Original Article

Prospective Study of Growth Factor Concentrate Therapy for Treatment of Melasma

Abstract

Background: Melasma is a common acquired pigmentary skin disorder. Currently, there are various treatment options available but none is effective universally. **Objective:** Assess the role of Yuskin®, a growth factor concentrate (GFC) therapy, a modified platelet rich plasma (PRP) technique for the treatment of melasma. **Materials and Methods:** Subjects of Fitzpatrick skin type IV–V, of either gender, more than equal to 18 years of age, with a clinical diagnosis of melasma were enrolled in the study. Total three sessions of GFC monotherapy were given with one-month interval (day 0, day 30, and day 60) and follow up of subjects was done at day 90 for the final clinical assessment. **Results:** Out of 40 subjects enrolled, 30 subjects completed three GFC sessions and 26, completed day 90 follow-up. Statistically significant decrease in the mean mMASI scores was observed at all visits compared to baseline ($P < 0.005$ for each visit). Totally, 66.7% of severe melasma subjects showed improvement to mild to moderate category. Significant improvement in mean mMASI score was seen in subjects who had mild to moderate melasma at baseline ($P < 0.05$). Overall, aesthetic improvement was reported in 88.5% of subjects. Side effects reported were mild such as injection site pain, erythema, oedema and bruising, and resolved spontaneously within a few hours to few days of onset. **Conclusion:** Significant improvement in melasma was observed with GFC monotherapy, which needs further confirmation in larger randomized controlled studies. Overall, it was well tolerated. Thus, GFC therapy can be a safe, effective, and new option in the armamentarium of melasma management.

Keywords: *Growth factor concentrate, Melasma area and severity index , Melasma, mMASI, platelet rich plasma*

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Introduction

Melasma is a common acquired pigmentary skin disorder. It is characterized by a symmetrical macular pigmentation of sun-exposed areas of the face including forehead, nose, and over the malar and mandibular region.[1,2] Melasma commonly affects females compared to males and especially those with darker skin with Fitzpatrick phototypes IV through VI. It mostly affects patients in their 30s and 40s. Various factors like exposure to sunlight, cosmetics, pregnancy, hormonal treatments, thyroid dysfunction, phototoxic drugs, and anticonvulsant medications and genetics have been implicated in the pathogenesis of melasma. However, the exact pathogenesis of melasma is not fully known.[1,3] The prevalence of melasma in Southeast Asian population is about 40%. However, it varies according to geographical location and race.[4,5] In a random sample of 2000 pregnant women in India, prevalence of melasma was 50.8%.[6] In another prospective study conducted in a tertiary care hospital in India, prevalence of melasma was found to be 20.5% in men.[7] Moreover, an Indian study of 312 consecutive melasma patients found a 4:1 female to male ratio.[8]

Currently, there are various treatment options available including anti-pigmenting agents, chemical peels and lasers but none of them is effective universally. Many times, these treatment modalities are not satisfactory and their outcomes do not meet the patients' expectations, making melasma a challenging cosmetic problem.[9-12]

The platelet-rich plasma (PRP), plasma with concentrated platelets is a relatively old technique, which is used in many branches of medicine. PRP by the virtue of its autologous in nature, minimal chances of side effects and its action through

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concentrated growth factors, is become popular in last two decades in aesthetic dermatology for alopecia, wound healing, skin rejuvenation, and acne scars.[13-15] More recently PRP has been used as a novel treatment option for challenging dermatological condition of melasma.[15,16] Studies have reported statistically significant improvement in Melasma Area and Severity Index (MASI) score with PRP treatment and highlighted the potential effect of PRP in the treatment of melasma and hyperpigmentation.[17-20] However, available literature suggests that limited research was done to assess PRP effectiveness in treating melasma. Yuskin®, growth factor concentrate (GFC) therapy is a modified PRP technique, where patient's blood is processed, so as the final outcome has a high concentration of growth factor released after platelet activation.[21] Therefore, we conducted a prospective study to assess the potential effect of GFC therapy for the treatment of melasma.

