Session Number and Title:

F056 - Late-breaking Research: Procedural Dermatology

Intralesional Tranexamic Acid Versus Platelet Rich Plasma in Melasma Treatment. A Split Face Comparative Study

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Introduction

Melasma distresses patients due to the fact that it mainly affects the face, being easily visible and constantly present in everyday life. In this context, it has a negative impact on the quality of life of patients, affecting their psychological and emotional well-being, which often motivates them to search for a dermatologist. Patients commonly report feelings of shame, low self-esteem, dissatisfaction, and the lack of motivation to go out. Suicidal ideas have also been reported in the literature [1].

Melasma is generally a clinical diagnosis consisting of symmetric reticulated hypermelanosis in three predominant facial patterns: centrofacial, malar, and mandibular. The major clinical pattern in 50–80% of cases is the centrofacial pattern, which affects the forehead, cheeks, nose, upper lip, and chin. The malar pattern is restricted to the malar cheeks and nose, while mandibular melasma is present on the jawline and chin [2].

There is no universally effective specific therapy. No single therapy has proven to be of benefit to all patients as the sole therapy. Combinations of modalities can be used to optimize management in difficult cases. Existing agents have varying degrees of efficacy and relapses are frequent [3].

Intralesional injection of tranexamic acid (4mg/ml) using 100u/ml insulin syringe can be used in melasma treatment. About 0.05ml is applied intradermally on the lesion at 1cm interval in at monthly intervals for 3 months was proven to be safe and effective therapy [4].

Plasminogen activator (PA) synthesis and plasmin activity in cultured keratinocyte are both induced by UV irradiation. Plasmin then activates the phospholipase A2, which liberates Arachidonic acid (AA) from membrane phospholipids. Arachidonic acid is a precursor to Prostaglandin-E2 (PGE2) and leukotriens. They subsequently activate melanogenesis. Also, Plasmin leads to the release of basic fibroblast growth factor, which is a potent melanocyte growth factor.

Hence, 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 [5].

Plasmin also can significantly increase the amount of single chain urokinase PA (Sc-uPA) in keratinocyte which induce tyrosinase activity, increased cell perimeter, and increased dendrites in dose depending manner in melanocytes.

Hence, TA can stop the keratinocyte-activate-melanocyte pathway. Thus, it was concluded that sc-uPA generated by keratinocytes increased the activity of melanocytes in vitro, and the blocking of this pathway may be the mechanism through which TA reduces hyperpigmentation [6].

TA can actually prevent the activation of melanocytes by sunlight, hormonal influence, and injured keratinocytes (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 melanocytes [7].

The platelet rich plasma (PRP) is a generic term used to describe a plasma suspension obtained from whole blood, prepared so as to contain platelet concentrations higher than those normally found in circulating blood [8]. It contains not only a high level of platelets but also the full complement of clotting factors, the latter typically remaining at their normal, physiologic levels. It is enriched by a range of growth factors (GFs), chemokines, cytokines, and other plasma proteins [9].

Melasma was reported to be successfully treated with PRP in a Turkish study. The researchers reported improvement of more than 80% of melasma at the end of the third sessions. They did not provide any other treatment or post treatment care besides prescribing the use of a sun-screen product. There had been no recurrence of melasma for 6 months [10].

The pigmentary improvement which occurs after PRP is probably more related to increase in the skin volume. Platelet derived growth factors found in PRP are involved in hyaluronic acid synthesis which increases

skin tone and volume, thereby providing a more glowing skin with a feeling of reduced pigmentation [11].
The aim of this study was to evaluate and compare the efficacy and safety of intradermal injection of TA and PRP in the treatment of different types of melasma.

