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Efficacy of intralesional tranexamic acid in melasma: Assessment with Melasma Area Severity Index and Dermatology Quality of Life Index

Melazmada intralezyonel traneksamik asidin etkinliği: Melazma Alan Şiddet İndeksi ve Dermatoloji Yaşam Kalite İndeksi ile değerlendirme

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Abstract

Background and Design: Melasma is a common hypermelanotic condition, mostly observed in women, which affects their psychological, emotional, and social well-being as well as their quality of life. Although melasma is relatively resistant to treatment, various therapeutic options have been attempted until date. Recently, microneedling and microinjection tranexamic acid were performed. To compare the therapeutic effectiveness of triple combination therapy with tranexamic acid injection and assess the impact of response on melasma by comparing the pre- and post-treatment Melasma Area Severity Index (MASI) and Dermatology Quality of Life Index (DLQI) scores.
Materials and Methods: A total of 70 melasma patients were selected and assigned to two groups of 35 patients each based on the interventional randomized control study. One group was treated with a topical triple combination therapy-hydroquinone (2%), mometasone (0.1%), and tretinoin (0.025%), and the other group with injectable tranexamic acid. The MASI scores and DLQI were assessed for both the groups of patients at the baseline and then 6 weeks later along with serial photographs.
Results: Significant reduction in MASI and DLQI scores were noted in the intralesional tranexamic acid group of patients (p=0.032). The mean change in MASI with tranexamic acid was 1.22 and with DLQI was 2.03.
Conclusion: Injectable tranexamic acid is a promising treatment option for melasma. Further studies are however warranted with a larger sample size and for a longer duration to determine its long-term benefits. Treatment of melasma is beneficial for the patient both physically and emotionally.
Keywords: Intralesional tranexamic acid, Melasma Area Severity Index, Dermatology Life Quality Index

Öz

Amaç: Melazma, çoğunlukla kadınlarda görülen, psikolojik, duygusal ve sosyal iyilik hallerinin yanı sıra yaşam kalitelerini de etkileyen yaygın bir hipermelanotik durumdur. Melazma tedaviye nispeten dirençli olmasına rağmen, bugüne kadar çeşitli tedavi seçenekleri denenmiştir. Son zamanlarda hastalığın tedavisinde mikroiğneleme ve mikroenjeksiyon ile traneksamik asit uygulanmaktadır. Bu çalışmanın amacı üçlü kombinasyon tedavisinin traneksamik asit enjeksiyonu ile terapötik etkinliğini karşılaştırmak ve tedavi öncesi ve sonrası Melazma Alanı Şiddet İndeksi (MAŞİ) ve Dermatoloji Yaşam Kalitesi İndeksi (DYKİ) skorlarını karşılaştırarak yanıtın melazma üzerindeki etkisini değerlendirmektir.
Gereç ve Yöntem: Çalışmaya toplam 70 melazma hastası seçildi ve girişimsel randomize kontrollü çalışmaya göre her biri 35 hastadan oluşan iki gruba ayrıldı. Bir grup topikal üçlü kombinasyon tedavisi-hidrokinon (%2), mometazon (%0,1) ve tretinoin (%0,025) ve diğer grup enjekte edilebilir traneksamik asit ile tedavi edildi. MAŞİ skorları ve DYKİ, her iki hasta grubu için başlangıçta ve 6 hafta sonra seri fotoğraflarla birlikte değerlendirildi.
Bulgular: Hastaların intralezyonel traneksamik asit grubunda MAŞİ ve DYKİ skorlarında anlamlı azalma kaydedildi (p=0,032). Traneksamik asit ile MAŞİ'deki ortalama değişiklik 1,22 ve DLQI ile 2,03 idi.
Sonuç: Enjekte edilebilir traneksamik asit, melazma için umut verici bir tedavi seçeneğidir. Bununla birlikte, uzun vadeli faydalarını belirlemek için; daha büyük bir örneklem büyüklüğü ve daha uzun bir süre için daha ileri çalışmalara ihtiyaç vardır. Melazma tedavisi hastaya hem fiziksel hem de duygusal olarak faydalıdır.
Anahtar Kelimeler: İntralezyonel traneksamik asit, Melazma Bölgesi Şiddet İndeksi, Dermatoloji Yaşam Kalitesi İndeksi

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Introduction

Melasma is a common hypermelanotic condition presenting mostly in women and characterized by symmetrical brownish pigmentation over photo exposed areas such as the face[1,2].

