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International Journal of Current Research and Innovation in Pharma Sciences

Journal homepage: https://www.ijcrips.com/

Review Article

TRANEXAMIC ACID TO TREAT MELASMA

Arati N Machale[1]*, Ashwini Andhale[1], Santosh Waghmare[1], Hemant Kamble[1].

[1]Shri Wagheshwar Gramvikas Pratishthan's Loknete Shri Dadapatil Pharate College of Pharmacy A/p-Mandavgan Pharata, Tal-Shirur, Dist-Pune, 412211.

ARTICLE INFO

Article history:
Received 07-06--2022
Accepted 12-06-2022
Available online 15-06-2022

Keywords:
Melasma,
tranexamic acid,
mechanism of action

ABSTRACT

Melasma is a common acquired disorder of hyperpigmentation that commonly affects those with skin of color. Tranexamic acid (TXA) is a novel treatment for melasma that has a multimodal mechanism of action. To provide a comprehensive review of the literature regarding the evidence on the mode of action, safety profile, and efficacy of TXA in the treatment of melasma. The literature was searched for publications on TXA in the treatment of melasma using MEDLINE, Scopus, and Google Scholar. The abstracts of the articles were screened and reviewed for relevance. The selected articles were read in detail for inclusion and also the relevant references were traced. This review is an attempt to evaluate the role of TA by various routes in melasma and offer suggestions for future directions of research. The abstracts of the articles were screened and reviewed for relevance. The selected articles were read in detail for inclusion and also the relevant references were traced. This review is an attempt to evaluate the role of TA by various routes in melasma and offer suggestions for future directions of research..

INTRODUCTION:

Tranexamic acid (TA), a by-product of amino acid lysine, was once synthesized in 1962 with the aid of the Japanese researchers, Shosuke and Okamoto. The antifibrinolytic exercise of the transisomer of TA was once first described in 1964 and given that then it has been used in a range of clinical settings and also to decrease blood loss in the course of a variety of surgeries.[1,2] The theoretical issue about multiplied thromboembolic effects, although none have been reported, has resulted in more than a few guidelines no longer recommending its activities use. At current TA is recommended for use in emergency trauma surgery, cardiovascular surgery, elective oral surgery, hip and knee arthroplasty procedures, spinal surgery, heavy menstrual bleeding and hereditary angioneurotic oedema.[3,4]

*** Corresponding author.**

E-mail address: aratimachale@gmail.com

Arati N Machale.

[Doi: 10.1000/ijcrips/2022/02]

Tranexamic acid (trans-4-(Aminomethyl)cyclohexanecarboxylic acid, TA), a plasmin inhibitor, is used as a hemostatic agent to deal with ordinary fibrinolysis to stop immoderate bleeding.

It is a artificial derivative of the amino acid lysine and exerts its effect by way of competitively inhibiting the activation of plasminogen activator (PA) thru reversible interactions with its lysine-binding sites, consequently inhibiting PA from converting plasminogen to plasmin.[5] TA is a highly new drug for melasma and was first mentioned in 1979 when Nijo Sadako tried to use it to treat a affected person with chronic urticaria. [6]This was once an accidental discovering but precipitated studies of TA on melasma sufferers. As a skin-lightening agent, TA has been used as a topical, intradermal microinjection, and oral agent. Although TA has emerged as a plausible remedy for melasma, it has now not been accepted via Food and Drug Administration of the United States for melasma and remedy remains controversial. Consequently, in this study, we carried out a systematic review to consider the therapeutic effect of TA for treating melasma.[7,8]

A has recently been proven to be high quality in treating melasma but the researchers have used more than a few empirical protocols, with and besides adjuvants, which has made it particularly tough to understand and assign TA its location in the massive

armamentarium of melasma therapies. We have tried to overview the fundamentals of TA pharmacology as is already acknowledged from its preceding non-dermatological makes use of in order to apprehend its position in melasma. An strive has additionally been made to encompass and interpret the a number relevant studies of TA in melasma to establish the most beneficial dose and route of administration for the first-class results.

Melasma is a benign pigmentary disease that is specially common in Asian women. The pathogenesis of melasma is still uncertain and its cure stays a challenge. Topical skin-lightening dealers remain the mainstay of cure but have variable success. In sufferers who are refractory to topical therapy, intense pulsed mild or laser interventions may also be a 2d line option; however, the said success charges of these strategies are low and paradoxical darkening is a recognized side-effect.

