Original Research Article

The effect of Intense-pulsed light and modified kligman's formula versus Intense-pulsed light alone in the treatment of moderate to severe melasma

Abstract:

Background: Melasma is a common pigmentary disorder that poses therapeutic challenges, so a variety of treatment modalities have been used in targeting pigmentation of melasma such as laser, Intense-pulsed light (IPL) and topical depigmented agents.

Objective: To compare the efficacy and safety of Intense-pulsed light (IPL) with triple combination (modified kligman formula) versus IPL alone in the treatment of melasma.

Methods: Forty-one patients with melasma (20 group-A and 21 group -B) were selected, mostly of skin type III, IV and V. Treatment is performed by using a session of IPL then daily use triple combination of 4% hydroquinone, 0.05% Tretinoin and 0.1% mometasone furoate at night and glycerin cream as moisturizer in the morning and with use of sunscreen in group -A for 4 sessions while group -B patients were treated by IP alone at 4-week intervals. All the patients were photographed before starting the therapy and at the end of four IPL sessions.

Results: Most of the patients in both groups had showed a good improvement in their melasma with the use of our treatment with adequate sun protection. The Melasma Area and Severity Index (MASI) scores significantly decreased in both groups after the treatment especially in epidermal types and also mixed types though no statistical difference was established among final MASI values of patients with dermal type in group-B.

Conclusion: The use of IPL sessions and triple mixture cream seems to be more effective than IPL sessions alone. It is an easy and a good option for patients with melasma. Adverse effects were minimal and acceptable with good satisfaction rate among patients.

Keywords: Intense-pulsed light, triple mixture, modified Kingman's formula, melasma. IPL.

Introduction:

Melasma is an acquired irregular brown or sometimes grey-brown hypermelanosis affecting areas of sun exposure with a large psychological impact. The condition is seen most commonly on the face of women with skin types IV to VI. Most people with melasma have a history of daily or intermittent sun exposure. Melasma is most common among pregnant women, especially those of Latin and Asian descents. People with olive or darker skin, like Hispanic, Asian, and Middle Eastern individuals, have higher incidences of melasma [1, 2].

Melasma is a complex multifactorial disorder whose pathogenesis is not well understood. The two most important causative factors are sunlight and genetic predisposition and the pathogenesis of melasma is not yet fully understood [3 ,4]. Melasma evolves from alterations in several skin layers and cell types to hyper functional melanocytes, which produce and transfer mature melanosomes to the whole epidermis. Recent evidence suggests that angiogenetic factor is involved in the pathogenesis of melasma. Moreover, it has been suggested that dermal inflammation induced by accumulation of UV irradiation may be associated with activation of fibroblasts, which result in the up-regulation of stem cell factor in melasma dermal skin leading to increased melanogenesis [5-7].

On the basis of Wood's light examination (320-400 nm), melasma can be classified to three types: Epidermal type, dermal type and mixed type [8]. The severity of this disease is calculated on the basis of Melasma Area and Severity Index (MASI). The MASI score is an index used to quantify the severity of melasma and changes during therapy. The maximum value of MASI is 48 and means severe hyperpigmentation [9].

The treatment of melasma includes many options like: general measures (mostly sunscreen), topical depigmenting agents (like hydroquinone, azelaic acid, Kojic acid, retinoid, corticosteroids), chemical peels (superficial, medium and deep), ILP therapy, laser therapy, cryotherapy and dermabrasion [10-12].

Kligman's triple combination formula has been one of the most popular treatment options in melasma over the last three decades. The original Kligman's formula has been modified in many ways over the years and the most recent modification that has been introduced is a triple combination of 2% hydroquinone, 0.025% tretinoin, and 1% mometasone [13].

Intense-pulsed light (IPL) was developed in the late 1990s and involves the use of a xenon-chloride lamp that emits light that is non-coherent not collimated and has a wide

spectrum (500–1200 nm). The advantage of IPL lies in the flexibility of parameters. The wavelength, fluency, number, duration, and delay of pulses can be changed for each patient to effectively target chromophore. Hence, it can be used for the treatment of a variety of conditions such as vascular lesions, hair removal, and melanocytic lesions. However, there are very few studies on the treatment of melasma with IPL [14,15].

The purpose of the present work is to compare the efficacy and safety of ILP with triple combination of 4% hydroquinone, 0.025% Tretinoin and 0.1% mometasone furoate versus IPL alone in the treatment of moderate to severe melasma.