Materials and Methods

Study design

This was a multicenter, prospective, open label, single arm study. Study was designed and conducted according to the Declaration of Helsinki and after approval by the local institutional ethics committee (dated 1st March 2019). Written informed consent from all the subjects was obtained before participation in this study and after being informed about the study procedures, expected outcomes, and side effects.

Study population

Subjects of Fitzpatrick skin type IV–V, of either gender, more than equal to 18 years of age, with a clinical diagnosis of melasma including Wood's lamp examination were enrolled in the study. Subjects enrolled were willing to comply with the study protocol and willing to abstain from spa/facial treatments or any other treatment during the study that would significantly affect the efficacy of study treatment.

Pregnant lactating women, use of oral contraceptive pills, history of hypertrophic scars or keloids, current cutaneous infection, blood disorders, platelet count <1,50,000 µl, a systemic disease resulting in an immunocompromised state, intake of systemic chemotherapy, skin cancer and any significant current and past medical history and treatment, in the investigator's opinion, could adversely affect the safety of subject or could impair the assessment of study results were excluded.

Study procedure

GFC was prepared as per instructions given in company-provided pack insert.[21] About 16 ml of subjects' blood was withdrawn with aseptic precaution into the kit and was processed to give final outcome of about 8 ml of GFC. Before to the GFC injection procedure face area was cleaned with alcohol 70% and sterile saline. A topical anesthetic cream (lidocaine cream 5%) was applied on the face for 40 min and cleaned again with saline. GFC thus collected (about 8 ml) was injected intradermally using 30–31 gauge needle and with the patient seated in the inclined position. About 0.1–0.2 ml of GFC was injected per injection all over the face including the affected area. Injection sites were spaced out from each other approximately 0.8 to 1 cm. Total three sessions of GFC monotherapy were given with one month interval (day 0, day 30 and day 60) and follow up of subjects was done at day 90 for the final clinical assessment.

Post-procedure, subjects were instructed to avoid washing the face for 24 hours. They were also instructed to use sunscreens before sun exposure. Subjects were instructed to sleep with the head elevated at least for one night to minimize any swelling. Subjects were advised not to use any other treatments for their melasma as it could have affected the study assessment.

Complete physical examination, recording of vitals were done at every visit. Any adverse drug reactions (ADR) during the procedure and since previous visits were recorded. Subjects were also asked to report any ADR telephonically, as and when they appear in-between the study visits. Digital photographs in a standard fixed specification were taken for each patient before starting the study treatment at every treatment visit and at a follow-up visit, and were analyzed by a blinded independent dermatologist.

Study outcome parameters

The primary efficacy endpoint was mean changes in modified MASI (mMASI) score at the end of the study compared to baseline in the mITT (Modified Intention to Treat) population. mMASI score at all visit was obtained by applying the following equation,[22]

$$[0.3A(f) \times D(f)] + [0.3A(rm) \times D(rm)] + [0.3A(lm) \times D(lm)] + [0.1A(c) \times D(c)]$$

Where A = area, D = darkness, f = forehead, rm = right malar, lm = left malar and c = chin. The darkness was scored as 0 = absent, 1 = slight, 2 = mild, 3 = marked and 4 = severe. Scoring of the area of involvement was as follows: 0 (absent), 1 (<10%), 2 (10–29%), 3 (30–49%), 4 (50–69%), 5 (70–89%) and 6 (90–100%). The total score ranges from 0 to 24. It was further categorized into mild (0–8), moderate (8–16) and severe (16–24).

Clinician assessment of overall aesthetic improvement from baseline was done using a 5-point Physician Global Aesthetic Improvement Scale (PGAIS), based on a comparison of the subject's previous visit photographs to the current visit photographs [Table 1]. Subject assessment of overall aesthetic improvement from baseline was done using Subject Global Aesthetic Improvement

Scale (SGAIS), based on a subject's comparison of the own previous visit photographs to the current visit photographs [Table 1].[23]

Safety was assessed using ADR reporting, physical examinations, and recording of vital signs at each visit. All safety endpoints were summarized descriptively for the safety population.

