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Original article

Photobiodynamic therapy: a new alternative for the treatment of Melasma

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Abstract. *Introduction:* Melasma is a common acquired disorder of facial hyperpigmentation with frequent recurrence after treatment. *Objective:* To evaluate the effect of a multimodal photodynamic therapy on the treatment of melasma. *Methodology:* A multimodal therapy that combines the topical application of antioxidant molecules, tyrosinase inhibitors, melanogenesis blockers, antioxidants, and anti-inflammatory molecules, with UV-free photomodulation based on HDD light (I.o. 530± 10 nm) and colloidal gold as photoactivator was applied to 28 female patients affected by melasma. The presence of defined brown spots of variable extension (melasma) and red areas (vascular alterations) on the face of the patients was evaluated before and 6 weeks after finishing the treatment. Wood's lamp, VISIA system and 3D Digital Photography were used. The treatment was applied in 4 phases (peeling, photodynamic serum, HDD light and depigmenting mask) under medical supervision. *Results:* 28 volunteer patients, diagnosed with melasma, of Latino origin with a predominance of phototype III on the Fitzpatrick scale, participated in this study. 86% of the patients, in addition to melasma, exhibited red areas, indicative of vascular alterations. 75% of the patients had been previously treated in the last two years with other treatment modalities and exhibited a relapse. The 3D digital photographs showed that all the patients improved in the resolution of the spots after the treatment. The improvement was significant, decreasing both the brown hyperpigmented areas and the red vascularized areas. The values obtained on the VISIA scale by the total group of patients before and 6 weeks after completing the treatment confirmed a significant improvement ($p<0.005$) in terms of the resolution of UV spots, brown spots as well as in the red areas and better pigment distribution of the affected sensitive area. *Conclusions:* The results of this work are preliminary. However, they showed for the first time, that this therapeutic approach was effective, although necessary to evaluate the effect in these patients later in time, and did not cause any discomfort or inflammatory complications after its application, in any of the patients.

Key words: tyrosinase inhibitors, photodynamic therapy, colloidal gold, melasma, vascularization

Introduction

Melasma is a common acquired disorder of facial hyperpigmentation caused by a complex interplay of genetic, hormonal, and UV exposure factors[1]. It is characterized by the presence of moderately symmetrical irregular spots, which primarily affect sun-exposed areas such as the forehead, cheeks, and the area under the nose[2]. It is linked to a functional disorder of melanogenesis.

Melanocytes are known to be found in the basal layer of the epidermis and the lower part of hair follicles. These cells produce melanin, a pigment whose primary function is to absorb ultraviolet radiation. The primary function of Melanocytes is to produce these pigments via melanogenesis. This process consists of a series of

reactions catalyzed by various enzymes that convert tyrosine into melanin pigments. The melanin produced can be of two types: eumelanin and pheomelanin, which have different proportions in humans. Melanocytes synthesize and deposit the melanin pigment in specific organelles called melanosomes. Perinuclear melanin caps are formed by the transfer of melanosomes from melanocytes to neighboring keratinocytes[3]. Melanosomes are found in cutaneous and ocular melanocytes, as well as retinal pigment epithelium cells. Eumelanin is a brown or black melanin with a high molecular weight that is insoluble in most solvents. Pheomelanin is a yellow-orange pigment that is soluble in alkali[3,4]. These two pigments share a common precursor, dopaquinone, which is formed by the oxidation of tyrosine by the enzyme tyrosinase. Eumelanin and pheomelanin have distinct synthesis pathways. In addition to tyrosinase, the synthesis of eumelanin (eumelanogenesis) requires the presence of three other enzymes: tyrosinase-related protein-1 (TYRP1), tyrosinase-related protein-2 (TYRP2), and dopachrome tautomerase (DCT), whereas pheomelanin (pheomelanogenesis) requires the incorporation of sulfur. The activity of the enzymes in the melanogenesis process and the availability of tyrosine or sulfur compounds determine the eumelanin/pheomelanin ratio. Melanogenesis occurs after the MITF gene (microphthalmia-associated transcription factor) is activated, which is responsible for the synthesis of tyrosinase, TRP1 and TRP2. MITF is required for melanocyte embryonic development and postnatal viability[3,4].