Melasma affects the psychological, emotional, and social well-being of a person, impacting their quality of life[3,4]. Quality of life is defined as the capacity to perform daily activities appropriate to a person's age and his/her major role in society[5]. The Melasma Area Severity Index (MASI) is used for the clinical evaluation of the extent and severity of melasma and the Dermatology Quality of Life Index (DLQI); a 10-item questionnaire is used for the assessment of the quality of life owing to its high degree of reliability, reproducibility, and appreciably[1,6].

Although melasma is relatively resistant to treatment, various treatment options used include triple combination topical therapy, such as hydroquinone, retinoids, and corticosteroids. Other topical agents such as kojic acid, azelaic acid, and ascorbic acid are also used. Chemical peel and lasers are also some other treatment options. Recently, tranexamic acid has been introduced as a new treatment modality for melasma[7].

In this study, injectable tranexamic acid and topical triple combination therapy were used as a treatment modality for melasma, and the response to the treatment was assessed based on the MASI and DLQI scores and compared between the groups.

This is the first of its kind study comparing the efficacy of 2 treatment modalities in melasma, correlating the improvement of each modalities with the change in the quality of life of the patient. Due to the limited number of studies on the comparison of the efficacy of various treatment modalities and the paucity of literature in this aspect from the Indian subcontinent, we attempted to undertake this study.

Materials and Methods

This is a prospective hospital-based interventional, randomized control study conducted at the department of dermatology over 1 year from November 2018-2019 after obtaining institutional ethical clearance.

The study was approved by the Sri Devaraj Urs Medical College Institutional Ethics Committee (approval number: DMC/KLR/IEC/263/2019-20, date: 25.02.2020).

The sample size was estimated based on the DLQI scores from the study by Morgaonkar et al.[4], which reported an average DLQI score of 9.92 with a standard deviation of 7.41. Expecting at least 40% improvement in DLQI scores with injection tranexamic acid when compared with triple combination therapy with 80% power and α error of 5%, the estimated sample size per group was set to 63. Expecting a dropout rate of 15% during the study, the final sample size estimated is 70.

A total of 70 female patients presenting with newly diagnosed melasma were enrolled in the study and only a few dermatological disorders that could interfere with the evaluation of melasma, such as lichen planus pigmentosus, ashy dermatoses, and photo contact dermatoses, were excluded. Moreover, patients using cyclosporine, acitretin, or potentially photosensitizing drugs, estrogen and/or progesterone preparation, anticoagulants, hormone replacement therapy, any systemic co-morbidities, or with bleeding disorders were excluded.

After obtaining the informed consent from the patients, 64 patients were included in the study, of which 6 were lost to follow-up and did not complete the treatment as per protocol. The patients were randomly divided into two groups of 32 each using computer-generated block randomization. To avoid selection bias, randomization of the sample selection was essential. MASI and DLQI scores were assessed at the first visit for all patients.

In the first group, the patients received a fixed-dose, triple combination product-hydroquinone (2%), mometasone (0.1%), and tretinoin (0.025%) once daily for 6 weeks. The other group was administered with intralesional tranexamic acid. Tranexamic acid was available as a 5 mL ampoule containing 500 mg of the drug. Before injection, a topical anesthetic agent of lignocaine and prilocaine was applied over the affected areas and left for 45 min. Two units (0.2 mL) of tranexamic acid were drawn with a 30-gauge insulin syringe of 40 U/mL. The remaining 38 units (0.8 mL) of normal saline was drawn to obtain a final concentration of approximately 4 mg/mL of tranexamic acid. Intradermal injections were administered at the site of melasma, keeping a distance of around 1 cm from each injection. Weekly injections were repeated for 4 weeks[8,9]. Both the groups were advised to use sunscreen (of sun protection factor 50) for daily use and with instructions to avoid direct sun exposure.

Clinical improvement was recorded and digital photographs were taken every week; the MASI and DLQI scores were record again at the end of 6 weeks to assess the response to treatment in both the groups, although the treatment was stopped at the end of 4 weeks in the intralesional tranexamic acid group. The study methodology is summarized in Figure 1.