Tranexamic acid

The simple chemical shape is trans-4-aminomethylcyclohexanecarboxylic acid (trans-AMCHA) [Figure 1].[9,10] It inhibits the plasminogen activator with the aid of reversibly blockading the lysine binding web sites on both plasminogen and plasmin, a molecule accountable for degradation of fibrin which is a protein that varieties the framework of blood clots. Thus, it prevents clot breakdown and helps in stopping the bleeding whilst exhibiting no impact on blood coagulation parameters like platelet count, activated partial thromboplastin time and prothrombin time. The coagulation, inflammation and immunological pathways are recognised to be inter-related with involvement of sure frequent elements and steps which have an effect on these responses. Plasmin is additionally regarded to play a position in activation of complement, neutrophils and monocytes and its inhibition accordingly may additionally also have an antiinflammatory effect.[11–13]

Classically TA has been used orally at a dose of 0.5–1.5 g two or three instances daily and intravenously 0.5–1 g by way of slow injection three instances day by day for controlling the blood loss from most important trauma, postpartum bleeding, surgery, teeth removal, nose bleeds and menorrhagia.[12,13] It has also been used as local intraarticular injections in arthroplasty approaches and as 5% mouthwashes for oral procedures.[11]

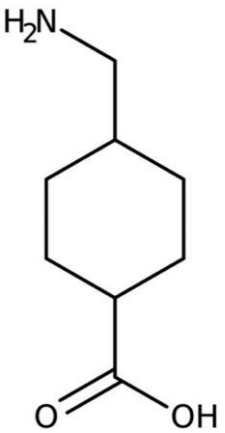

Figure 1: Structure of Tranexamic acid

The use in melasma of tranexamic acid effects from the formation of a reversible complex of the drug with plasminogen. Human plasminogen incorporates lysine binding websites that are vital for interactions now not only with synthetic antifibrinolytic amino acid derivatives but additionally with α2-antiplasmin and fibrin. One of these binding websites has a high affinity for tranexamic acid [dissociation steady (Kd) = 1.1 μmol/L]; the others have low affinity solely (Kd = 750 μmol/L).[14] Tranexamic acid nearly completely blocks the interplay of plasminogen and the heavy chain of plasmin with the lysine residues of fibrin monomer, especially via its binding to the excessive affinity lysine binding website online of plasminogen. Saturation of this web page with tranexamic acid prevents binding of plasminogen to the floor of fibrin (fig. 2).[15] This system retards fibrinolysis because, although plasmin is nonetheless formed, it is unable to bind to fibrinogen or fibrin monomer. Conversely, when the binding website of plasmin is blocked with the aid of tranexamic acid, inactivation via α2-antiplasmin can't proceed.[16] Comparisons of the binding potencies of tranexamic acid and EACA in fibrinolytic check structures have shown tranexamic acid to be more potent through a thing of between 6 and 10.[17] Tranexamic acid competitively inhibits the activation of trypsinogen via enterokinase and, at concentrations four time greater, noncompetitively inhibits the proteolytic action of trypsin. The drug also weakly inhibits thrombin.[18]

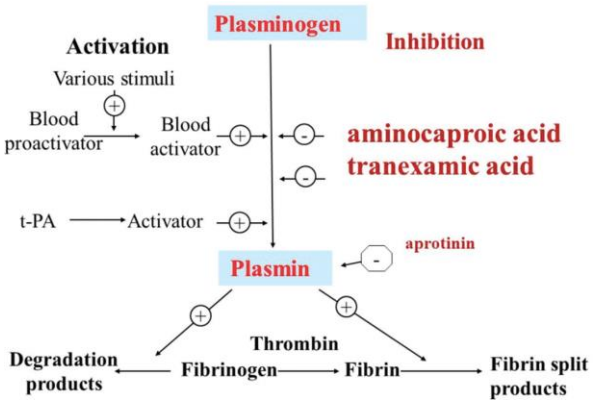

Figure 2: Mechanism of action of Tranexamic acid in clotting system[19]

