial melanoses are Group of pigmentary disorders that share a common clinical feature of alteration of pigmentation over the face. These are difficult to treat and affect the DLQI of the patients. Tranexamic acid is an antifibrinolytic agent which has found to efficacious in a difficult to treat facial melasma like melasma. It targets the vascular and pigment component of melasma providing a rapid and a sustained improvement.

Various studies in different doses and routes in different dermatoses are required to elucidate the exact efficacy of the drug. This article highlights the important dermatological aspects of tranexamic acid in detail.

Keywords: Melasma, tranexamic acid, TXA, plasmin, melanogenesis.

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INTRODUCTION:

Tranexamic acid (TXA) is an anti-fibrinolytic agent known for decades which has shown a multitude of effectiveness in controlling bleeding in trauma, abnormal uterine bleeding, menorrhagia, hemophilia, and various surgeries like arthroplasty and cardiopulmonary bypass surgeries. Thereby reducing the need for postoperative blood transfusion and mortality.[1]

Though its effects in melasma has been demonstrated way back in 1979.[2] It is an old wine in a new bottle which has attracted the attention of dermatologists recently in the past few years to use it in a refractory, resistant disorder like melasma. It has shown promising effects in all the routes administered like topical, oral or intradermal with minimal side effects.
HISTORY:

Tranexamic acid is a traditional haemostat which was used extensively for menorrhagia in the year 1968.[3] It was FDA approved for the same in 1970. It was also used as an adjuvant in the prophylaxis of hereditary angioedema[4]

The effect of this drug in melasma was an accidental discovery when NijoSadko in the year 1979 treated a patient with chronic urticaria with tranexamic acid who incidentally had melasma. During subsequent follow ups at the end of 2-3 weeks he noticed reduction in pigmentation of melasma. Then he did the 1st trial of TXA in melasma in which 12 patients were treated with 1.5g TXA daily along with vitamin B, C and E for 5 months. Results showed that 11/12 patients had reduction in pigmentation at the end of 4 weeks.[2]

CHEMISTRY:

Tranexamic acid is trans-4-aminomethylcyclohexanecarboxylic acid. It is an anti-fibrinolytic drug/hemostat used in bleeding and clotting disorders.[5]

MECHANISM OF ACTION:

Tranexamic acid prevents the conversion of plasminogen to plasmin. It has multi-faceted actions in the pathogenesis of melasma like reduces UV induced melanogenesis and reduces angiogenic factors production thereby reducing the vascularity.

- UV rays have both direct and indirect effect on the up regulation of melanogenesis. Direct effect is by the upgradation of the melanocyte proliferation, migration and stimulation of melanogenesis. Indirect effect is by the production of cytokines like IL-1 and ET-1 and the peptides like ACTH and α-MSH by the UV damaged keratinocytes.
- UV rays acts on the skin and results in increased production of plasminogen activator by the keratinocytes leading to increased production of plasmin[6]
- Tranexamic acid prevents the UV induced melanogenesis in skin and has no role in the normal skin. It reversibly binds to the lysine binding site of the plasminogen thereby preventing the interaction of plasmin with plasminogen.[6]
- UV rays activate the p53 that binds to the POMC (propiomelanocortin) and increases its expression which is then cleaved to ACTH, α-MSH, B-MSH and γ-MSH. The α-MSH acts on the MCR-1 (melanocortin 1 receptor) that is expressed on the keratinocytes and activates adenyl cyclase that triggers the production of cAMP which further activates the protein kinase A (PKA), which phosphorylates the cAMP response element binding protein (CREB), leading to the up-regulation of MITF and increases the production of eumelanin.[26] Tranexamic acid reduces the upregulation of MITF by activating the ERK(extracellular signal regulated kinase) pathway.

ROLE OF PLASMIN IN MELANOGENESIS:
Release of PGE2: Plasmin stimulates phospholipase-A2 that cleaves glycerophospholipid to arachidonic acid. Arachidonic acid is converted to its metabolites like prostaglandins and leukotrienes. Among these PGE2 stimulates melanogenesis.[8]

Increases α-MSH [9]

Increases basic fibroblast growth factor (FGF), that promotes the melanogenesis.[9]

Stimulates angiogenesis by increasing free and diffusible VEGF which in turn acts on the VEGF receptors situated on the keratinocytes to promote release of plasminogen and arachidonic acid that promotes melanogenesis[9][10]

Pregnancy and OCP also have been shown to increase the plasminogen activator in turn increasing plasmin

FORMULATION:

It has been used topically (liposomal formulation, gel, cream), orally and intradermally.