Statistical Analysis

Descriptive analysis was performed by mean and standard deviation for quantitative variables and the frequency and proportion for categorical variables. Non-normally distributed quantitative variables were summarized by the median and interquartile range. All quantitative variables were analyzed for normal distribution within each category of an explanatory variable through visual inspection of histograms and normality Q-Q plots. Shapiro-Wilk test was also conducted to assess normal distribution. Shapiro-Wilk test $p>0.05$ was considered to indicate normal distribution.

For normally distributed quantitative parameters, the mean values were compared between the study groups using an independent sample t-test (2 groups). The change in the quantitative parameters before and after the intervention was assessed by paired t-test. The categorical outcomes were compared between the study groups using the chi-square test/Fisher's exact test (if the overall sample size was <20 or if the expected number in any one of the cells was <5, Fisher's exact test was applied). $P<0.05$ was considered to indicate statistical significance. IBM SPSS version 22 was used for statistical analyses.

Results

A total of 70 patients were screened, out of which 6 patients were lost to follow-up and 64 subjects were included in the final analysis (Table 1).

Among the study population, 32 (50%) patients were included in the topical group and 32 (50%) in the tranexamic acid group. The mean age in the topical group was 35.59±6.54 and in the tranexamic acid group, it was 35.19±7.55. The difference in age between the two

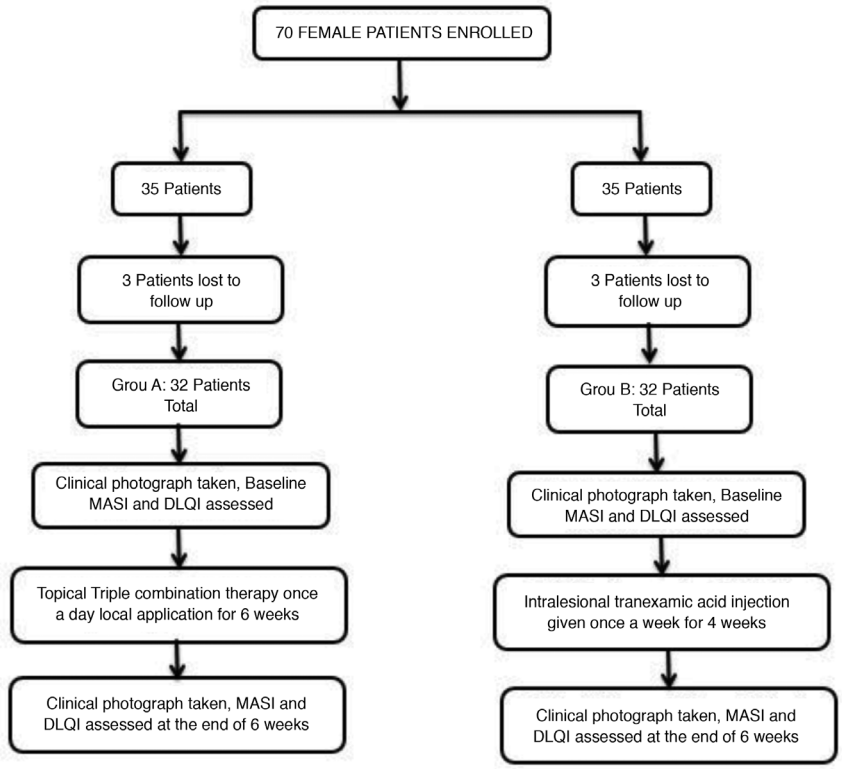

Figure 1. Summary of the study methodology

MASI: Melasma Area Severity Index DLQI: Dermatology Quality of Life Index

Table 1. Descriptive analysis of group in the study population

	Topical triple combination therapy	Injectable tranexamic acid
Number of patients	32	32
Occupation		
Homemaker	12 (37.5%)	11 (34.37%)
Agriculturist	11 (34.37%)	13 (40.62%)
Officework	9 (28.12%)	8 (25%)
Duration of sun exposure		
<2 hours	21 (65.62%)	20 (62.5%)
2-6 hours	10 (31.25%)	12 (37.5%)
>6 hours	1 (3.125%)	0
Usage of sun screen	12 (37.5%)	13 (40.62%)

groups was not statistically significant (p=0.819). The majority of patients in the topical group were homemakers (37.5%), while those in the intralesional tranexamic acid group were agriculturists (40.62%). The duration of sun exposure for the majority of patients in the topical group was <2 h (21; 65.62%), while that in the tranexamic acid group, it was 20 patients (62.5%). The usage of sunscreen was by 12 patients (37.5%) in the topical group and by 13 patients (40.62%) in the tranexamic acid group.