Mechanism of Action

Tranexamic acid was discovered to inhibit bleeding by using its outcomes on the conversion of plasmin and for this reason in consequence stopping fibrinolysis over 50 years ago.[20] Its most important use in the 1990s was to result in hemostasis in surgical procedures and for the therapy of menorrhagia.[21] Aside from haemostatic effects, TXA also shows both anti-inflammatory and antiallergic properties. Tranexamic acid, which is a artificial by-product of the amino acid lysine, binds to lysine residues of plasminogen and prevents its conversion to plasmin (Figure 3). [22,23]

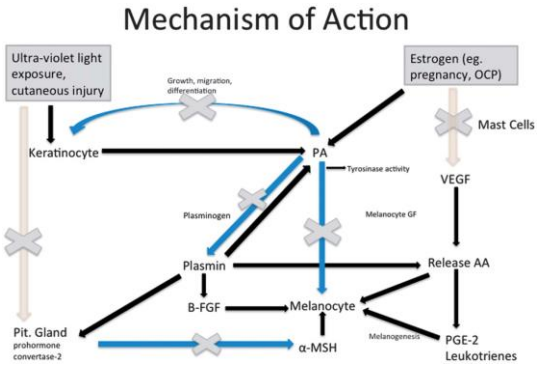

Figure 3. Tranexamic acid, Mode of action [24]

Pharmacokinetic Properties

Data from healthful volunteers showed most plasma concentrations of tranexamic acid to be reached within three hours of oral administration.[25] The presence of meals had no effect on gastrointestinal absorption or different pharmacokinetic traits of the drug (table II).[26] After intravenous administration of tranexamic acid (single dose of 1g), removing followed three exponential phases, with over 95% of the dose being excreted unchanged in the urine.[27] Total clearance (CL) ranged from 6.6 to 7 L/h (110 to 116 ml/min) in the 3 men and women who participated in this study. Mean whole urinary excretion in phrases of quantity of drug administered was959 mg/g. Other facts have proven that about 30% of an intravenous dose of 10 mg/kg is recovered in the urine throughout the first hour after administration; the total excretion rises to 45% after 3 hours, and to approximately 90% after 24 hours.[28,29]

At therapeutic plasma concentrations (5 to 10 mg/L), tranexamic acid is weakly (approximately 3%) certain to plasma protein: this appears to be absolutely accounted for by binding to plasminogen.[30] The drug crosses the blood-brain barrier and diffuses swiftly into joint fluid and synovial membranes.[31] Excretion in breast milk is low: the concentration of tranexamic acid in breast milk of lactating female 1 hour after the ultimate dose of two days' cure was once about 1% of the height serum concentration. The drug additionally passes thru the placenta. [27,30]

Formulations available: Tablets: Only TA-500 mg, 250 mg; combination of 250 mg TA with proanthocyanadin

Injections 100mg/ml

Topical creams (0.05g/50 ml) in combination with various whitening agents like kojic acid, mulberry extract, arbutin, vitamin E, etc. [2–4]

Doses of TXA used for melasma in studies to date have ranged from 500 to 1,500 mg daily.18,52 A typical dose is 250 mg twice daily. Treatment is usually continued for 8 to 12 weeks.52 This is in contrast to menorrhagia for which the dose is 3.9 to 4 g daily for up to 5 days per month.35

Contraindications to Tranexamic Acid Therapy

Contraindications to remedy include comorbidities such as renal dysfunction, malignancy, cardiovascular, respiratory disease, modern-day anticoagulant therapy, and history of thromboembolic disease, consisting of DVT, PE, arterial thrombosis, stroke,and subarachnoid hemorrhage. Other danger factors for thromboembolism such as pregnancy, hormonal contraception or alternative therapy, smoking, and lengthy distance journey need to additionally be taken into account when assessing suitability and need to be considered as an exclusion criterion if present.53 Patients must be screened carefully through careful records for contraindications and dangers and because of this given cautious directions to screen for facet consequences prior to initiation of remedy with TXA.[32,33]