PHARMACOKINETICS:

Peak concentration is attained after 3 hours of oral intake. Bioavailability of tranexamic acid is 34% and is weakly binds to 3% of plasma proteins and exclusively. Around 95% of tranexamic acid is excreted unchanged in urine hence dose adjustment is warranted in renal dysfunction. Only a small portion of drug is metabolised in liver. The total cumulative excretion after an intravenous dose is approximately 90% after 24 hours.[11]

DOSE IN DERMATOLOGICAL CONDITIONS:

- Oral: 250-500mg 2-3 times /day[12]
- Intradermal: 4mg/ml [12]
- Topical – 3% or 5% gel/ creams
- It is also used as a prophylactic therapy in hereditary angioedema at a dose of 2-4g/day.[11]

SIDE EFFECTS:

- **Topical TXA** – Minimal side effects are reported. They include erythema, stinging, burning, xerosis.[13]

- **Oral tranexamic acid**: Side effects include nausea, diarrhoea, oligomenorrhea, palpitations. At high doses – venous thromboembolism, CVA and pulmonary embolism has been reported[14]. In melasma we use low doses hence the side effects are minimal. But still to be on the safer side doing a coagulation profile of the patient before starting the patient on this drug is mandatory.
Intradermal – Pain, edema, burning, irritation\(^[12]\)

CONTRAINDICATIONS:

- Contraindications of melasma include bleeding and clotting disorders, Drug hypersensitivity, Defective colour vision, Stroke, Family history of coagulation defects, Ischemic heart disease, Venous thromboembolism\(^[16]\)

PREVIOUS STUDIES WITH TRANEXAMIC ACID

Tranexamic acid is safe and efficacious in all routes of administration in melasma like Intralesional/microneedling [table 1], topical [table 2], oral [table 3], and rosacea [table 4] as evidenced by the previous studies.

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Methodology</th>
<th>No. Of patients</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>Lee et al(^[16])</td>
<td>A pilot study in which intradermal injection of TXA at a dose of 4mg/ml was given. Patients were followed up at 8 and 12 weeks</td>
<td>100</td>
<td>There was a significant reduction in the MASI score from 13.22±3.02 at baseline to 9.02±2.62 at end of 8 weeks to 7.57±2.54 at the end of 12 weeks.</td>
</tr>
<tr>
<td>2013</td>
<td>Budamakuntla et al(^[17])</td>
<td>In this open labelled RCT, patients were equally divided into 2 groups. One group was given localized microinjections of TXA and other group was treated with TXA microneedling done at monthly intervals and followed up for three months.</td>
<td>60</td>
<td>Microneedling group showed more reduction in MASI 44.41% when compared to microinjection which showed 35.72% improvement</td>
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Table 2

<table>
<thead>
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<tbody>
<tr>
<td>2019</td>
<td>Khuraiya et al(^[13])</td>
<td>In this split face trial with 5% topical tranexamic acid on one side of face (left side) application and in the other half triple combination(right side)application was done with a daytime sunscreen application of SPF 30. Patients were followed up every 2 weeks for 3 months.</td>
<td>25</td>
<td>the mean MASI score of tranexamic acid group reduced from 3.3 to 1.08 whereas in triple combination group , it reduced from 3.7 to 1.2 . side effects seen with tranexamic acid were mild like erythema, irritation and telangiectasia</td>
</tr>
<tr>
<td>2014</td>
<td>Ebrahimim and</td>
<td>In this double blinded split face</td>
<td>50</td>
<td>Significant reduction in</td>
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Naeni[18] trial, patients applied 3% TXA vs 3% HQ + 0.01% dexamethasone each on 1 side of face two times per day. Duration of study was 12 weeks. MASI scores was seen in both Groups but comparison of efficacy was not statistically significant between 2 drugs. However side effects were more in HQ Group.