The distribution of patients according to the Fitzpatrick skin types in both groups was not statistically significant (p=0.368) (Table 2). The difference in the proportion of melasma patterns between the two groups was not statistically significant (p=0.965) (Figure 2).

The mean MASI score at the baseline was 2.09±0.59 in the topical group and 2.38±0.61 in the intralesional tranexamic acid group. The mean MASI in the 6th week was 1.96±0.63 in the topical group and 1.16±0.37 in the intralesional tranexamic acid group, which was statistically significant in the intralesional tranexamic acid group (p=0.021) and not in the topical group (p=0.879) (Table 3).

The mean DLQI score at baseline was 3.38±0.61 in the topical group and 3.78±0.61 in the intralesional tranexamic acid group. In the 6th week, the mean DLQI was 3.29±0.75 in the topical group and 1.75±0.67 in the intralesional tranexamic acid group, which was statistically significant in the intralesional tranexamic acid group (p=0.01) and not in the topical group (p=0.703) (Table 4).

In the topical group, the mean change in MASI (0.13) and DLQI (0.09) was not statistically significant (p=0.62), while that in the intralesional tranexamic acid group, the mean change in MASI (1.22) and DLQI (2.03) was statistically significant (p= 0.032) (Table 5; Figure 3-5).

The graphical correlation of changes in the MASI and DLQI scores at 0 and 6 weeks in both the topical and intralesional tranexamic acid groups is depicted in Figure 6.

Discussion

Melasma is a common disorder presenting symmetrically over the face as hyperpigmented macules and patches[7]. Three clinical patterns of hyperpigmentation were noticed over the face-mandibular, centrofacial, and malar[2,3]. It was noticeable frequently in the women of skin types III-V[1]. This is a condition commonly recorded in women of the child-bearing age group, although various factors such as

Table 2. Comparison of Fitzpatrick skin type between the two groups

Fitzpatrick skin type	Group		Chi-square	p-value
	Topical (n=32)	Injectable tranexamic acid (n= 32)		
Type 3	4 (12.5%)	1 (3.125%)	2,000	0.368
Type 4	21 (65.62%)	24 (75%)		
Type 5	7 (21.87%)	7 (21.87%)		

Table 3. Comparison of mean MASI score between the two groups

Parameter	Group (mean ± SD)	
	Topical (n=32)	Injectable tranexamic acid (n=32)
MASI 0 week	2.09±0.59	2.38±0.61
MASI 6 week	1.96±0.63	1.16±0.37
p-value	0.879	0.021

SD: Standard deviation, MASI: Melasma Area Severity Index

Table 4. Comparison of mean of DLQI between two groups

Parameter	Group (mean ± SD)	
	Topical (n=32)	Injectable tranexamic acid (n=32)
DLQI 0 week	3.38±0.61	3.78±0.61
DLQI 6 week	3.29±0.75	1.75±0.67
p-value	0.703	0.01

SD: Standard deviation, DLQI: Dermatology Quality of Life Index

Table 5. Comparison of mean of change in MASI and change in DLQI between the two groups

Parameter	Group (mean ± SD)	
	Topical (n=32)	Tranexamic acid (n=32)
Change in MASI	0.13	1.22
Change in DLQI	0.09	2.03
p-value	0.62	0.032

SD: Standard deviation, MASI: Melasma Area Severity Index, DLQI: Dermatology Quality of Life Index