Statistical analysis

Data from the subjects' case record form were entered in a Microsoft spreadsheet and were analyzed with the same. Descriptive statistics were derived. Categorical data were presented as frequency and percentages. Continuous data were presented as mean and standard deviation. Parametric paired data were analyzed using a two-tailed paired t-test, whereas the Wilcoxon signed-rank test was used to analyze non-parametric matched data. *P* value < 0.05 was considered statistically significant for all comparisons.

Results

A total of 40 adult melasma patients of mean age 45 ± 12 years (age range: 25 to 70 years, including 5 males and 35 females) with Fitzpatrick skin types IV and V were enrolled in the study. Total 30 subjects received recommended three sessions of GFC monotherapy and 26 subjects completed one month follow-up (11, lost to follow up; 2, deviation from protocol; 1, dropped out because of injection site ADR). Following GFC therapy, we found a statistically significant decrease in the mean mMASI scores at all visits compared to baseline ($P < 0.005$ for each visit) [Figure 1].

When subjects were classified based on their mMASI score severity categories, it was found that only 7.7% of subjects were having severe melasma at the end of the study compared to 23.1% at the start of the study. Proportionate increase in percentage of subject is seen in mild melasma category [Figure 2]. A significant improvement in mean mMASI score was seen at the study completion in subjects who had mild to moderate melasma at the baseline ($P < 0.05$) [Figure 3].

Clinician assessment using PGAIS showed, overall aesthetic improvement in 88.5% of subjects at the end of the study. Improvement from baseline was noticeable as early as day 30 with one GFC session in 55.9% of subject. No worsening of the condition was seen in any subjects [Figure 4]. Similarly, Subjects' own assessment using SGAIS showed, overall aesthetic improvement as shown in Figure 5. All side effects reported by subjects were mild such as injection site pain, erythema, oedema, and bruising, and resolved spontaneously within a few hours to few days of onset. Changes in skin appearance of 39-year-old female before the GFC therapy at day 0 and one month after the three sessions of GFC therapy at day 90 are shown in [Figure 6a and b], respectively. Similarly, [Figure 7a] shows skin appearance of 50-year-old female at day 0 and [Figure 7b] at day 90.

Discussion

Melasma is a challenging dermatological condition, which has a considerable psychological impact on the individual. It adversely affects the individual's quality of life as appearances play a significant role in self-perception as well as social interactions.[24] It has been observed that

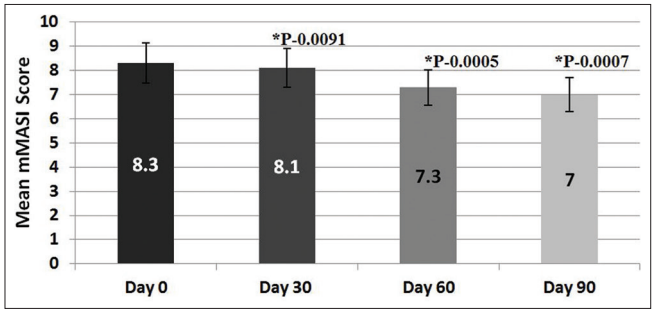

Figure 1: Mean change in mMASI at different study visits. *Compared to baseline, using two-tailed paired t-test, *P* value <0.05- Statistically significant. *n* = 40, Day 0; *n* = 34, Day 30; *n* = 30, Day 60; *n* = 26, Day 90

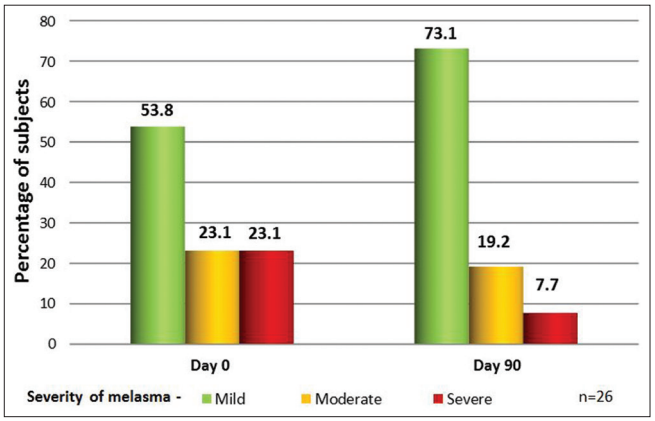

Figure 2: Change in percentage of subjects based on the severity of melasma. mMASI score, mild: 0-8, moderate: 8-16 and severe: 16-24

