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INTRALESIONAL TRANEXAMIC ACID-EFFECTIVE AND SAFE WAY OF TREATMENT FOR MELASMA.

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Abstract
Even though melasma is primarily a cosmetic concern, this condition can dramatically impact the quality of life of affected patients and causes depression and frustration, reducing their psychosocial quality of life. Currently, there are numerous treatment modalities for melasma but it is a challenging condition for dermatologists due to its chronicity and with a high recurrence rate after treatment. However, for the satisfactory outcomes, role of the recent developments, tranexamic acid (TA) was evaluated. A quasi experimental study was done to evaluate the efficacy and safety of tranexamic acid (TA). Group A Patients were administered intralesional injection (4 mg/ml) of Tranexamic acid (TA) weekly for 6 weeks and group B patients were treated with oral Tranexamic acid 250 mg 12 hourly for 12 weeks. The response to treatment was assessed by The Melasma Area and Severity Index (MASI) score. The study showed the MASI scores at the baseline, 4 weeks, 8 weeks and 12 weeks in group A were 15.23±1.21, 5.14±2.25, 3.11±1.14 and 2.21±2.01 respectively and in group B 14.77±1.11,10.21±4.25, 7.57±5.25 and 6.22±4.16 respectively. The mean MASI significantly reduced in group A compared to group B. The present study showed that among the group A patients, 44% rated excellent (>75% reduction) in outcome, and only 8%(<25% reduction) was unsatisfactory and among group B patients, 16% rated excellent in outcome, and 18% was unsatisfactory. Side effects were negligible. Study results concluded that intralesional injection of tranexamic acid produces effective results without significant side effects.

Key words: melasma, intralesional tranexamic acid, oral tranexamic acid, treatment of melasma.

Introduction:

Melasma is the most common cause of acquired facial melanosis, due to a disorder in melanogenesis.[1] Melasma is manifested by symmetrically distributed, hyperpigmented macules and patches at frequently sun-exposed areas of the skin, especially on the face.[2] On the basis of histopathology, three types of Melasma are there: Dermal Melasma, which exists with color of greyish blue and faded margin. Second type is Epidermal Melasma, which has well margined

border and it appears in brown color and the third one is indeterminate or mixed Melasma.[3] Several factors like UV radiation, pregnancy, hormonal activity, thyroid abnormalities, and medications trigger the synthesis of melanosomes and increased melanosomes transfer to keratinocytes.[4] Treatment of melasma poses a great challenge due to recurrence and refractory nature. Various treatment modalities are available, these include sunscreens, hypo-pigmenting agents, dermabrasion, chemical peels, and laser therapy.[1,5] However, these treatments can yield adverse effects such as mottled hypopigmentation, irritation, acneiform eruptions, and rebound hyperpigmentation.[6]

Tranexamic acid (TA), a newer treatment modality for melasma is a hemostatic agent, has hypo pigmentary effect and also prevents ultraviolet-induced pigmentation.[7,8] In addition to its hemostatic effects, it also exhibits anti- allergic and anti-inflammatory effects in angioedema like conditions.[9] Its anti-inflammatory property appears to be related to its inhibitory effect on melanogenesis. [10,11] In 1979, Nijor used Tranexamic acid (TA) to treat chronic urticarial patients, this was accidental discovery and reported the action of tranexamic acid in melasma.[12] Tranexamic acid when administered in its oral and topical forms or injected locally reported to improve melasma. Tranexamic acid (trans-4-aminomethylcyclohexane-carboxylic acid; TA) is a plasmin inhibitor, with the synthetic derivative of amino acid lysine that works by reversibly blocking lysine binding sites on plasminogen molecules to inhibit the plasminogen activator (PA) from converting plasminogen to plasmin.[13]

The main mechanism of the hypopigmentation effects of TA is due to its antiplasmin activity, with a structural similarity relative to tyrosine that can inhibit tyrosinase competitively.[3,14] Whereas, plasmin transforms the vascular endothelial growth factor (VEGF) into a diffusing form, which demonstrates a crucial role of tranexamic acid following histological examination in the reduction of erythema and vascularities as well as the number of mast cells in the dermis.[15,16] In clinical studies, localized intradermal TA injection observed efficacious for melasma treatment,[17-19] with a significant decrease in pigmentation,[18] and no systemic side effects.[6] This study aimed to evaluate the efficacy and safety profile of intradermal Tranexamic acid (TA) injection for the treatment of melasma.