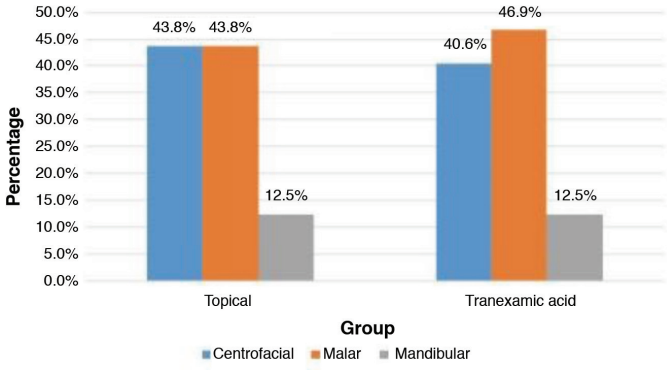

Figure 2. Cluster bar graph for comparison of the melasma patterns between the two groups (n=64)

genetic factors, sun exposure, and hormonal factors contribute to its pathomechanism[4].

Multiple treatment options are available such as sunscreens, topical hydroquinone, topical triple combination therapy, chemical peels, and lasers (Q-switched) Neodymium:Yttrium Aluminum Garnet (Nd:YAG) laser, Alexandrite laser, Ruby laser, and Erbium Yttrium Aluminum Garnet (Er:YAG laser), and Intense Pulsed Light[10-12].

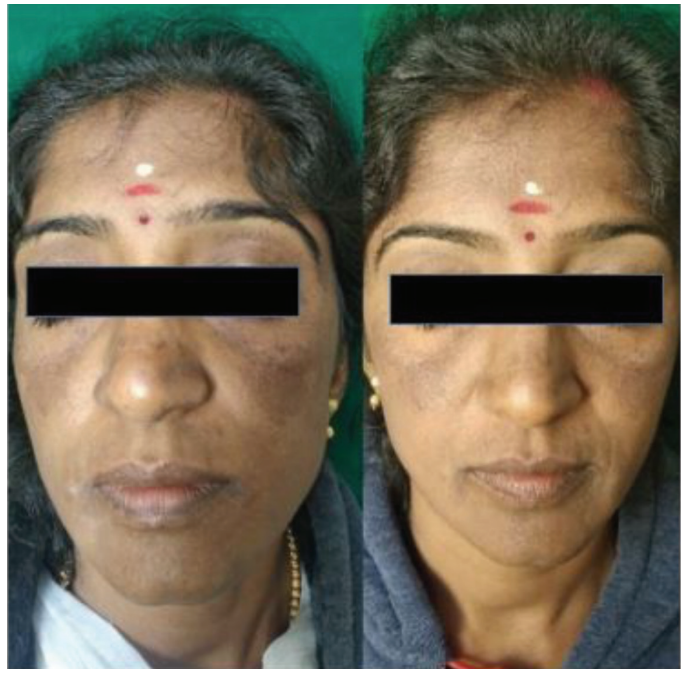

Figure 3. Before and after 6 weeks of treatment with topical triple combination therapy

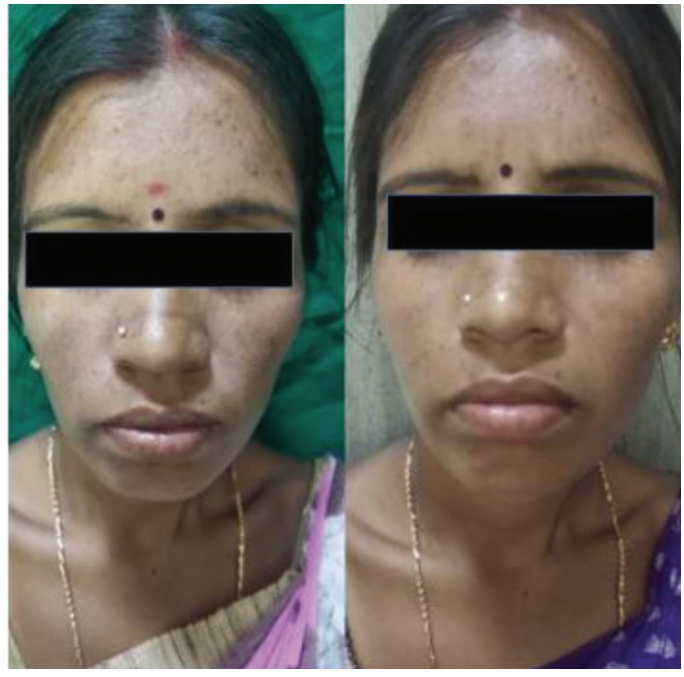

Figure 4. Before and after 6 weeks of treatment with intralesional tranexamic acid therapy