Studies on histopathology have demonstrated that melasma-affected skin contains more melanocytes and is more active in melanogenic enzymes, compared to unaffected skin from the same individual[5]. In this area there is also an increase in vascularity as well as solar elastosis and changes in the basement membrane attributable to actinic damage. Clinicians have long struggled with the therapeutic management of melasma.

Rather than a single treatment agent, a combination of topical bleaching agents, chemical peels, mesotherapy, and laser treatments is frequently used to improve results. Relapses, however, are almost unavoidable in a large proportion of patients[6], deteriorating their quality of life. It is important to note that melasma is a disease that is more common in sun-exposed areas such as South America and Asia[7–9]. It is thought that ultraviolet B radiation increases the expression of melanocyte-specific genes and stimulates the release of key factors involved in melanin synthesis. There is a significant increase in melanin in both the epidermal and dermal layers of affected skin, possibly as a result of abnormal crosstalk between melanocytes and other cells[10].

The use of bleaching products based on compounds that selectively inhibit melanogenesis, such as kojic acid, hydroquinone and arbutin, has been reported among other various treatments for melasma. Tyrostat, derived from the plant Rumex spp., is an inhibitor of the tyrosinase enzyme, which works by modulating the activity of the TYR, TYRP1 and TYRP2 genes[11]. However, the results of these topical treatments have been disappointing. Thus, with varying degrees of success, a variety of lasers and light devices have been used in the treatment of melasma. Q-switched lasers (QSL), fractional lasers, ablatives, and Intense Pulsed Light (IPL). The efficacy of these modalities varies, and the spots recur with somewhat frequently in a significant proportion of patients[12,13].

Tranexamic acid (TA), on the other hand, has recently emerged as a promising agent, showing multimodal efficacy on both the pigmentation and vascular components of melasma, as well as inhibition of mast cell activation induced by UV[14–16]. When compared to conventional indications, oral TA demonstrated remarkable efficacy in patients with recalcitrant melasma at low therapeutic doses (500 mg/day)[16]. However, concerns about potential systemic side effects prompted the topical application of TA[17]. Nonetheless, this compound cannot passively penetrate the skin due to its hydrophilic structure. As a result, it must be combined with adjuvant techniques such as liposomes or physical modalities (microneedles, laser) to aid in the transdermal delivery of the product[17].

Many skin conditions, on the other hand, are treated with phototherapy, which is a non-invasive treatment based on the use of light with specific wavelength and power characteristics, such as visible (400-770 nm), infrared (770 nm to 1000 m), as well as ultraviolet light (322 nm)[18]. Photodynamic therapy involves administering a photosensitive compound

that accumulates in target cells. Afterwards, a light source on the lesion with a wavelength matching the absorption spectrum of the photosensitizer is applied, exerting its effect after excitation. Photo-activation of the sensitizing product in the target tissue causes oxidative damage in a wide range of cellular targets, resulting in the therapeutic effect[18]. It is a non-invasive technique, approved by the FDA for the treatment of different diseases, including cancer[19]. It can also be used in conjunction with other treatment methods to increase its efficacy. The photosensitizer is the key component in PDT, and when exposed to light, it can produce reactive oxygen species (ROS). Nanotechnology advancements have led to the development of nanomaterial-based photosensitizers, also known as nano-photosensitizers, which have improved photostability, compared to first-generation chromophores as well as its efficiency in stimulating monatomic oxygen generation[20]. Nowadays functionalized nanoparticles made of gold (Au) and iron (Fe_3O_4), are used as chromophores, and their activation by radiation (NIR or LED) results in the generation of thermal energy or, more specifically, reactive oxygen species (ROS), specifically monatomic oxygen[21]. The use of these chromophores may facilitate skin penetration of co-administered topical agents. This new form of photodynamic therapy is what has been called Photomodulation therapy. Based on these technological advancements, multimodal therapy options combining topical melanogenesis inhibitors such as TA with laser have recently emerged on the market[16]. Combination of topical tyrosinase inhibitors such as TA, melanostatin and Tyrostat with photodynamic therapy using colloidal gold as a photosensitizing chromophore, accompanied by the use of anti-inflammatory and skin regenerative products are currently being used. Despite the fact that they have been used successfully in aesthetic clinics, these protocols have not been evaluated in observational studies or clinical trials.