Materials and Methods:

This is a comparative therapeutic trial conducted in a dermatological center in Sulaymaniyha, Iraq. A total of 41 patients with melasma were included, their ages ranged between 24 to 56 years (mean age was 36). Patients were divided into two groups (A and B):

1. Group -A (n=20); treated by IPL session followed by a triple mixture of Tretinoin (0.025%), Hydroquinone (4%) and mometasone furoate (0.1%).

2. Group -B (n=21); treated by IPL session once every four weeks.

All patients had melasma for more than one year, with the history of multiple previous therapies for melasma. Each patient has been interviewed and a full history was taken with emphasis on the progress of melasma, previous and present medications for melasma as well as history of contraceptive pills, daily sun exposure, history of pregnancy and family history. Not all patients with melasma were suitable candidates for this study. Patients with the following criteria were excluded: Pregnancy, History of keloid tendency, History of recurrent herpes simplex, History of systemic retinoid e. g. isotretinoin intake during last six months, History of chemical peeling or any other surgical procedures on the face during last six months, Patients with psychological problems which may lead to non compliance/Patients who could not keep themselves away from sun exposure.

The patients divided into group -A (20 patients) and group -B (21 patients) before starting our treatment. The procedure was fully described to each patient including its duration which lasting maximum of 4 months in which four IPL sessions will be done once every 4 weeks, also they were informed about the side effects that he or she may

face from IPL and triple mixture. All these were made as an informed consent paper and signed by the patient with one of his or her relatives.

For each patient in either group, examination of melasma has been done by Wood's light before starting the treatment to detect the type of melasma whether it is epidermal, dermal or mixed.

All patients have been photographed before starting the peeling process (as a baseline documentation) and then every 4 weeks, with the last photo taken 4 weeks after the last session. All photographs were obtained in the same place with same distance and fixed illumination.

The method of treatment in Group -A: (The patients in this group were treated with IPL sessions and triple topical mixture).

Intense pulse light (IPL) sessions**:** using cutoff filters of 550 nm, pulse of 5–10 ms, pulse delay of 10–20 ms, and low fluence 8–16 J/cm2.

Triple mixture cream**:** All patients with melasma received a maintenance regimen of Tretinoin (0.025%), Hydroquinone (4%) and mometasone furoate (0.1%), applied at night. The patients were instructed to apply medication all over the face, after mixing in an equal proportion on the palm.

The method of treatment in Group -B: The patients in this group were treated by IPL session once every four weeks and physical sunscreen at daytime for 4 months, with avoidance of any other concomitant therapy for melasma.

Evaluation of the patients and follow up**:** Follow-up evaluation of patients was done regularly at 4-week intervals during IPL sessions. Changes in clinical appearance as well as MASI scores were assessed. Photographs of right, left profiles and full face were taken for each patient to assess the improvement of lesions.

Scoring System: Three investigators have independently evaluated the clinical responses as well as the serial photographs of the patients. Scores were given as follows: 0% (no response), 1-25% (minimal response), 26-50% (mild response), (51-75% moderate), Greater than75% (significant).

Statistical Analysis: Statistical package for social science (SPSS) program version 23 was used for statistical analysis. Before starting therapy, a baseline assessment was done as well as calculation of melasma area severity index (MASI scoring). Statistical analyses were used in all parameters. Paired t-test was used to compare the mean of

MASI change resulting from treatment. P values of less than 0.05 were considered significant.

Results:

A total of 41 patients: 20 patients in group –A (15 females and 5 males) and 21 patients in group -B (14 females and 7 males) with melasma were included in our study. The patient`s mean age was 36 years (range between: 24-56). They had Fitzpatrick's skin types III, IV and V. All types of melasma were present among the patients and the duration of facial pathology was for more than one year with multiple previous treatments.

I. Group – A (IPL session + triple topical mixture):

Ten (66.7%) females were married and 5 (33.3%) were unmarried. Among married females, 8 (80%) gave history of pregnancy. Regarding the drug history; which is a common cause of melasma; almost one half of married females (n=5, 50%) used contraceptive pills.

Seven (35%) patients had a family history of melasma. Six (30%) patients had Fitzpatrick's skin type III, and 14 (70%) had skin type IV. Thirteen (65%) patients were sunscreen users and 7 (35%) of them non-users. Fourteen (70%) patients were indoor workers.

Ten (50%) of patients had an epidermal type of melasma based on Wood's light examination, 7 (35%) patients had mixed type and 3 (15%) patients had a dermal type.

Side Effects: No severe side effects were reported after IPL sessions and the topical triple mixture apart from mild erythema and dryness of skin observed in some of the patients. Three (15%) patients suffered from transient post inflammatory hyperpigmentation. No scarring was recorded in the present series of patients.

