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Evaluation of Efficacy and Safety of Combined Therapy of Melasma by using Azelic, Glycolic and Kojic Acid (Unitone and Neotone)

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Abstract

Background: Melasma is one of the most common disorders of brown hyperpigmentation, which affect primarily the face and later on some other sites of the body , seen most commonly in women during the reproductive period and may seen in men . Many options are used in the treatment of melasma, most commonly: hydroquinone, tretenoin, corticosteroid, azelic acid, glycolic acid, kojic acid, triaximinic acid, ascorbic acid, intralesional glutathione, and lastly medical procedures, like: microdermabrasion, chemical peel, laser and light therapy.

Objective: To evaluate the efficacy and safety of combined therapy (azelic, glycolic and kojic acids) in the treatment of melasma (UNITONE and NEOTONE) .

Patients and Methods: A cross-sectional study in which (585) patients complaining of melasma (577 females and 8 males), their age ranged from (17-50) years, with a mean age of 46.15± years. Treated by application of azelic acid (20% cream) for two hours at night, then washed and followed by topical application of combined cream consisted of (5%) glycolic acid and (1%) kojic acid throughout the night and washed in the morning, with application of sun block of ≥50 SPF, and oral ascorbic acid (500mg) tablet twice in the morning and evening .

Results: Out of 585, 98% was females with a mean age of (46.15±8) years. Eight percent of the patients of MAIS score-1, (22.05%) of score-2, (51.28%) of score-3 and (18.8%) of score-4. Regarding the response to therapy: (44.78%) of patients showed complete clearance of the disease, (48.85%) with good response, (1.7%) of poor response and (5.47%) showed relapse of the melasma after discontinuation of the therapy, and they were retreated by the same combined formula, (93.75%) of them cleared completely and (6.25%) showed good response. Ninety percent of patients developed a variable degree of irritation, erythema and burning sensation, at the beginning of the treatment and after (10-15) days, most of them tolerated the therapy.

Conclusion: Combined therapy of azelic, glycolic and kojic acids was effective and safe in the treatment of melasma and this combination was

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superior and alternative to the ordinary and corner therapy of hydroquinone and corticosteroid.

Keywords: Combination therapy, azelic, glycolic, kojic, ascorbic acids, MASI, MSI

Introduction

Melasma (face mask) is one of the most common disorders of brown hyperpigmentation, which affects primarily the face and later on some other sites of the body, most commonly in women, during the reproductive age, rarely seen in men [1]. The etiology of melasma remain obscure, but many etiological factors are implicated which include [1-3] : Hormonal changes, Prolong exposure to sun light, Genetic predisposition, Skin irritation , And some endocrinological.

The chief complain of melasma is brownish hyperpigmentation most commonly seen on the face, less commonly on the neck, shoulders, arms and the forearms [1]. Clinically facial melisma is classified into three types: the centrofacial, which is the most common type, which affect the forehead, cheeks, the upper lip and the chin, the molar type, is the second common type, seen on the maxillary area and the nose, and less commonly the mandibular type, which affect the ramus of the mandible [1,2,4].

The diagnosis is made clinically and may be confirmed, by Wood's lamp examination or histopathological examination (1,2,4,5). The severity of melasma is assessed by two scores, either melasma area and severity index (MASI) or melasma severity index (MSI). According to MASI, (which means degree and severity of pigmentation), melasma is scored into five scores (0-4): zero= normal skin, 1= just visible pigmentation, 2= mild melasma, 3= moderate, 4= sever melasma, while according MSI (which means surface area of melasma), melasma is scored into four scores (1-4): 1≤10% of surface area, 2=11-30%, 3=31-60%, 4>60% [6].