Patients and methods

Twenty three patients with different forms and degrees of melasma were enrolled from the outpatient clinics of Dermatology at Zagazig University hospitals. The study was carried out in the period between July 2017 and July 2018 after approval of the Institutional Review Board (IRB#:3754/14-6-2017). A written informed consent was obtained from all subjects after complete description of the study.
The exclusion criteria of this study included pregnant or nursing women, women taking contraceptive pills at the time of the study or during the past 12 months, any known bleeding disorders or the concomitant use of anticoagulants, patients with known platelet dysfunction syndrome, critical thrombocytopenia (<50,000/ul) or any hemodynamic instability and patients on any concurrent oral or topical therapy for melasma 1 month before.
All patients were subjected to general examination and dermatological examination to assess skin type, site, type and severity of melasma assessed by a Modified Melasma Area and Severity Index (MMASI) scoring system. Four areas of the face are evaluated: forehead (F), right malar region (MR), left malar region (ML) and chin(C), corresponding to 30%, 30%, 30%, and 10% of the total face respectively. Amount of pigmentation involved by melasma in these four areas (AF, AMR, AML, and AC) is graded as a numerical value: 0: no involvement; 1: less than 10% involvement; 2: 10–29%; 3: 30–49%; 4: 50–69%; 5: 70–89%; and 6: 90–100%. Severity of melasma is graded upon two factors; darkness (D) of melasma compared to the normal skin and homogencity (H) of hyper pigmentation. These are assessed on a scale from 0 to 4 the rating scale for both darkness and homogencity of melasma is as follows; 0: absent; 1: slight; 2: mild; 3: marked; and 4: maximum. MMASI score is then calculated according to the following formula for each half of the face: MMASI = 0.15 (D + H) AF + 0.3 (D + H) AM + 0.05 (D + H) AC.
Wood's light was used to assess the depth of the pigment. Melasma was classified into epidermal, dermal and mixed types, based on the location of pigment determined clinically by the color of pigmentation and by Wood's light examination. In dermal melasma, there is greyish blue pigmentation which did not show accentuation during Wood's light examination. In epidermal melasma, there is light brown pigmentation which show accentuation during Wood's light examination. Mixed

melasma is a combination of epidermal and dermal melasma. Color enhancement with Wood's light is seen in some places of the skin, but not others.
Digital photographs of both sides of the face were taken by Sony DSC-WX70 camera at baseline, before and after every session. The results were assessed at the end of treatment using the MMASI and any adverse events were also recorded.

Methods
Before treatment, an informed consent was taken from all patients. Each patient was asked about his goals, concerns and expectations about the treatment to avoid unrealistic expectations. Possible side effects of each procedure were explained such as pain and erythema. Sunscreen was strictly used throughout treatment and afterwards.
A topical anesthetic cream (EMLA Cream) was applied on both sides of the face for 30 to 45 minutes under occlusion before the injection. As standard protocol, the right side of the face is subjected to intralesional injection with TA using 100U/ml insulin syringe. About 4mg of TA is drawn in 100U/ml insulin syringe and diluted with debocaine up to 1 ml to get the concentration of 4mg/l of TA. Tranexamic acid was collected from Kapron 5ml ampoules with a concentration of 100mg/ml. About 0.05ml is applied intradermally for the lesion at 1cm interval to a maximum 8 mg to the entire affected lesion.
The left side of the face was treated with intralesional injection of PRP using 100U/ml insulin syringe for superficial microinjection. About 10 ml blood was collected from the patient into a special tube from UNEX-MED EGYPT that Launch Zoom PRP Italy in Egypt and centerifuged for 10 minute at 3500 rpm. After centrifugation, two layers were formed over the gel and erythrocytes remained under it. Platelet-poor plasma (PPP) was the yellow fluid at the top of the tube and collected using a syringe. PRP was the buffy coat over the gel and withdrawn with a long canula. We obtained approximately 1.5 cc from each individual at each procedure. The injections are administrated into papillary dermis. Approximately 1 ml of PRP is injected intradermally for the lesions. The patients are reviewed after 1 week for any side effect.
The procedure was done three times at monthly interval (o, 4, 8 weeks) and patients were followed up for another 3 months.
The patients were advised to avoid excessive sun exposure and to apply a broad - specrum sunscreen with a sun protection factor above 30 during day time.
The degree of improvement of patients were assessed at the end of treatment and graded along four scales: more than 75% lightening (excellent); 51 to 75 (good); 26 to 50% (moderate); and 0 to 25% (poor).

Any side effects observed such as pain, post procedure erythema and edema were recorded at each session.

Results

This study included 23 female patients with facial melasma. Their ages ranged from 32-50 years with a mean±SD 38.35± 3.94. Only 6 patients (26.1%) had positive family history of melasma while 17 patients (73.9%) had no family history.

Regarding to predisposing factors, melasma in 13 patients (56.5%) had a relation to pregnancy, while 10 patients (43.5%) had no relation to pregnancy. Regarding sun exposure, 6 patients (26.1%) reported mild exposure to sun, while 11 patients (47.8%) reported moderate exposure to sun and 6 patients (26.1%) reported severe exposure to sun.

According to the pattern of melasma, 8 patients (34.8%) had centrofacial pattern, 14 patients (60.9%) had malar pattern and only one patient had mandibular pattern representing 4.3% of patients. According to Fitzpatrick skin type, 5 patients (21.7%) were of skin type II, 14 patients (60.9%) were of skin type IV and four patients (16.4%) were of skin type IV.