In the epidermal type; mean MASI score was 25.74±6.6 before session of IPL and topical treatment and became 3.94±2.6 after the fourth session, and was statistically highly significant (p value<0.001).

In the mixed type; mean MASI score before session of IPL and topical treatment was 18.53±5.5 and became 10.31±4.9 after the fourth session. (p-value <0.001 which is statistically highly significant).

In dermal type, mean MASI score before session of IPL and topical treatment was 24.44±4.5, then after the four sessions became 16.20±4.5, (p-value <0.001 which is statistically highly significant).

In epidermal type, 2 (20%) patients showed moderate response, and 8 (80%) showed significant response (p- value<0.05). In mixed type of melasma, 3 (42.9%) patients showed mild response, and 4 (57.1%) showed moderate response. In contrast, all patients with dermal type (n=3, 100%) showed a minimal response. A statistically significant improvement in clinical response was established in this group especially epidermal type.

So, after completion of all sessions of IPL + triple topical mixture, there was a statistically significant improvement in clinical response and statistically significant decrease in the mean MASI score particularly in patients with the epidermal type in whom the response was highly significant.

Side Effects: No significant side effects were noted in this group apart from dryness and erythema in some patients from topical treatment and erythema following IPL therapy and transient hyperpigmentation in few patients which resolved after period of time .

II. Group -B (IPL alone):

Nine (64.3%) of the females were married. Among married females, 6 (66.7%) had previous pregnancies. Family history was positive in 9 (42.8%) patients. History of contraceptive pill was positive in 8 (88.9%). Seven (33.3%) patients had skin type III, 13 (61.9%) type IV, and 1(4.8%) skin type V. Fourteen (66.7%) patients were sunscreen users. Fifteen (71.4%) patients were indoor workers. On Wood's light examination, 11 (52.4%) patients had epidermal, 7 (33.3%) had mixed and 3 (14.3%) had dermal type.

In epidermal type, the mean MASI score before IPL treatment was 25.36±5.9, and became 12.63± 4.1 after the end of the sessions. P- value<0.001(statistically highly significant). **In the mixed type**, the mean MASI score before IPL treatment was 29.51± 5.52 and became 18.06± 3.3 after fourth treatment, P- value<0.001(statistically highly

significant). **In the dermal type,** mean MASI score was 20.40± 4.49 and after 8 weeks of IPL treatment became 18.88 ±4.1, the P- value was 0.271 which is statistically not significant (if the P- value < 0.05 is statistically significant).

In epidermal type of melasma, 1 (9.1%) patient had got no response, 2 (18.2%) showed mild response, 5 (45.4 %) showed moderate response and 3 (27.3%) had significant response. However, among patients with mixed type of melasma, 4 (57.1%) showed mild response, and 3 (42.9%) showed moderate. In dermal type, 1 (66.6%) showed no response, 1 (16.7%) minimal, 1 (16.7%) had moderate response. A statistically significant improvement in clinical response was observed in this group especially epidermal type.

In this group, the difference in the clinical response and the mean MASI score after completion of all sessions of IPL treatment was statistically significant (p -value <0.05). **Side Effects:** No significant side effects were noted in this group apart from erythema following IPL therapy and transient hyperpigmentation in few patients which resolved after 4 weeks.

Regarding the total mean MASI score for both groups; in group**- A** before treatment was 24.63±5.8 and became 16.41±4.7 After treatment, so the difference was 14.50±7.7 (p- value <0.001 which is statistically highly significant). While group**- B** before treatment was 22.87±6.2 and became14.50±3.5 after treatment. Thus, the difference of the total mean MASI in group -B was 10.34±0.83 and the p- value <0.001 which is statistically highly significant.

Discussion

Treatment of melasma is challenging with no cure available yet. Even so, treatment modalities are many and varied-each promising more than the last. [10] Hence, this study was done to evaluate the effect of IPL and triple mixture in the treatment of moderate to severe and dark skin phenotype.

A high prevalence of melasma in adult females was noted, this is a natural phenomenon because of the female hormonal activity during pregnancy together with the use of contraceptive pills which was reported to exacerbate melasma [1]. This study includes 12 (29.3%) males which is more than reported in the previous studies which may indicate a new trend among males taking care about their face appearance.