Therefore, we investigated the effect of a multiple therapy combining antioxidant molecules, tyrosinase inhibitors, melanogenesis blockers, antioxidants, and anti-inflammatory agents with phototherapy based on HDD (High Density Diodes) light in a spectrum of I.o. 530 10 nm (green light), using colloidal gold as a photoactivator, on the improvement of melasma lesions.

Methods

A longitudinal observational study was conducted to assess the effect of photomodulatory therapy using enzyme inhibitors and TFBD on the improvement of melasma lesions.

Study population

28 female patients with an average age of 45.7 ± 8.6 years were studied in Caracas, Venezuela (Latitude: 10,491, Longitude: -66,902 10° 29′ 28″ North, 66° 54′ 7″ West). Because of its location, Caracas has a tropical high-altitude climate with consistent temperatures (media annual de 21.1°C) throughout the year. Caracas receives approximately 8.54 MJ/m^2 of radiation[21]. The skin phototype was determined based on the Fitzpatrick scale[22].

The study was conducted under the patients' informed consent and was approved by the UNIMEL Ethics Committee.

Melasma lesions

Melasma was clinically assessed using Wood's lamp[9] as well as the VISIA[23] and 3D Digital Photography systems. The presence of melasma (defined brown spots of variable extension) and red areas indicating vascular disorders in the patients was evaluated. In addition to the photographic record, the VISIA system compares the area, darkness, and heterogeneity of a specific patient's spots to a scale of percentiles built from ideal parameters with healthy skin of a population of individuals of the same gender, age, and skin type. The 100th percentile corresponds to normal skin free of blemishes. The 1st percentile corresponds to skin with significant differences in skin color homogeneity and/or the presence of dark brown spots that vary in extent, characterizing melasma, as well as red areas[23]. A 3D camera allows an algorithm to reconstruct skin conditions from photographs, restoring their three-dimensionality. Long exposure shots add photons to each pixel over time. A region-by-region analysis of each individual's traits based on a similar population is performed using the average values at the respective heights and widths of images[24].

Photomodulation treatment

A multimodal treatment system that included tyrosinase inhibitors as well as photodynamic therapy with colloidal gold as a photosensitizer was performed (Skin ox Dark Spots, SKINOX, Skymedic EU). The procedure was carried out under the supervision of a doctor at the Laser Aesthetic Medical Unit (UNIMEL) in Caracas, Venezuela. It consists of 4 phases:

1. Phase I: Peeling

   First, the patients' facial skin was cleaned to remove make-up and degrease. This step is essential to optimize the effectiveness of the peeling. Next, a 4 mL dose of the Peeling solution was applied with the following composition:
   - Glycolic Acid 7% (Keratolytic Activity)
   - Kojic Acid 5% (Inhibits the enzyme tyrosinase)
   - Mandelic Acid 10% (Stimulates the production of fibroblasts)
   - Salicylic Acid 2% (bactericidal activity)
   - Phytic Acid 10% (Keratolytic)
   - 5% Tranhexamic Acid (Inhibits the activity of the tyrosinase enzyme)

   The product was applied distributing over the entire face. It was left to act for 3 minutes and was neutralized with water.
2. Phase II: Application of the photodynamic serum.