Materials and Methods:

A quasi-experimental study was done in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University from July 2021 to June 2023 for a period of 2 years. A total of 100 patients with melasma, who did not respond to topical therapy, age above 18 years, patient with dermal-type melasma (according to Wood's light examination) with bilateral symmetric melasma were included in the study. Exclusion criteria included pregnancy and lactation within 12 months prior to the study, oral contraceptive pill use, a history of coagulation and thrombotic disorder, use of anticoagulants, allergy to Tranexamic acid (TA), treatment for melasma within six months prior to the study, acute febrile illness, and history of herpes simplex lesions on the face and history of immuno-suppression/HIV infection. This study was approved by Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University. All patients signed a written informed consent form. Patients were randomly divided into group A and Group B by lottery method. Group A Patients were administered intralesional injection (4 mg/ml) of Tranexamic acid (TA) weekly for 6 weeks and group B patients were treated with oral Tranexamic acid 250 mg 12 hourly for 12 weeks after taking informed consent. The response to treatment was assessed by MASI on 4 weeks, 8 weeks and 12 weeks after stopping treatment. Statistical analysis was done using SPSS software version 23. Frequencies were presented as numbers and percentages. χ^2 and Fisher's exact tests were used to test the differences between the categorical variables. A p value less than 0.05 was considered significant.

Outcome measures: Based on standard guidelines, the MASI was used to evaluate the involved area, darkness, and homogenocity of hyperpigmentation. For calculating the involved area (A), the right side of the forehead, the cheek, and the chin were calculated as 15%, 30%, and 5% of the

whole face, respectively. Similar areas on the left side of the face were calculated in the same way, reaching a total of 100%. The final score ranged between 0 and 6 (0 = no involvement, 1 = 0%−9%, 2 = 10%−29%, 3 = 30%−49%, 4 = 50%−69%, 5 = 70%−89% and 6 = 90%−100%). Darkness (D) is evaluated based on a 0−4 scale: scale 0 means the absence of any darkness; scale 1 is a light brown color; scale 2 is a brown color; scale 3 is a dark brown color; scale 4 means black. Homogeneity (H) is measured on a 0−4 scale, from the minimal to the maximal grade of homogeneity. At last, the MASI score is calculated by multiplying the A score by the sum of D and H for each of the six regions. The maximum score for each side is 24, and the minimum is zero.
MASI score: 0.15(A)(D + H) + 0.3(A)(D + H) + 0.05(A)(D + H).Patients were visited, and the MASI score, and potential side effects were evaluated at baseline and after 4, 8, 12, and 24 weeks of treatment.

Intervention of intralesional injection of Tranexamic acid (TA): Patients data, including age, disease duration, and family history of melasma, were recorded. Wood's light examination was done; patients were divided into three subtypes; dermal-type melasma, epidermal type and mixed-type melasma. Patients (dermal type only) of group A were asked to apply topical anesthetic cream (EMLA®, 2.5% lidocaine and 2.5% prilocaine) on the face for 45 minutes, then wash it off before treatment with 4 mg/mL intradermal TA injection. The 30-gauge needles were injected intradermally into the melasma lesion at a 1-cm intervals. To keep the distance of injections at 1 cm intervals, the distances measured with a ruler and marked them with a pen. Thirty minutes after the procedure, the spots were cleaned with an alcohol pad. TA was prepared under sterile conditions and drawn in a 100-U/mL insulin syringe, then diluted with normal saline up to 1mL for the 4mg/mL of concentrated TA (about 0.05 mL/1 cm^2), with an ice pack applied to relieve pain.
All patients were prescribed a broad-spectrum sunscreen with a sun protection factor of 50 for the study period. The follow-up period included assessments at baseline and 4, 8 and 12 weeks using the Melasma Area and Severity Index (MASI score). Patient satisfaction and adverse side effects were also evaluated at each follow-up visit and the patients were examined at monthly intervals to look for any relapse or side effects, such as pain, post procedure erythema, or edema, were recorded at each session.