Table 1: Definitions of PGAIS and SGAIS

Score	Degree	Description
1	Very Much Improved	Optimal cosmetic result.
2	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal
3	Improved	Obvious improvement in appearance from initial condition
4	No Change	The appearance is essentially the same as the original condition.
5	Worse	The appearance is worse than the original condition

PGAIS: Physician Global Aesthetic Improvement Scale; SGAIS: Subject Global Aesthetic Improvement Scale

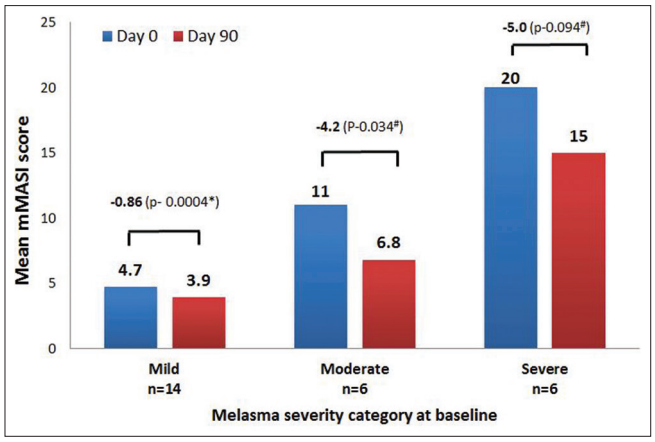

Figure 3: Mean change in mMASI based on the severity of melasma at baseline. *Using two-tailed paired t-test, # Two-tailed Wilcoxon signed-rank test for matched pairs, *P* value < 0.05- Statistically significant; *n* = 26. mMASI score, mild: 0-8, moderate: 8-16, and severe: 16-24

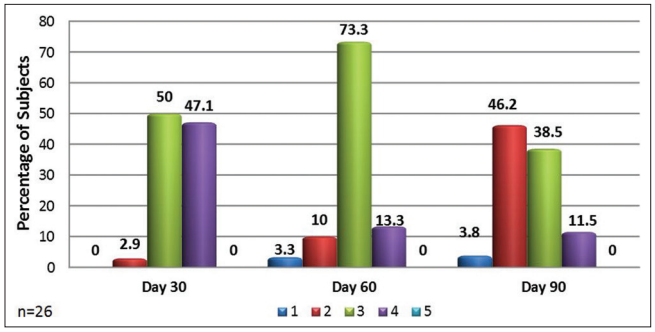

Figure 5: Distribution of SGAIS at different study visits. SGAIS: Subject Global Aesthetic Improvement Scale; 1: Very Much Improved, 2: Much Improved, 3: Improved, 4: No Change, 5: Worse

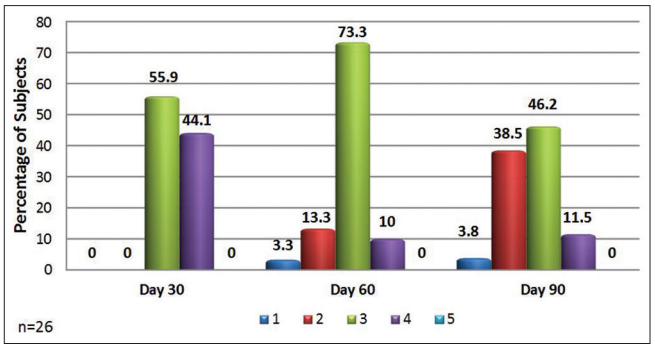

Figure 4: Distribution of PGAIS at different study visits. PGAIS: Physician Global Aesthetic Improvement Scale; 1: Very Much Improved, 2: Much Improved, 3: Improved, 4: No Change, 5: Worse