   Subsequently, the photodynamic serum was applied with the following composition:
   - Hyaluronic Acid LW 0.5% (superficial hydration)
   - Hyaluronic Acid HW 0.3% (Deep hydration)
   - Nicotinamide 1% (Antioxidant/Thyroxine Inhibitor)
   - Albatin 0.1% (Inhibits the activity of the tyrosinase enzyme)
   - Melanostatine 4% (Blocks the activity of the tyrosinase enzyme)
   - Tyrostat 2% (Blocks the formation of melanin)
   - 2% Tranhexamic Acid (Blocks the activity of the tyrosinase enzyme)
   - Colloidal Gold 2% (photodynamizing molecule)
   - Luminia Granatum 1% (Antioxidant and anti-inflammatory)

   A protective and occlusive plastic sheet (feel paper) was placed on the face, neck, and décolleté. It was left 10 minutes without removing.
3. Phase III: HDD Light Application

   Subsequently, the FOTOAGE mask was placed on the plastic protector and the HDD light emission program was selected in a spectrum of I.o. 530 ± 10 nm (green light), for 15 minutes. Subsequently, the mask and plastic were removed, and the face was cleaned to remove the remains of the Product.
4. Phase IV: Application of the depigmenting mask

   After completing phase III, a depigmenting mask was applied with the following composition
   - Azelaic Acid 15% (Keratolytic)
   - Ferulic Acid 5% (Antioxidant/Neutralizes free radicals)
   - Kojic Acid 5% (depigmentation)
   - Salicylic Acid 2% (bactericide)
   - Phytic Acid 1% (inhibits tyrosinase)
   - Arbutin 5% (inhibits tyrosinase)
   - Albatin 0.1% (blocks melanogenesis)
   - Kopcinol 2% (inhibits tyrosinase)
   - Melanostatine 4% (blocks tyrosinase)
   - Tyrostat 2% (blocks melanogenesis)
   - 5% Tranhexamic Acid (blocks tyrosinase)
   - Turmeric Zen 2% (Anti-inflammatory)
   - Arabian Cotton 2% (antioxidant)
   - Luminia Granatum 1% (antioxidant and anti-inflammatory)

The mask (3 mL) is applied during the consultation and left to act for at least 30 minutes and up to 8 hours. If the application lasts more than an hour, the patient can remove it at home with water.

Results

This study included 28 women who had been diagnosed with melasma and agreed to participate in the

study through an informed consent. According to the Fitzpatrick scale, 71% of the patients had Phototype III skin, 15.5% had Phototype IV skin, and 13.5% had Phototype V skin. None of the patients had light skin phototypes like I and II, or very dark skin phototypes like VI.

It was observed that 86% of the lesions on the patients' faces also had red areas, indicating a vascular component in the lesions. About 75% of the patients had previously been treated with other therapeutic modalities and relapsed within the previous two years.

Figure 1 shows the effect of treating each patient with a combination of tyrosinase inhibitor enzymes combined with photomodulation therapy with HDD light, using colloidal gold as a photosensitizer. In all patients, there is a noticeable improvement in the resolution of hyperpigmented lesions as well as red vascularized areas.

Figure 2 illustrates the values obtained on the VISIA scale for the total group of patients before and after six weeks of completing the full treatment using tyrosinase inhibitors in conjunction with TFBD and colloidal gold as a photosensitizer on both cheeks. It can be observed that there was a significant improvement in the resolution of UV spots, brown spots that are characteristic of melasma, as well as in the red areas that indicate increased vascularization of the lesion.

Discussion

The combined effect of a mixture of known topical melanogenesis inhibitors with photodynamic therapy using colloidal gold as a sensitizing molecule was evaluated on a group of women living in the tropics and with phototype III predominance. It was confirmed that melasma is frequent in women living in a south American country, who have also been shown to be more resistant to treatment[9]. Sun exposure, even for short periods, is strongly associated with the development of melasma and its recurrence in these patients[9,10]. Nevertheless, there is evidence that other risk factors, such as hormonal components, which are commonly associated with pregnancy, oral contraceptives and thyroid disorders, influence the development and progression of this hypermelanosis in Venezuelan women also affecting treatment effectiveness[6]. From a histological standpoint, excess melanin in melasma lesions is present in the epidermis, upper dermis, or a combination of both. This deeper melanin accumulation is normally associated with macrophage extra vascularization, in which macrophages engulf extracellular melanin granules and migrate to deeper layers of the skin, making the treatment much more difficult[1].