According to previous reports, the family history of melasma patients suggests the importance of genetic factors, pregnancy and sun exposure in the pathogenesis of this condition [1-3]. In the present study; 7 (35%) of the patients in group-A and 9 (42.8%) among group -B had positive family history of melasma respectively. The rate of indoor workers was 38 (84.4%) in group -A and 34 (79.1%) in group –B.

Among married females, 8 (80%) gave history of pregnancy in group-A and 6 (66.7%) in group-B. Contraceptive pills were used by 5 (33.3%) patients in group-A and by 8 (57.1%) in group -B. These indicate that causes like contraceptive pills, genetic (family history) and pregnancy have had important role in developing melasma in this study.
Many types of treatment were used for melasma as topical therapy, IPL and laser, mainly in fair-skinned individuals. People with higher skin phototype are usually resistant to therapy and therapeutic results are unsatisfactory [14]. In the present study, good response was obtained despite a high rate (65.9%) of type IV.

Lasers and IPL have revolutionized the treatment of dermatological disorders but its place in the management of melasma and PIH is still controversial. The use of laser and light technologies to treat melasma has been investigated in numerous clinical trials. Intense-pulsed light (IPL), fractional 1550-nm non-ablative laser, pulsed dye laser (PDL), copper-bromide laser, and Q-switched neodymium-doped yttrium aluminum garnet laser (QS Nd: YAG) have all demonstrated successful outcomes [16].

In this study, group -A was treated by IPL followed by triple mixture of Tretinoin (0.025%), Hydroquinone (4%) and mometasone furoate (0.1%) at night with sunscreen daily for time of the next IPL session. On the other hand, group -B patients were treated by IPL session once every four weeks. The treatment in both groups yielded a statistically significant decrease in MASI values but it is more better in group –A (group-A=14.50±3.5 while group-B= 16.41±4.7) and also the regarding the dermal type in group-B the change in MASI score was statistically not significant while it is significant in group-A , this is maybe due to several factors like synergistic effects of both IPL and topical triple mixture, also the IPL may increase the transepidermal delivery of topical treatment which may effects the dermal type [17].

Conclusion: the use the IPL sessions and triple mixture was safe and effective treatment for severe types of melasma and is more effective than IPL sessions alone, especially for dermal type, with a very low risk of complications and an excellent satisfaction rate among patients. Appropriate maintenance therapy should be selected to avoid relapse of melasma.

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Table 1: changes in the total mean MASI score Before and after treatment for each type of melasma in group -A.

Types of melasma	**Mean of MASI score before treatment sessions in group-A**	**Mean of MASI score after treatment sessions in group-A**	**p-value**
Epidermal	25.74±6.6	3.94±2.6	<0.001
Mixed	18.53±5.5	10.31±4.9	<0.001
Dermal	24.44±4.5	16.20±4.5	<0.001

P- value<0.001(statistically highly significant).

Table 2: changes in the total mean MASI score Before and after treatment for each type of melasma in group -B.

Types of melasma	**Mean of MASI score before in group –B**	**Mean of MASI score after therapy in group -B**	**p- value**
Epidermal	25.36±5.9	12.63±4.1	<0.001*
Mixed	29.51±5.52	18.06±3.3	<0.001
Dermal	20.40±4.49	18.88±4.1	0.271 ns**

***P- value<0.001(statistically highly significant).**

**** P- value<0.05(statistically significant< 0.05).**

Table 3: changes in the total mean MASI score Before and after treatment for study groups.

Groups of study	Total mean MASI score Before treatment	Total mean MASI score After treatment	P- Value
Group- A	24.63±5.8	16.41±4.7	<0.001
Group- B	22.87±6 .2	14.50±3.5	<0.001