Therapeutic Efficacy

The efficacy of tranexamic acid in a variety of symptoms has been

notably reviewed previous- ly in Drugs. In order to assessment 'best evidence', this area is constrained to wholly published, randomized managed trials assessing tranexamic acid for the prevention of extra blood loss or the therapy of different prerequisites in which antifibrinolytic therapy is considered to be potentially beneficial. The focus is on large (‡30–50 patients per cure arm), randomized controlled trials of tranexamic acid in grownup patients, with the emphasis on new records published since the previous review. Ran-domized controlled trials of a smaller size, or in- volving non-standard use are temporarily cited for completeness. Of the achievable nonhaemor- rhagic symptoms for tranexamic acid, published, randomized controlled trials had been reachable only for hereditary angioneurotic oedema. [34,35]

Tranexamic acid in melasma

Melasma, additionally recognised as chloasma or mask of pregnancy, is a common, acquired, hyperpigmentary disease normally affecting females.Though the genuine patho mechanism of melasma is unknown many etiological elements have been implicated in its causation as properly as aggravation. [2–4] Though asymptomatic, the overwhelming beauty have an effect on for many sufferers leads to brilliant emotional and psychosocial misery which outcomes in their seeking treatment. Despite the availability of a extensive variety of therapeutic choices its therapy stays challenging as pigmentation can also fade but often recurs. All the therapeutic modality's purpose at lowering the formation of melanin from melanocytes (topical agents) and eliminating pre-existing melanin pigment (peeling and laser). However, they inevitably may spark off the melanocytes through irritation, infection or with the aid of injuries to keratinocyte that leads to recurrence or PIH. Various topical and bodily healing procedures are thus, continuously being tried and evaluated both as stand-alone redress as nicely as in exceptional combinations. [36–38]

The effect of TA in melasma was a serendipitous discovery through Nijo Sadako [16] in 1979 when he used TA to deal with a patient with chronic urticaria who also had melasma and discovered that the melasma severity of the patient also decreased after 2-3 weeks. He then tried oral TA in a dose of 15-gram day by day along with nutrition B, C, E supplements for 5 months in 12 sufferers of melasma who showed lightening of lesions within four weeks of beginning therapy in eleven patients. Human keratinocytes are recognised to secrete urokinase kind plasminogen activator, which will increase the pastime of melanocytes in vitro. Tranexamic acid is believed to act in melasma by way of stopping the activation of melanocytes from ultraviolet (UV) light, hormones and injured keratinocyte via the inhibition of plasminogen activator device present in epidermal basal cells and keratinocytes. It additionally reduces melanocyte tyrosinase endeavor by means of suppressing the production of prostaglandins and has an additional effect on the dermal blood vessels as it decreases the angiogenesis by way of inhibition of vascular endothelium increase factor (VEGF) [Figure 3]. By all these moves it no longer only improves the melasma, but may also also reduce the probability of recurrence. [39–41]

Since the record by way of Sadako, TA has been tried by using more than a few investigators in melasma in various schedules and strengths and even lower doses of tranexamic acid i.e. 500mg/day have been stated to be effective.

Despite the reports of its efficacy in melasma, there were ethical issues about the use of an antifibrinolytic drug for a beauty condition. As it's topical use was once additionally considered to be nice in both oral and other surgeries to control blood loss, this inspired the researchers to consider the efficacy of topical formulations and intradermal use of TA even in melasma.

Intralesional injections are aimed at making use of an sufficient amount of medicine immediately at the challenging location and averting systemic effects. Furthermore, direct injection to the involved web sites allows decrease dosage of tablets to be used. TA has also been used as intradermal injections as well as with microneedling at varying intervals from weekly to monthly treatments in melasma. Traditionally used as a collagen induction therapy for facial scars and pores and skin rejuvenation, microneedling is widely used as a transdermal transport device for therapeutic capsules and vaccines. Microneedling transport system offers a minimally invasive and painless method of transdermal drug administration but has even proven an enchancment when used on my own in a preliminary find out about on melasma.