Many therapeutic options are used in the treatment of melasma, although some times it clear spontaneously, especially those due to pregnancy and contraceptive pills, when the causes are removed and may relapsed even after successful therapy [1,2,4,7]. These therapeutic options include: hydroquinone (2-5%), corticosteroids, tretinoin, combined therapy (triple, Kligman formula: hydroquinone, tretinoin and corticosteroid), an additional topical medications like: azelic, glycolic, kojic and triaximinic acid, intralesional injection of glutathione and lastly, microdermabrasion, chemical peel, laser and light therapy[1, 4,8].

Azelic acid is naturally occurring nonphenolic saturated, nine carbon dicarboxylic acid that competitively inhibit tyrosinase, also it inhibit DNA synthesis and mitochondrial enzymes, thereby induce direct cytotoxic effects on melanocyte [9]. Ascorbic acid has antioxidant properties and affects melanogenesis, by reducing dopaquinone to DOPA and preventing free radicals production and absorption of UV radiation, used orally or topically as (5-25%) cream. Glycolic acid is an alpha-hydroxy acid, which decrease pigmentation by peeling and desquamation, as well as direct reduction in melanin formation, by inhibition of tyrosinase. Kojic acid is naturally occurring hydrophilic fungal product derived from certain species (Acetobacter, Aspergillus, and

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Penicillium), act by inhibition of the production of free tyrosinase, and also act as potent antioxidant (1-4%) concentration [10]. The aim of this study was to evaluate the efficacy and safety of combined therapy (azelic, glycolic and kojic acid) in the treatment of melasma with out usage of the corner therapy the hydroquinone.

Patients and Methods

Design of the research

A cross-sectional study, in which a total number of (585) patients complaining of Melasma was seen and treated in a private clinic, in Kalar City, Al-Sulaymmania Provence, Iraq, for the period, 15-Jan.2016 to 15-Jan.2017. They were (577) females and (8) males, their ages ranged from (17-50) years, with a mean age of (46.15±8) years, all of them of Fitzpatrick's skin types 3 and 4. They were fully interrogated regarding the complain, age, occupation, outdoor work, reproductive life (including menstrual cycle, pregnancy, contraceptive pills and hormonal therapy), duration of the disease, progression and therapy used, any skin and systemic disease and if these diseases were treated or not and what type of therapy used for the treatment of these diseases. The disease was diagnosed clinically and confirmed by using Wood's lamp. The severity of the melasma was assessed by using the MASI scoring.

After a written concept was obtained, all patients were treated by topical application of (20%) azelic acid cream for two hours at night, then washed and followed by topical application of cream consisted of (5%) glycolic acid and (1%) kojic acid, overnight and washed in the morning, then a sun block of SPF≥50 was applied every three hours, and oral ascorbic acid (vitamin-c), (500mg) tablets in the morning and at night after meal as an antioxidant. The patients were followed up and examined every two weeks by the observer and patients satisfaction, to evaluate the response to therapy, which continue for (25-60) days in most of the patients (72.99%) Table(1).

Statistical Analysis

All data collected have been entered on an excel sheet, Chi-square test was used to assesse the statistical variants of the result. The response to therapy was graded into three grades: either complete clearance, good response (75-90%lightining, i.e. only trace of light brown pigmentation, MASI score-1) or poor response (resistant cases).

Results

A cross-sectional study in which (585) patients with melasma were included, they were (577, 98.6%) females and (8, 1.4%) males, with a mean age of (46.15±8) years. They were treated by combination therapy of: azeli, glycolic, kojic and ascorbic acid, as described in methods and patients were advised to use sun screen after discontinuation of therapy.

Table (2) revealed the results of MASI scoring of the patients involved in the study, they were (110, 18.8%) patients of score-4 (sever hyperpigmentation), (300,51.28%) patients of score-3(moderate hyperpigmentation), (130,22.05%) patients of score-2 (mild hyperpigmentation) and (45,7.6%) patients of score-1 (just visible light brown pigmentation). Regarding the duration of therapy (Table-1), (427, 72.99%) patients used therapy for (25-60) days, (139, 23.89%) patients for (61-150) days and (19,3.12%) patients used the therapy for (151-300) days .