It was found that most of the patients had melasma lesions with vascular alterations. In this respect, it has been reported that, while hyper pigmented plaques are the most common clinical feature of melasma, the presence of telangiectatic erythema is almost ubiquitous, most likely as a result of solar elastosis caused by chronic UV ray exposure[2]. Histological studies have shown an increase in the number and size of blood vessels within melasma lesions[25]. This vascularization of melasma plaques has been attributed to the activity of proangiogenetic mediators such as the vascular endothelial growth factor (VEGF), stem cell factor (SCF), and inducible nitric oxide synthase (iNOs)[26].

The application of topical agents such as azelaic acid, kojic acid, retinoids, topical steroids, glycolic acid, mequinol, arbutin, and tranhexamic acid is not a novelty, and represents a minimally invasive and aggressive option that most patients tolerate[27]. However, because topical medications cannot penetrate enough to reach hyperactive melanocytes in deeply localized dermal melasma, their efficacy is variable and, in many cases, does not prevent recurrence of lesions in a short time[27]. In this preliminary study, topical application of various inhibitors of tyrosinase enzyme activity[11,14,27] were used as part of a treatment modality based on the principles of photo modulation[28]. The results showed that combining these topical agents with photodynamic therapy results in a more effective treatment, significantly reducing the intensity and extension of the melasma spot, as well as the vascularity, as evidenced by the lightening of the detected red areas by both 3D digital photography and the VISIA system. In this TFBD system, colloidal gold was used as a photosensitizer. When exposed to light, colloidal gold particles, like a conventional photosensitizer, exhibit photoluminescence as well as the ability to generate reactive oxygen species (ROS)[29]. The activation of colloidal gold particles, producing ROS and thermal energy, may result in a transient localized inflammatory process that facilitates melanin destruction and deeper penetration of tyrosinase inhibitors, thereby decreasing pigment formation (Figure 3).