2019 Khurana et al[12] Patients were equally divided into 2 groups, one group was given intralesional tranexamic acid (4mg/ml) and the other group was given oral tranexamic acid 250mg twice a day. Patients were followed up monthly once for 3 consecutive months. 64 The oral tranexamic acid group showed more significant response than the intralesional group.

**Table 3**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>2012</td>
<td>Karn et al[14]</td>
<td>RCT in which patients were divided equally in 2 groups. Group A was given oral TXA 250 mg BD for and Group B was treated with routine topical measures for 3 months. Assessment was done at 8 and 12 weeks</td>
<td>260</td>
<td>Masi score at baseline was 11.08±2.91 vs 8.95±2.08 at week 8 and vs. 7.84±2.44 at week 12; p&lt;0.05 for both). While among group B patients the p value was not significant.</td>
</tr>
<tr>
<td>2012</td>
<td>Wu et al[19]</td>
<td>Patients were treated with oral tranexamic acid 250 mg BD for 6 months and the patients were followed up for 6 more months for recurrence.</td>
<td>74</td>
<td>Results showed excellent response in 10.8%, good response in 54% and fair response in 31.1% and poor response in 4.1%. The recurrence rate was 9.5%.</td>
</tr>
<tr>
<td>2013</td>
<td>Cho et al[20]</td>
<td>RCT comparing oral tranexamic acid with low fluenceNd:YAG and IPL (Group A ) and only Nd:YAG and IPL(Group B) for 8 months.</td>
<td>51</td>
<td>The mMASI score reduction in Group A was 11.33±7.07 to 6.21±5.04 and in Group B was 11.70±6.72 to 8.93-5.89. More reduction in mMASI was seen with Group A.</td>
</tr>
<tr>
<td>2013</td>
<td>Shin et al[21]</td>
<td>This is a comparative study in which one group was treated with 1064 Qs Nd:YAG alone and another group was treated with 1064 Qs Nd:YAG andoral TXA - 500mg/day. 2 sessions of low fluenceNd :YAG was given in both groups. Patients were evaluated every 4 weeks for 8 weeks</td>
<td>48</td>
<td>At the end of 4 weeks, significant decrease in the mMASI was seen in both groups. They found the results were superior with combination than in laser alone patient group</td>
</tr>
<tr>
<td>2014</td>
<td>Aamir et al[22]</td>
<td>Patients were given 250 mg of oral tranexamic acid along with broad spectrum</td>
<td>65</td>
<td>15 patients had excellent response, 41 patients had good response and 8 patients had fair response</td>
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</table>
sunscreen for 6 months, 4 weekly once follow up was conducted. This was followed by treatment with sunscreens alone for next 6 months to assess the recurrence during this period patients were assessed 3 months once.

Recurrence was seen only in 8 patients.

2015 Padhi and Pradhan[23] In this RCT, Patients were divided into 2 Groups. Group A was treated with fluocinolone based triple combination and Group B was treated with oral TXA 250mg BD with fluocinolone based triple combination for 8 weeks and followed up for a period of 6 months.

Results showed that Group B showed faster pigment reduction than Group A. No recurrence was seen.

2017 DelRosario et al[24] Double blinded RCT in which patients were treated with sunscreen & oral TXA 500mg /day for 3 months. Then only sunscreen for 3 months vs placebo and sunscreen.

Tranexamic acid Group showed 49% reduction in mMASI score when compared to the placebo Group which was 18%.

Table 4

<table>
<thead>
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<tbody>
<tr>
<td>2019</td>
<td>Bageorgou et al[25]</td>
<td>Tranexamic acid solution infused in wet dressing (500mg/5ml) vs microneedling with tranexamic acid wet dressing. Dressings were kept for 20 mins. Patients were followed up every 15 days for 4 sessions</td>
<td>20</td>
<td>Investigator Global Assessment of Rosacea Severity Score (IGA-RSS) improvement was statistically significant in both groups and was found to be better in microneedling group.</td>
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Conclusion:

Tranexamic acid is a newer modality of treatment for melasma that is cost effective, easily available and has minimal side effects targeting the vascular and pigment component of melasma and inhibiting the plasmin production. Further studies in various other pigmentary disorders are required to know the exact efficacy of this drug.

References


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