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The study revealed Table(3), that (262,44.78%) patients showed complete clearance of the disease, with MASI score-zero, (281,48.85%) patients had good response, with MAIS score-1, (10,1.7%) patients of poor response (resistant to therapy) and (32,5.47%) patients showed relapses of the disease after discontinuation of therapy and they were retreated by the same formula, of them (30,93.75%) patients cleared completely and (2,6.25%) patients showed good response . Ninety percent (527) of patients developed variable degree of irritation at the beginning of treatment, with erythema and burning sensation, and after (10-15) days, most of them tolerated the therapy.

The response according MASI score Table (4),in those patients with complete clearance of the disease, there was done grading of different MASI scores to score-zero (clear, normal skin) with P=0.05, patients with good response, shows done grading of MASI score to score-1 (just light hyperpigmentation), P=0.02, while patients with poor response, there was either down grading of MASI scores from 4 to 3 or 3 to 2 or 1, or there was no response (resistant cases) P=0.1.

Table (1): Duration of therapy in patients with melisma

Duration in days	No. of patients	Percentage%
25-60	427	72.99
61-150	139	23.89
151-300	19	3.12

Table (2): Number of patients according to MASI scores (severity of melasma)

MASI score	No. of patients	Percentage%
1	45	7.6
2	130	22.05
3	300	51.28
4	110	18.8

Table (3): Number of patients according to response to therapy

Response	No. of patients	Percentage%	P-value
Cleared	262	44.78	0.05
Good	281	48.5	0.02
Poor	10	1.7	0.1
Relapsed	32	5.47	0.05
Total	585	100	

Table (4): Response to therapy according to MASI scores

Response	No. of patients	Percentage%	MASI score before therapy	MASI score after therapy	P-value
Cleared	262	44.78	1,2,3,4	0	0.05
Good	281	48.85	2,3,4	1	0.02
Poor	10	1.7	1,2,3,4	1,2,3,4	0.1
Relapsed	32	5.47	1,2,3,4	0	0.05
Total	585	100			

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Figure (1): Before treatment

Figure (2): After treatment

Discussion

This study using an alternative, second line therapy to the old corner therapy ,(hydroquinone or the triple Kingman's formula), in the treatment of melasma (mask face), which was used for long time and giving a variable response, duration of therapy, and side effects like exogenous ochronosis and satellite pigmentation [1,2,3,11].

Regarding the mean age of onset of melasma, in this study it was (46.15±8) years, which differ from that done in India (33.45) years [12]), and in Singapore (42.3) years [13]. When compared with other studies done in different areas in USA, using the ordinary therapy (triple formula) and new therapy like: azelic, kojic and tranexamic acid (50-75%, cured or with good response) [14], this study was superior in the end results of treatment of melasma (92% cured or with good response). In comparison with fractional photothermolysis (60% cleared and good response) [15], also this study was superior.Another study done on Asian women's, using Q-switched neodymium-doped yatriam aluminum garnet laser (1064nm,QS-NdYAG)[16], showed

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temporary poor response as compared with this study.

This study was parallel to that done in India, using (50%) glycolic acid facial Pell (91% improvement) [17], but it was superior to another study using (1%) tretinoin solution weekly application for (6-12) weeks (50% improvement) [18], and also highly superior to that study used to evaluate intradermal microinjection of tranexamic acid, performed on women with melasma in South Korea (only 9.4% showed good response [19].

Conclusions

It was concluded that combination therapy of azelic, glycolic, kojic and oral ascorbic acid was superior to other studies using the old hydroquinone and triple formula as well as laser and photothermolysis therapy.

Recommendations

I recommend to use emollient cream with topical Azelic acid to decrease irritation and increase patient compliance also recommend to use maintenance cream as Glycolic, Kojic acid after the treatment course to avoid relapse.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: Ethical approval was obtained from the College of Medicine / University of Diyala ethical committee for this study.