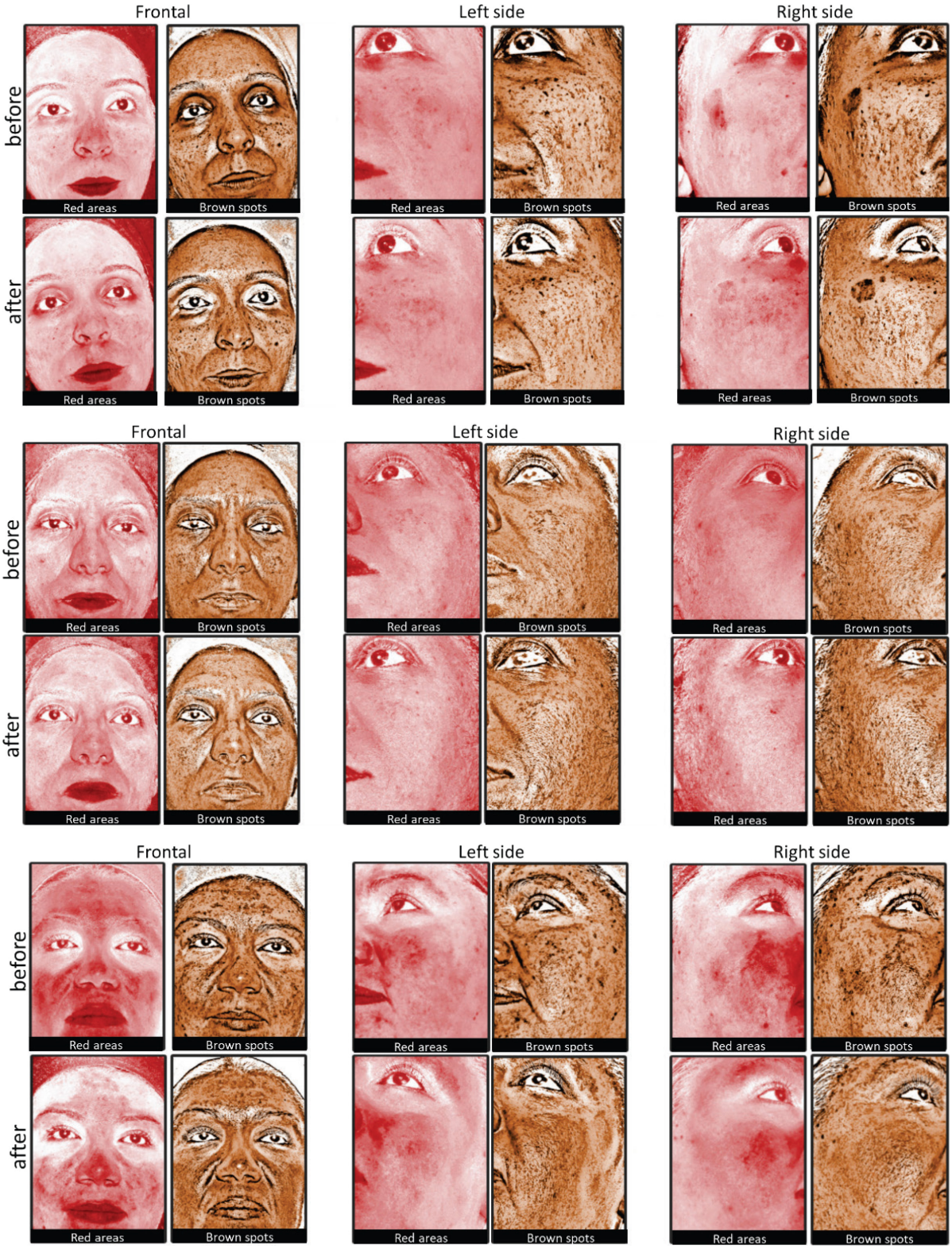

Figure 1. Effect of Photomodulation treatment using the combination of serum containing tyrosinase inhibitors with Photodynamic therapy using colloidal gold as a photosensitizing molecule on red areas and melasma spots in 3 different patients.

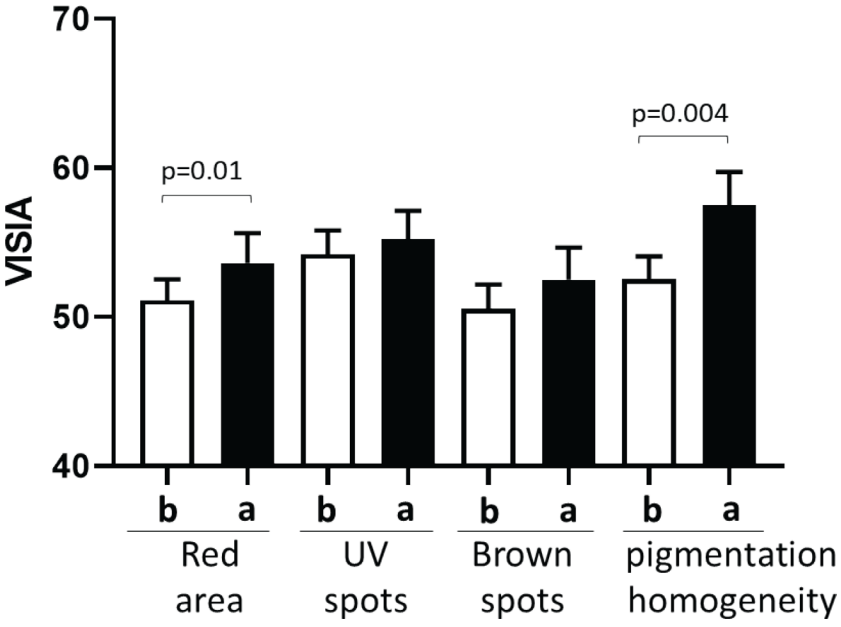

Figure 2. It describes the VISIA scale values obtained from the entire group of patients before (b) and after (a) 6 weeks of completing the full treatment on both cheeks. There was a significant improvement in the resolution of UV spots, brown spots and red areas.