According to Wood's light examination of melasma 4 patients (17.4%) had dermal melasma, while 9 patients (39.1%) had epidermal melasma and 10 patients (43.5%) had mixed melasma.

The duration of disease among the patients ranged from 1-15 years with a mean ±SD 6.43 ± 3.76. There was no statistically significant difference between MMASI for both sides of the face before treatment.

In TA side:

There was a statistically significant difference as regard MMASI between baseline with a mean ± SD (6.92 ± 5) and at end of treatment with a mean ± SD (2.83 ± 2.97).

According to the degree of improvement, 4 patients (17.4%) showed moderate improvement, 8 patients (34.8%) showed good improvement and 11 patients (47.8%) showed excellent improvement.

There was a statistically significant inverse correlation between the duration of melasma and the degree of improvement (decrease in disease duration among excellent improved cases).

There was a statistically significant correlation between the site of melasma and the degree of improvement (increase in frequency of malar site among excellent improved cases).

There was no correlation between the age, type of melasma, skin type and the degree of improvement.

In PRP side:

There was a statistically significant difference as regard MMASI between baseline with a mean± SD (7.54± 4.67) and at end of treatment with a mean± SD (4.6± 3.41).
According to the degree of improvement, 2 patients (8.7%) showed no improvement, 3 patients (13%) showed poor improvement, 8 patients (34.8%) showed moderate improvement, 7 patients (30.4%) showed good improvement and 3 patients (13%) showed excellent improvement.
There was a statistically significant correlation between the site of melasma and the degree of improvement (increase in frequency of malar site among excellent improved cases).
There was no correlation between the age, duration of melasma, type of melasma, skin type and the degree of improvement.
Finally, there was a statistically significant difference in the percent of change of MMASI between both sides of face.
There was statistically significant difference between the both sides of the face in the degree of improvement with increase frequency of excellent and good response among TA side.

Complications of the treatment:

In TA side, 18 patients (78.3%) suffered from transient pain at the site of injection, while 5 patients (21.7%) suffered from transient pain and erythema. Similarly, in PRP side, 18 patients (78.3%) suffered from transient pain at the site of injection, while 5 patients (21.7%) suffered from transient pain and erythema. There was no statistically significant difference between the both sides in complications.

Conclusion:

We concluded that Intradermal microinjection of TA appears to be a potentially promising therapeutic tool that can be easily performed, and produces relatively rapid results without significant side effects. For this reason, it may be used as part of melasma treatments, especially for the dermal and mixed melasma. The intrdermal microinjection of PRP was also a valuable therapeutic modality for the treatment of melasma with no permanent side effects but it was less effective than TA.

References

1 Handel AC, Miot LD and Miot HA. Melasma: a clinical and epidemiological review. *An Bras Dermatol* 2014*; 89:771-82.*

2 Ogbechie-Godec OA and Elbuluk N. Melasma: an Up-to-Date Comprehensive Review*. Dermatol Ther* 2017*; 7:305-18.*

3 Rigopoulos D, Gregoriou S and Katsambas A. Hyper-pigmentation and melasma. *J Cosmet Dermatol* 2007*; 6:195-202*.

4 Budamakuntla L, Loganathan E, Suresh H, et al A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. *J Cutan Aesthet Surg* 2013*; 6:139–43.*

5 Ebrahimi B and Naeini FF. Topical tranexamic acid as promosing treatment for melasma. *J Res Med Sci* 2014*; 19:753-57.*

6 Maeda K and Tomita Y. Mechanism of the inhibitory effect of tranexamic acid on melanogenesis in cultured human melanocytes in the presence of keratinocyteconditioned medium. *J Health Sci* 2007*; 53:389–96.*

7 Tse W and Hui E Tranexamic acid: an important adjuvant in the treatment of melasma. *J Cosmet Dermatol* 2013*; 12:57-66.*

8 Alshami S. Treatment of periorbital hyperpigmentation using platelet rich plasma injections. *AJDV* 2014*; 3:87-94.*

9 Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. *Skin Appendage Disord* 2018*; 4:18-24.*

10 Çayırlı M, Çalışkan E, Açıkgöz G, et al. Regression of melasma with platetlet rich plasma treatment. *Ann Dermatol* 2014*; 26:401-2.*

11 Chatterjee M and Vasudevan B. Recent advances in melasma. *Pigment Int* 2014*; 1:70-80*.