Patient satisfaction: A questionnaire was given to patients at the end of treatment to assess their degree of improvement. The patient's self-assessment was graded along four scales of pigmentation lightening: more than 75% lightening (excellent); 51 to 75% (good); 26 to 50% (moderate); and 0 to 25% (unsatisfactory).

Results: The study showed the MASI scores at the baseline, 4 weeks, 8 weeks and 12 weeks in group A were 15.23±1.21, 5.14±2.25, 3.11±1.14 and 2.21±2.01 respectively and in group B 14.77±1.11,10.21±4.25, 7.57±5.25 and 6.22±4.16 respectively. The mean MASI significantly reduced in group A compared to group B at 4^{th}, 8^{th} and 12^{th} weeks. The present study showed that among the group A patients, 44% rated excellent (>75% reduction) in outcome, 26% good(50-75% reduction), 22% moderate(25-50% reduction) and only 8%(<25% reduction) was unsatisfactory and among group B patients, 16% rated excellent in outcome, 24% good, 42% moderate and 18% was unsatisfactory. Overall improvement in our study in group A was 92% and group B 82%. Side effects were negligible; erythema and burning pain in the injection site were observed and disappeared within 1 hour after injection. There were no systemic side effects, such as nausea, vomiting, abdominal pain, headache, hypomenorrhea, or spotting menstruation.

Table 1: Comparison of MASI Score (Melasma area severity index) between two groups.

MASI Score	Group A	Group B	P Value
At the baseline	15.23±1.21	14.77±1.11	0.13^{ns}
First visit at 4^{th} weeks,	5.14±2.25	10.21±4.25	0.00^{s}
Second visit at 8^{th} weeks	3.11±1.14	7.57±5.25	0.00^{s}
Third visit at 12^{th} weeks	2.21±2.01	6.22±4.16	0.00^{s}

Table 2: Outcome at the end of follow up between two groups.

Outcome	Group A	Group B	P value
Excellent (>75% reduction)	22(44%)	8(16%)	$<0.05^S$
Good(50-75% reduction)	13(26%)	12(24%)	
Moderate(25-50% reduction)	11(22%)	21(42%)	
Unsatisfactory(<25% reduction)	4(8%)	9(18%)	

Discussion:

The study showed the MASI scores at the baseline, 4 weeks, 8 weeks and 12 weeks in group A were 15.23±1.21, 5.14±2.25, 3.11±1.14 and 2.21±2.01 respectively and in group B 14.77±1.11,10.21±4.25, 7.57±5.25 and 6.22±4.16 respectively. The mean MASI significantly reduced in group A compared to group B at 4^{th}, 8^{th} and 12^{th} weeks. Muneeb et al conducted a study where they injected 0.05ml (4mg/ml) of tranexamic acid intradermaly in melasma lesion at 1cm interval with a 30 guage needle after topical anesthetic application. Improvement was assessed at 4, 8 and 12 weeks using MASI score. After completion of study, MASI score in the 12th week significantly decreased compared to the baseline. For the mean modified MASI score after treatment a decrease was shown from 2.73±1.07 at baseline to 2.16±1.07, 1.74±0.94 and 1.17±0.82 at weeks 4th, 8th & 12^{th} respectively. Changes in the MASI score slightly decreased since week 4th and showed statistically significant difference at week 8th ($p < 0.05$).[20]