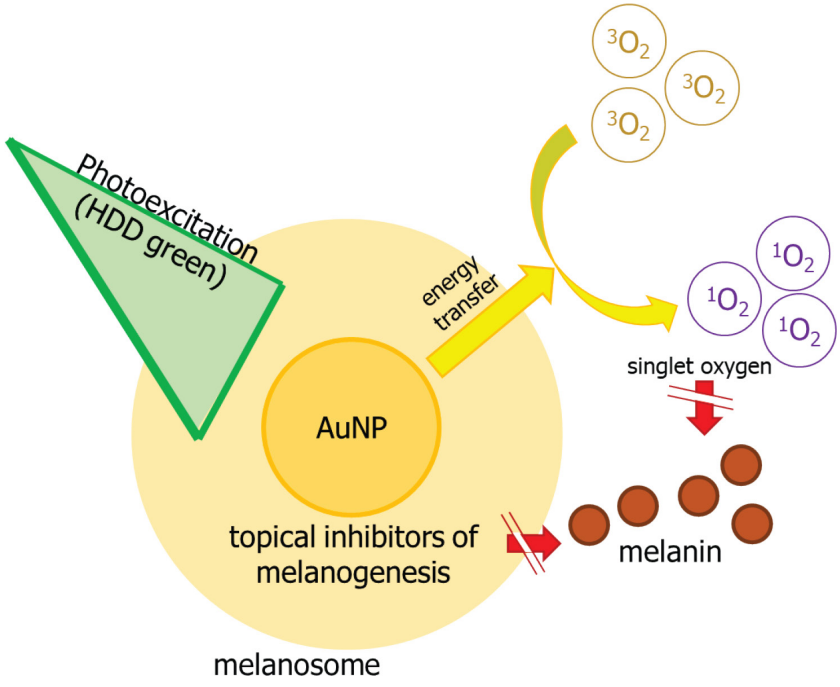

Figure 3. Scheme of photodynamic therapy using colloidal gold as a sensitizing agent combined with the simultaneous application of tyrosinase enzyme inhibitors.

Earlier studies have shown the cosmetic efficacy of PDT using aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) as topical photosensitizers in combination with LEDs, resulting in significant improvements in patients with photodamaged skin and hyperpigmented areas[30,31]. Unlike traditional PDT with ALA or MAL, the use of colloidal gold as a sensitizing agent did not produce any secondary effects indicative of inflammatory processes in the patients, as well as symptoms of pain or discomfort after treatment. This could also be because the treatment is accompanied by the application of topical anti-inflammatory agents such as *Luminia granatum*[30]. Meanwhile, experimental studies have shown that PDT using gold nanoparticles conjugated with another C11Pc chromophore (derived from phthalocyanine) in amelanotic melanoma (B78H1) cells is efficient for selectively destroying cancerous tissues[32]. As a result of PDT, blood capillaries and endothelial cells surrounding cancerous lesions can be damaged extensively. This indicates that these antiangiogenic properties of TFBD, using gold nanoparticles in colloidal form, may have a significant importance in reducing inflammation-induced angiogenesis in melasma lesions. However, the results of this study only indicate that PBT using colloidal gold effectively decreases red areas, indicating a decrease in the angiogenesis of melasma.

The findings of this study are preliminary; more research is needed to determine the mode of action of PDT using colloidal gold as a skin sensitizing agent, as well as its effects when combined with topical tyrosinase inhibitors. Nevertheless, these findings demonstrated for the first time that this therapeutic approach was effective and did not cause discomfort or inflammatory complications in any of the patients after its application.

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