TA is regarded as pregnancy category B drug as no mutagenic pastime has been detected in in vitro and in vivo test systems. As it is only minimally excreted in breast milk, breastfeeding may additionally be continued, if required. [3,6,7] The in many instances suggested facet effects of TA are nausea, diarrhoea, vomiting and orthostatic hypotension. Rarely, disturbances in shade vision, anaphylactic shock, pores and skin response and acute renal cortical necrosis have additionally been documented. No hazardous foetal results have been reported. [42–44]

Oral tranexamic acid

A single find out about evaluated the different dosages of oral TA (500 mg, 750 mg, a thousand mg and 1500 mg per day) and

determined all the doses to be high quality but decrease doses than 500 mg have not been studied as yet for their effect.[45] Triple mixture creams and 4% hydroquinone lotions are the typical standard therapy for melasma. Oral TA when used with 4% hydroquinone gave beneficial results as compared to the sufferers the use of only 4% hydroquinone cream.[46] One study which in contrast oral TA 250 mg BD alongside with 3% topical TA with oral TA with 20% Azaleic acid determined each to be fine however a better response was once stated in the team receiving both oral and topical TA. Patients handled with IPL or Q switched Nd yag lasers showed higher effects when oral TA used to be used alongside with the procedures.[47] Most of the research used a dose of 250 mg B.D. introduced to the already ongoing topical therapy of melasma or laser tactics for a length of 12 weeks and commonly the outcomes confirmed a higher than 50% enchancment in the mMASI (modified melasma vicinity severity index) or MASI(melasma area severity index) or melanin index in the majority of the patients. Subjective pride was usually larger and a large lightening effect was once commonly seen through 2 months of therapy. Though in most of the research oral TA was given for 12 weeks however it was given safely in one study for eight months and in any other even upto two years without any sizable aspect effects. [48–52]

Topical TA

TA was used twice every day for 12 weeks in moderate melasma patients and 22 out of 23 sufferers confirmed improvement with lightening visible at 4 weeks. Fontana Masson stain showed a big decrease in the melanin content material in the epidermis. There was once a diminished variety of CD31-positive vessels, lowered expression of vascular endothelial boom aspect and downregulation of Endothelin.[53]

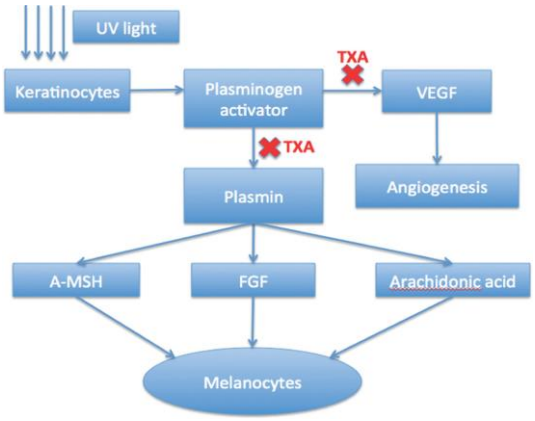

Figure 4: Mechanism of action of Tranexamic Acid in melasma [19]

Table 1: Studies of oral tranexamic acid

S. No	Author & year	Study design	No. of patients	Dose	Duration	Any other therapy	Outcome measure	Results	Side effects	Additional comments
1	Lajevardi et al., 2017[45]	parallel-group, assessor- and analyst-blinded, randomized controlled trial	100 patients divided into two groups	Test group- 250 mg TDS and hydroquinone 4% cream (HQ) at nightControl group- HQ 4% cream at night	3 months treatment + 3 months follow up	HQ 4% cream	-	At end of 6 months MASI score in the intervention group was 1.8 points lower than in the controls. Patient satisfaction was higher in test group (82%vs 34%)	No additional side effects were noted	Relapse rate was not significantly different (30% in test vs 26% in control)
2	Malik et al., 2019[46]	Prospective comparative study.	100 patients divided	All patients received oral TA- 250 mg twice	6 months	Group Atopical 3% TAtwice dailyGro	MASI	Mean MASI score decreased significan	-	Oral TA seems to perform better when