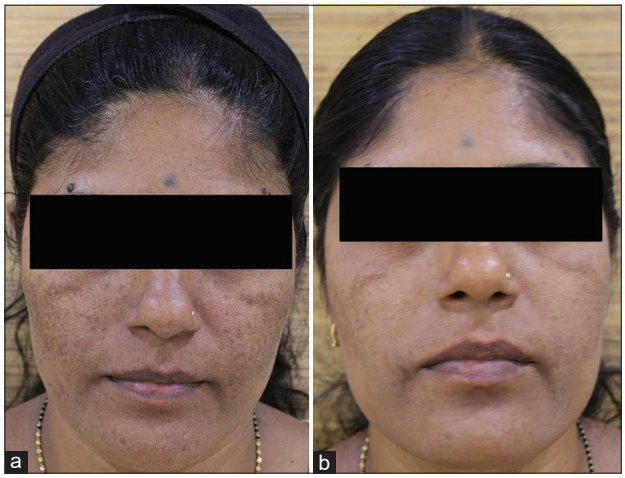

Figure 6: Skin appearance of 39-year-old female (a) before the GFC therapy at Day 0 (mMASI score: 10) and (b) one month after the 3 sessions of GFC therapy at Day 90 (mMASI score: 6.4)

PRP has a potential role in reducing pigmentation in melasma.[16-19] PRP essentially works by degranulation of the intracellular alpha-granules of the platelets to the release of growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin growth factor (IGF), and transforming growth factor-beta (TGF-β). These growth factors then stimulate the proliferation of fibroblast and epidermal cells, promote angiogenesis and induce collagen synthesis, to stimulate tissue regeneration and repair.[12-14] However, the exact mechanism by which PRP works in melasma is not known. Researchers have demonstrated in preclinical studies that TGF-β1 significantly inhibits melanin synthesis in a concentration-dependent manner and reduces the activity of tyrosinase, the rate-limiting enzyme in melanin synthesis. It is found that TGF-β1 exerts its action by reducing microphthalmia-associated transcription factor (MITF) promoter activity and inhibiting MITF, tyrosinase, tyrosinase-related protein-1 (TRP-1), and TRP-2 protein production. TGF-β1 also inhibits melanin synthesis via delayed extracellular signal-related kinase activation. Moreover, EGF was seen to decrease melanin production in melanocytes by inhibiting prostaglandin E2 (PGE2) expression and tyrosinase enzyme activity. Therefore, it is postulated that TGF-β1 and EGF are important growth factors released from platelets that would help to reduce the pigmentation of melasma. Moreover, along with other growth factors, these promote tissue repair which helps in the regression of melasma and overall facial rejuvenation.[25-27]

This study provides early evidence about the role of autologous growth factors derived from platelets as an innovative therapeutic option for the treatment of melasma. Our study showed GFC therapy significantly improved melasma as evidenced by the statistically significant decrease in mMASI scores from baseline (mean difference of mMASI score -1.3). Also, 41% of subjects with moderate to severe melasma shown regression in severity to mild form. Percentage reduction in mean mMASI score in our study was 15.67%. This can be because 90% of subjects were having a mixed type of melasma, which in general is more difficult to treat and usually require a more aggressive treatment approach.

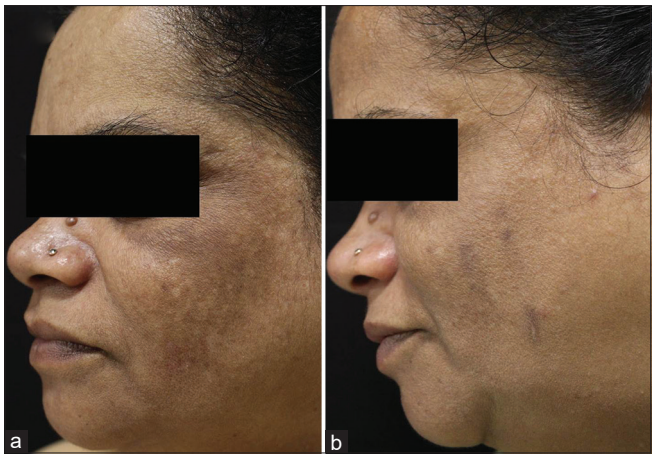

Figure 7: Skin appearance of 50-year-old female (a) before the GFC therapy at Day 0 (mMASI score: 14.1) and (b) one month after the 3 sessions of GFC therapy at Day 90 (mMASI score: 7.4)