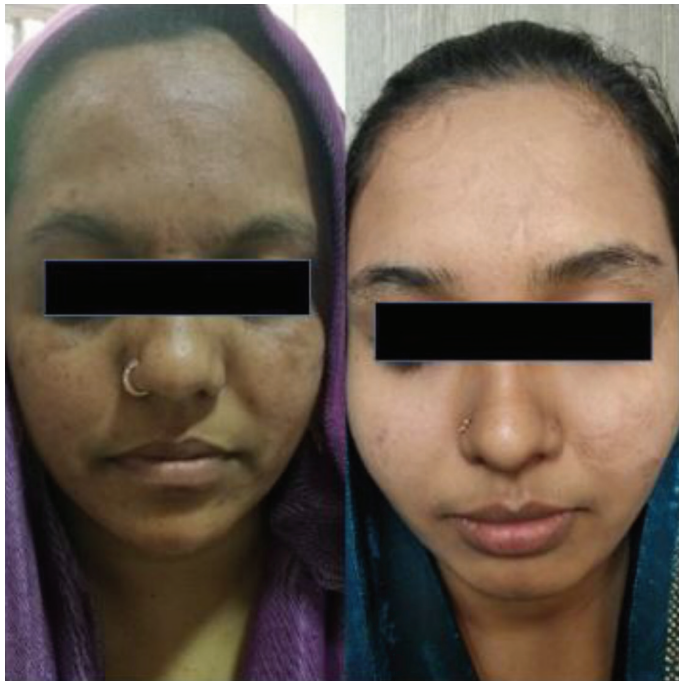

Figure 5. Before and after 6 weeks of treatment with intralesional tranexamic acid therapy

MASI: Melasma Area Severity Index, DLQI: Dermatology Quality of Life Index

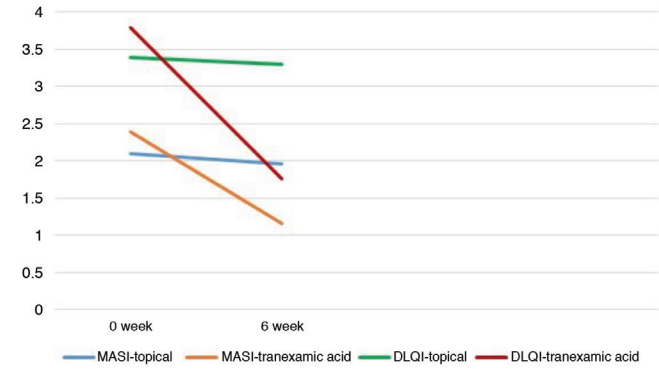

Figure 6. Graphical correlation between MASI and DLQI at 0 and 6 weeks in topical triple combination and intralesional tranexamic acid injection groups

Tranexamic acid is an upcoming treatment modality for melasma to be used in topical, oral, and intralesional forms. Tranexamic acid possesses anti-plasmin activity. Increased plasmin level increases the -melanocyte-stimulating hormone levels and fibroblast growth factors, which are potent melanocyte stimulators. Plasmin plays a role in angiogenesis by increasing the release of the free vascular endothelial growth factor (VEGF)[7].

Increased production of mast cell tryptase was noted in melasma owing to repeated damage by ultraviolet rays. Oral contraceptive pills and pregnancy also increase serum plasminogen activators that can activate the melanogenesis process. Various dermal changes in melasma, include angiogenesis, disruption of the basement membrane, and solar elastosis. Several mast cells may also be increased in the lesional dermis. All these factors together contribute to the refractory nature of melasma[7].

UV-induced pigmentation in melasma is prevented by tranexamic acid through interference with the plasminogen binding to the keratinocytes. This event reduces the free amino acids contents and prostaglandins in the melanocytes as well as prevents angiogenesis by reducing the levels of VEGF and endothelin-1, which is responsible for increased vascularity in melasma. Plasmin possess melanogenic and angiogenic activities. Hence, tranexamic acid is used as a treatment option for melasma[7,10]. Two recent studies suggest tranexamic acid as an upcoming treatment modality of melasma, although relevant studies are limited[13,14].