			into 2 groups	daily along with topical TA 3% in group A and 20 % azelaic acid in group B		up B- topical 20% azelaic acid once daily		tly in both groups. Group A improved more than group B but the difference was not statistically significant		combined with topical TA in comparison to Azelaic acid
3	Cho et al., 2013 [47]	Retrospective, comparative study	51 patients divided into 2 groups	Group A- oral TA 500 mg daily with IPL or laser treatmentsGroup B-only IPL or laser	8 months	IPL or low fluence QS Nd:YAG laser	mMASI scores	Group A showed more reduction in Modified MASI score	Transient headache	Oral TA may improve efficacy of laser or light based therapies for melasma
4	Khurana et al., 2019[32]	Prospective, randomized, comparative, open-label study	64 divided into 2 groups of 32 each	Group Alocalized microinjections (4 mg/ml) of TA monthlyGroup Boral TA 250 mg BD	3 months	-	Modified MASI scoresPhotographic assessment	Modified MASI score improved in the oral group by 57.5% as compared to 43.5% in the intralesional group	6-month2 in the oral group and 3 in the injection group showed relapse	Oral TA showed better efficacy than intradermal TA in this study but the effect of increasing the concentration or frequency of injections needs to be further assessed
5	Sharma et al., 2017	Randomized, comparative study	100 patients divided into 2 groups of 50 each	Group A- Oral TA 250 mg BDGroup B- Intradermal microinjections of TA of 4mg/ml at 4 weekly intervals	12 weeks	-	MASI score	Average reduction of MASI- 77.96 ± 9.39 in group A and 79.00 ± 9.64 in group B	Mild epigastric discomfort, hypomenorrhea, headache and injection site pain.	Both oral and intradermal injections of TA seem to be equally effective in melasma
6	Li et al.,2014[48]	Prospective, open study in 2011-2012	35	500mg TDS	16 weeks	Sunscreen with SPF 30	MASI scorePhysician assessmentPatient assessment	All patients had moderate to marked improvement	No serious adverse effects	Oral TA appears to be an effective and safe therapeutic option.

Table 2: Studies of topical tranexamic acid

S. No	Author & year	Study design	No. of patients	Dose	Duration	Any other therapy	Outcome measure	Results	Side effects	Additional comments
7	Ebrahimi et al., 2014[50]	Double-blind split-face trial	50	One half of face- topical 3% TA emulsionOther half of face- combined solution of 3% hydroquinone & 0.01% dexamethasone twice a day	12 weeks	Sun screen with SPF 30 or more	MASI score & patient satisfaction	No significant difference between the two sides but side effects of hydroquinone + dexamethasone were significantly prominent as compared with TA	Erythema, skin irritation, dryness, scaling	Topical TA showed similar efficacy to combined effect of hydroquinone and dexamethasone
8	Kim et al., 2016 [7]	Prospective study	23	Topical 2% TA emulsion twice a day + face mask with 2 % TA three times a week	12 weeks	Sun block	Modified MASI score & chromameter	22/23 showed improvement	None reported	Skin biopsies obtained from 10 participants showed decreased pigmentation, vascularity and Endothelin 1.
9	Ayuthaya et al. 2012 [54]	Double blind, randomized, prospective split face study	23	Topical 5% TA on one side with only vehicle on other side twice daily	12 weeks	Sunscreen	MASI,Melanin and erythema index physician and patient global assessment	18 patients showed a decrease in Melanin Index and MASI score also decreased on both sides but no difference between the sides.	Erythema was significant on the TA applied site as compared to the vehicle side	-
10	Banihashemi et al., 2015[35]	Split-face study	23	5% topical liposomal TA on one side and 4% hydroquinone cream on the other side twice daily	12 week	Sunscreen	MASI	mean MASI scores significantly reduced in both treated sides. Though a greater decrease was observed with 5% liposomal TA but it was not statistically significant	No serious adverse events occurred with TA but irritation occurred in three patients with hydroquinone	Topical TA seems to be as effective as 4% hydroquinone
11	Chung et al., 2016 [55]	Randomized, split-face	15	Topical TA vs vehicle applied on	12 weeks	IPL (4 monthly sessions)	Melanin index (MI) &	MI and mMASI decreased	No serious side effects	Topical TA also helped in

		study		randomly assigned side			mMASI score	significantly from baseline to 12 weeks after the last IPL treatment on the topical TA side but not on the vehicle side		preventing rebound pigmentation after IPL treatment
12	Tawfic et al., 2019 [56]	Randomized comparative split-face study	15	One side randomly assigned to topicalTA solution after the session immediately or intradermal microinjection of TA prior to the laser session	30 Weeks	Fractional CO2 over the entire face every4 to 6 weeks for 5 sessions	MASI score, melanin index (MI), and erythema index (EI)	Significant reduction of MASI score over both sides but no difference between the two sides	Mild pain.	Low power fractional CO2 laser is effective in melasma but whether the addition of TA adds to the benefit needs further evaluation
13	Laothaworn et al., 2018 [57]	Randomized, prospective, split-face, controlled trial	25	Topical TA 3%vs vehicle applied on randomly assigned side for 8 weeks	8 weeks	QSNdYag Laser1064-nmat baseline and at 4 weeks over entire face.	mMASI scores, Mexameter participant evaluation	Combination treatment showed significant decrease in the mMASI score as compared to laser-alone.	No serious side effects	-