A prospective study by Lee et al. observed the effect of localized TA intradermal microinjection (4 mg/mL) on 100 women with melasma. About 85 patients completed the study, and a statistically significant decrease was observed in MASI at 8 and 12 weeks.[7] In another study in 2009, Steiner et al. compared the effects of topical TA 3% with intradermal injection of TA in 18 women with melasma. Group A used 3% TA twice a day and injection with TA (4 mg/mL) weekly for 12 weeks was performed for group B. Seventeen patients completed the study. According to MASI score and calorimetric evaluation, both groups improved significantly, and no significant difference was observed between them.[21] During a prospective study, Budamakuntla et al. divided 60 patients into two groups. A group was under TA microinjection (4mg/mL) and another group under TA microneedling (4mg/mL) for 3 months (0, 4, 8 and 12 weeks) followed up for 3 months. In the microinjection group, 35.72% improvement was observed in MASI score, compared with 44.41% in the microneedling. Improvement in the micro-needling group was better than the microinjection group.[16] Sharma et al. during a study, investigated 100 patients (92 women and eight men) and divided them into two groups. One group was treated with oral 250 mg tranexamic acid twice a day and the other group was injected intradermally with TA 4 mg/ML every 4 weeks. The treatment period was 3 months. Mean reduction of MASI in the 12^{th} week was not significant, 77.96 in the oral group and 79.00 in the injection group.[22] Lueangarun et al conducted a study and observed that there was statistical significance for modified MASI scores of 24±1.36, 2.82±1.11, 2.46±1.36, 2.22±1.42, 2.16±1.02 and 1.95±0.75 points at baseline and weeks 4, 8, 12, 16, and 48, respectively.[23] In another prospective comparative study in 2018, Shetty et al divided 40 patients into two groups. Group A were treated with intradermal injection of TA (4 mg/mL) once at 3 week intervals (0, 3, 6, 9 and 12 weeks) for 12 weeks and group B were treated with oral tranexamic acid 250 mg twice a day for 12 weeks. According to MASI score reduction, difference was observed between them. Intradermal injection of tranexamic acid has a higher clinical improvement (35.6%) compared to oral tranexamic acid (21.7%).[24] Pazyar et al observed in their study that the initial MASI score for the tranexamic acid group was 6.1 (95% CI, 2.5 SD) and 3.5 (95% CI, 2.0 SD) at the end of the study ($P<0.001$). The MASI score decreased significantly in all follow-ups.[25] A study conducted by Gharib et al revealed promising results regarding the use of intradermal injection of tranexamic acid. The severity of melasma was reduced after treatment with intradermal injection of tranexamic acid in many patients in Group A. The difference in the MASI score in this study before and after treatment with intradermal injection of tranexamic acid was statistically significant ($p<0.001$). The mean MASI score after treatment decreased from 13.83±7.23 at baseline to 11.11±5.48, 7.17±3.9, and 5.49±3.91 at 4, 8, and 12 weeks, respectively.[26]

The present study showed that among the group A patients, 44% rated excellent (>75% reduction) in outcome, 26% good(50-75% reduction), 22% moderate(25-50% reduction) and only 8%(<25% reduction) was unsatisfactory and among group B patients, 16% rated excellent in outcome, 24% good, 42% moderate and 18% was unsatisfactory. Muneeb et al identified that the improvement after four weeks of treatment, 11 (7.0%) patients had excellent improvement and most of the patients i.e. 84(49.0%) had good improvement, 66 (39.0%) had fair and 9 (5.0%) had poor response. After 8 weeks, 52 (31.0%) patients had excellent response, majority of patients 93 (55.0%) had good improvement, 21 (12.0%) had fair and 4 (2.0%) had poor improvement. The improvement after 12 weeks of treatment showed that 71 (41.8%) had excellent improvement, 67 (39.4%) had good, 30(17.6%) had fair improvement and only 2 (1.2%) had poor improvement. The comparison of effectiveness after treatment of 4 and 8 weeks of treatment which is statistically significant p <0.05. The comparison for effectiveness after treatment of 4 and 12 weeks which is statistically significant p <0.05.The comparison of effectiveness after treatment for 8 and 12 weeks which is statistically not significant p 0.06.[20] Gharib et al evaluated the patient self-assessment of melasma improvement at week 12; 9, 15, and 4 patients (32.1%, 53.6%, and 14.3, respectively) graded their improvement as fair (26-50%), good (51-75% lightening) and excellent (>75% lightening), respectively.[26]

Side effects were negligible; erythema and burning pain in the injection site were observed and disappeared within 1 hour after injection. Despite local anesthesia, all studied patients in the tranexamic acid group experienced mild burning pain at the injection site, which was reported by Pazyar et al in their study.[15] There were no systemic side effects, such as nausea, vomiting, abdominal pain, headache, hypomenorrhea, or spotting menstruation.

Conclusion: Study results concluded that intralesional injection of tranexamic acid produces effective results without significant side effects. For this reason, it may be used as part of melasma treatments, especially for the dermal type. Larger studies will be needed to determine the optimal dosage, long term benefits, and any potentially additional adverse effects.

Conflict of interest

All authors of the manuscript have no conflict of interests to declare.

Ethical approval

This study was approved by Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

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