In this study, 64 patients were included and the patients were categorized into 2 groups based on the treatment modality. One group was administered with a topical triple combination therapy of hydroquinone 2%, mometasone (0.1%), and tretinoin (0.025%), while another study group was administered a weekly tranexamic acid intradermal injection for 4 weeks.

The mean age of the patients in the study was 35.39, which is similar to the report of a study with a mean age of 38.43 years[1].

Our study demonstrated a significant improvement in the MASI and DLQI scores after 4 sessions of weekly intralesional tranexamic acid as compared to 6 weeks of topical triple combination therapy.

In our study, the pre-treatment DLQI score was 3.38±0.61 for patients on topical treatment and 3.78±0.61 for patients treated with injectable tranexamic acid. DLQI in both groups showed improvement, although it was significant in the injectable tranexamic acid group (p=0.01).

Khurana reported an improvement of 43.6% of patients with melasma when treated with monthly injectable tranexamic acid (4 mg/mL) relative to that with oral tranexamic acid (250 mg twice daily for 3 months). No standard guidelines were established for providing intralesional injections of tranexamic acid for melasma. Only limited studies are available with tranexamic acid used for melasma[8].

The MASI scores in our study before treatment were 2.09±0.59 in patients with topical treatment and 2.38±0.61 in patients treated with injectable tranexamic acid. One study noted a baseline MASI of 3.7 before starting the topical triple combination therapy, and, after 12 weeks, it reached 1.2[15]. In our study, we noted a decrease of MASI to 1.96±0.63 at the end of 6 weeks, which was not significant (p=0.879). Another study noted a significant decrease in the MASI score after 20 weeks of using injectable tranexamic acid[16]. The study compared the effect of tranexamic acid microinjections and tranexamic acid microneedling in patients with melasma. A significant reduction in the MASI score was noted at the end of 8 weeks in the tranexamic acid microinjection group ($p<0.05$), which gradually improved up to 20 weeks of microinjection ($p<0.01$). This finding was comparable to that of our study, where a MASI score of 1.16±0.37 was recorded at the end of 6 weeks in the injectable tranexamic acid group (p=0.021).

No side effects were noted in patients treated with injectable tranexamic acid. However, a few patients in the topical group developed itching and erythema over the application site as compared to another study[15].

Intralesional tranexamic acid is an upcoming treatment modality for melasma. The strength of this study is that this is the first of its kind comparing two treatment options for melasma patients-topical triple

combination and intralesional tranexamic acid-correlated with pre-treatment and post-treatment MASI scores and DLQI scores.

Study Limitations

The limitations of this study are that patients in the intralesional tranexamic acid group were administered the injection once a week for 4 weeks. Although more number of sittings were warranted, it was restricted due to reduced patient compliance. The sample size of the study was also small. Long-term follow-up is required in the future to check for recurrence of melasma.

The efficacy of change in an interval of intralesional injections or the effect of the combination of topical therapy with intralesional injection also remains to be studied.

More research work needs to be done to understand another possible mechanism of action of tranexamic acid and the efficacy of other less invasive routes of administrating tranexamic acid, such as oral and transdermal patches, when compared to the intralesional route and further correlating with the quality of life of the patient.

Conclusion

Although both triple combination therapy and injection tranexamic acid revealed improvement in the MASI and DLQI scores in patients with melasma, a better outcome was noted in patients with injection tranexamic acid despite the 4 weeks of therapy. Tranexamic acid is easily available and affordable. Injection of tranexamic acid is a safe and an office-based procedure with relatively quick results. However, multiple injectable tranexamic acid studies as a therapeutic option for melasma, with a large patient profile and for a longer duration, are required.

Ethics

Ethics Committee Approval: The study was approved by the Sri Devaraj Urs Medical College Institutional Ethics Committee (approval number: DMC/KLR/IEC/263/2019-20, date: 25.02.2020).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K.R., R.T.S., A.A., Concept: S.K.R., R.T.S., A.A., Design: S.K.R., R.T.S., A.A., Data Collection or Processing: S.K.R., R.T.S., A.A., Analysis or Interpretation: S.K.R., R.T.S., A.A., Literature Search: S.K.R., R.T.S., A.A., Writing: S.K.R., R.T.S., A.A.

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