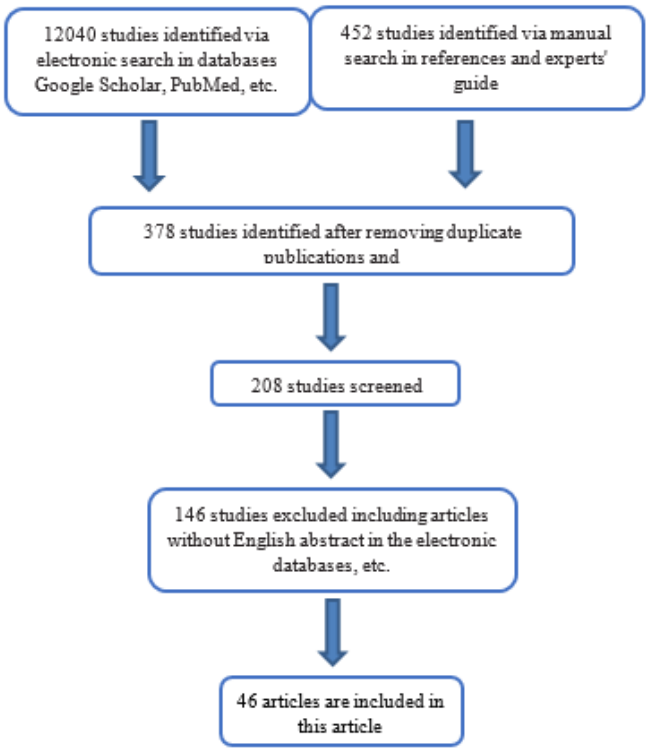

Figure 5: Flow diagram for the study review

CONCLUSION

Melasma is a recurrent and refractory trouble with a vast range of each clinical and procedural therapeutic preferences reachable for its management. Appropriate and really appropriate use of drug treatments which are wonderful and can be used for longer time is necessary to treat melasma besides any aspect effects. TA in all types (oral, topical) have shown promising consequences over the previous few years when used along with different remedies as nicely as when used as a stand-alone therapy.

TA has been tried at varying oral doses, varying topical concentrations and at various time intervals intradermally and also with and without a number adjuvant. Though nearly all the studies exhibit the recommended impact of TA there is still no consensus on the most fulfilling route, dose and timing of the remedy with TA in melasma. For oral TA effectiveness the length of remedy has been advised to be greater necessary than the dose. Future directions for lookup should include long-term protection of completed outcomes following the cessation of oral TA, as well as aggregate therapy with TA and different modalities, such as laser treatments. Newer research on the horizon have begun to observe laserassisted drug transport of topical tranexamic acid. There stays a major need for large-scale, randomized, placebo-controlled trials to validate the e¬ ectiveness of TA in melasma and decide the first-rate mode of delivery, Further studies are required to elucidate not only the best formulation, attention but additionally the function of renovation doses/ sittings and even if there might also be some function of combination or sequential therapy with oral and topical TA in the identical patient.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgements

I would like to thank Prof. for her help and assistance in writing this manuscript. I would also like to thank Principal of Shri Wagheshwar Gramvikas Pratishthan's Loknete Shri Dadapatil Pharate College of Pharmacy for his support on the manuscript.

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Author biography

Arati N Machale[1]*, Student

Ashwini Andhale, **Student**

Santosh Waghmare, **Student**

Hemant Kamble, **Student**

Cite this article: Arati N Machale, Ashwini Andhale, Santosh Waghmare, Hemant Kamble, tranexamic acid to treat melasma *International Journal of Current Research and Innovation in Pharma Sciences, 2022;1(1):5-15.*

[Doi: 10.1000/ijcrips/2022/02]