P -value <0.001 statistically highly significant

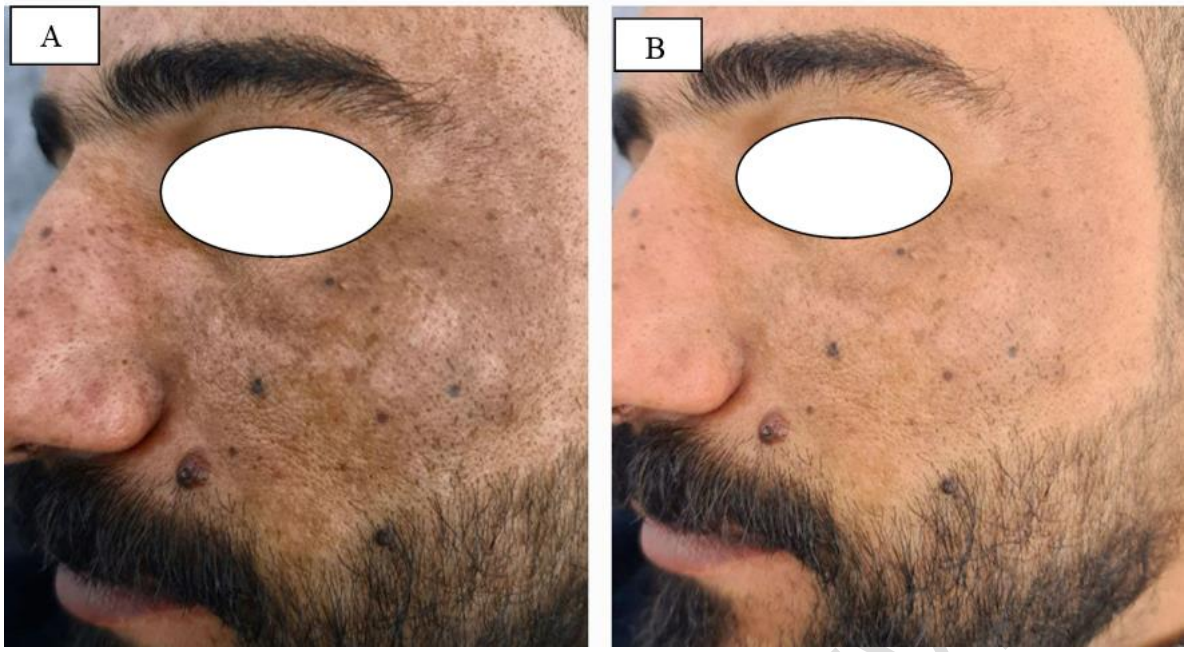

Figure (1): A 33 years old male with skin type 3 had epidermal type of melasma: **A**: Before treatment and **B**:After 3 sessions of IPL treatment and topical triple mixture depigmenting agents.

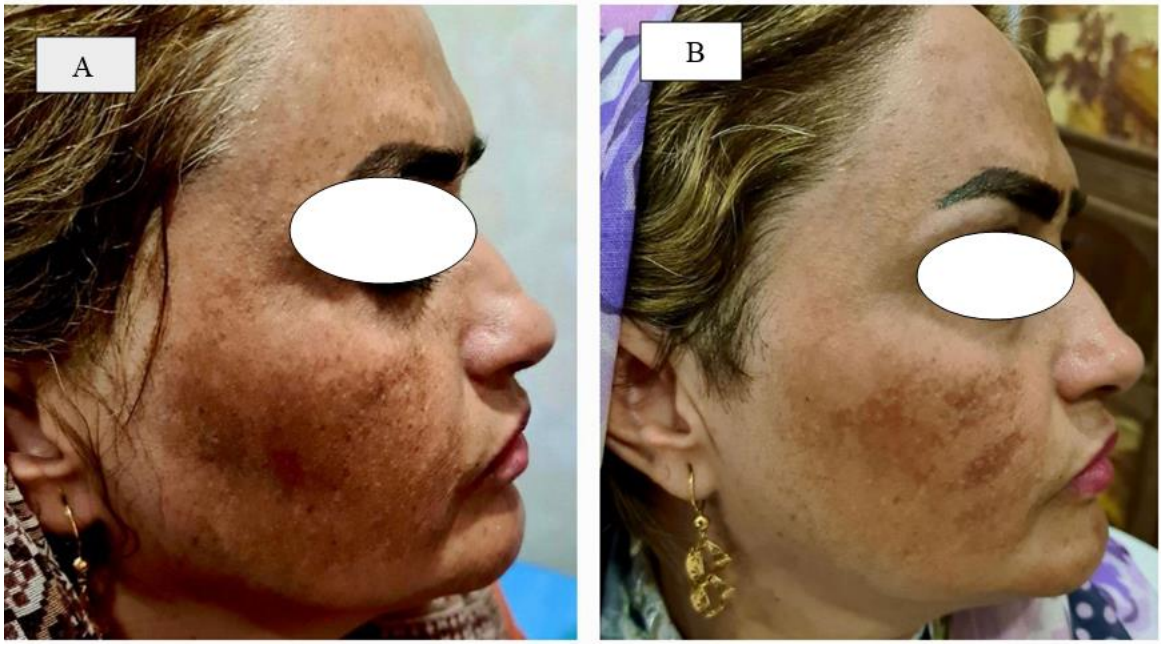

Figure (2): A 38 years old female with mixed type of melasma: **A**: Before treatment,

B: After 3 sessions of IPL treatment and topical triple mixture depigmenting agents.