Conflict of interest: Nil

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تقييم فعالية وسلامة العلاج المشترك للكلف باستخدام حمض الازيلك و الجليكوليك وحمض الكوجيك

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الملخص

خلفية الدراسة: الكلف هو واحد من الاضطرابات الأكثر شيوعا لفرط التصبغ البني ،والتي تصيب بالدرجة الاولى الوجه و بعض الاماكن الأخرى للجسم ، والتي شوهدت بشكل شائع في النساء خلال الفترة الإنجابية وقد شوهدت في الرجال ايضا.
يتم استخدام العديد من الخيارات في علاج الكلف ، والأكثر شيوعًا: الهيدروكينون ، التريتينوين ، الكورتيكوستيرويد ، حمض الأزيليك ، حمض الجليكوليك ، حمض الكوجيك ، احماض الفواكه ، حمض الأسكوربيك ، حقن موضعي للجلوتاثيون ، وأخير الإجراءات الطبية ، مثل: المايكرونيدلنك ، التقشير الكيميائي ، الليزر والعلاج الصوئي.
اهداف الدراسة: لتقييم فعالية وسلامة العلاج المشترك (أحماض الجليكوليك والجليكوليك والكوجيك) في علاج الكلف.
المرضى والطرائق: دراسة مستعرضة تضم (٥٨٥) مريض يشكو من الكلف (٥٧٧ إناث و ٨ ذكور) ، تراوحت اعمرهم من (١٧-٥٠) سنوات ، مع متوسط عمر ٤٦,١٥ ± ٨. تم العلاج بوضع حمض الأزيليك (كريم ٢٠ ٪) لمدة ساعتين في الليل ، ثم يتم غسله ويتبعه وضع الكريم المشترك الذي يتكون من حمض الجليكوليك (٥ ٪) وحمض الكوجيك (١ ٪) طوال الليل ويغسله في الصباح ، مع وضع الواقي الشمسي ≤٥٠ SPF في النهار ، وحمض الأسكوربيك عن طريق الفم (٥٠٠ ملغ) قرص مرتين في الصباح والمساء.
النتائج: من أصل ٥٨٥ ، كانت ٩٨ ٪ هم من الإناث مع متوسط عمر (٤٦,١٥ ± ٨) سنة.
٨٪ من المرضى كان مقياس MAIS SCORE-1
٢٢,٠٥ ٪ من المرضى كان مقياس MAIS SCOR-2
٥١,٢٨% من المرضى كانوا MAIS SCOR-3
١٨,٨٪ من المرضى كانوا MAIS SCOR-4
فيما يتعلق بالاستجابة للعلاج: (٤٤,٧٨ ٪) من المرضى أظهروا شفاءا تاما للمرض ، (٤٨,٨٥ ٪) مع استجابة جيدة ، (١,٧ ٪) من استجابة سيئة و (٥,٤٧ ٪) أظهرت انتكاس للكلف بعد توقف العلاج ، وقد تم اعادة علاجهم بنفس الطريقة حيث ان ، (٩٣,٧٥ ٪) تم شفائها بالكامل و (٦,٢٥ ٪) لاقى استجابة جيدة.عانى ٩٠٪ من المرضى بعض الاعراض الجانبية مثل تهيج البشرة ، احمرار و الحرقة في بداية العلاج وبعد (١٠-١٥) أيام تم التخلص من الاعراض الجانبية تدريجيا
الاستنتاجات: كان العلاج المشترك لأحماض Azelic و Glycolic و Kojic فعال وآمن في علاج الكلف وكان هذا المزيج متفوقًا وبديلاً للعلاج العادي مثل الهيدروكينون والكورتيكوستيرويد.
الكلمات المفتاحية: العلاج المشترك، حمض الازيلاك، حمض الجليكوليك، حمض الكوجيك، حمض الاسكوربك ، مقياس ماسي، مقياس الكلف
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