We also found a significant improvement in mean mMASI score in patients who had mild to moderate condition at the baseline. Suggesting, these are the group of patients who can be benefited significantly with GFC. Moreover, the progressive decline was seen in mMASI over study visits, indicating longer treatment may yield more improvement. However, improvement in severe melasma patients did not reach the significance, though the numerical improvement was observed. This may be because; it is more difficult to treat and require treatment for a longer duration. Also, the sample size of severe category group was small and requires a larger sample to draw any further conclusion.

These findings were similar to previous studies published.[19,20,28,29] Eman R. M. *et al*. observed a statistically significant decrease in mean mMASI score after three monthly PRP sessions. However, the reduction was only 28% in patients who had mixed type of melasma. The authors also noted statistically significant improvement among those with epidermal type than those with mixed type.[19] Yew CH *et al*. reported two cases of melasma treated with three monthly sessions of PRP in conjunction with Q-switched Nd: YAG and twice daily application of alpha arbutin. The authors observed about 33.5% and 20% improvement in the MASI scores of cases 1 and 2, respectively. They substantiated the lower percentage of improvement in case 2 was due to the higher Fitzpatrick skin phototype (V) and the more resistant mixed type of melasma.[20] Another, trial of 20 melasma patients treated with five fortnightly sessions of activated PRP injections reported 31.7% mean reduction in MASI scores. Authors reasoned lower percentage of improvement in MASI to irregular use of sunscreen lotions, higher Fitzpatrick skin phototype and mixed type of melasma which is generally resistant to all kind of therapies.[28] Latest split-face pilot study conducted in Thailand, injected PRP and normal saline intradermally in 10 patients every two week for four sessions. Study showed significant improvement in mean mMASI score by 1.03 ± 0.44 at the end of study compared to baseline.[29]

Pain during injections was the common side effect and was related to injection pricks. It was mild and lasted a maximum of up to one hour. It was well tolerated by all subjects. Subjects observed downtime in terms of erythema, oedema, and needle prick bruises after the procedure up to 24–48 hours except one subject who had swelling after first dose, which subsided after four days. Overall, GFC therapy was well tolerated by subjects. Side effects reported in our study were similar to side effects reported in studies published earlier.[19,20,28,29] Eman R. M. *et al*. reported more pain with microinjections of PRP using mesoneedle than with microneedling with dermapen and PRP application. Patients also observed less downtime with PRP microinjections.[19] Yew CH *et al*. reported minimal and tolerable ADRs with PRP. Subjects experienced mild erythema, oedema, and bruises after the PRP therapy which were resolved in four to five days.[20] Side effects reported by Sirithanabadeekul P *et al*. were of mild severity such as bruising and they resolved spontaneously within a few days.[29]

There are some limitations to the present study. The current study is a single-arm and enrolled a limited number of subjects. Therefore, larger randomized control studies would be required to confirm the findings of this study. Future studies with increased GFC sessions and longer-multiple follow-ups are required to assess the long-term effect of GFC.

Conclusion

We found that there was a significant reduction in melasma score with GFC therapy as a monotherapy, this needs further confirmation in larger randomized controlled studies. Based on encouraging results of GFC monotherapy in melasma and being a source of various growth factors, which are proven to reduce the pigmentation and stimulating skin rejuvenation; GFC therapy also need to be evaluated as an adjunctive to conventional treatment for melasma. Overall, GFC therapy was well tolerated. Thus, GFC therapy can be a safe, effective and new option in the armamentarium of melasma management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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