Efficacy and Safety of Topical Pidobenzone 4% as Adjuvant Treatment for Solar Lentigines: Result of a Randomized, Controlled, Clinical Trial

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\textbf{Introduction}

Solar lentigines are benign lesions characterized by a circumscribed macular patch of hyperpigmentation related to irregular melanin production. UV exposure promotes a local accumulation of melanin, which becomes more and more evident over time owing to the increased transparency of photo-damaged, thinned skin [1].

Although solar lentigines develop in subjects with phototype I-II preferentially, patients with higher phototypes can also be affected. Several physical and chemical therapeutic strategies are currently available for the treatment of solar lentigo [2, 3]. Chemical treatments mainly consist of whitening agents [4, 5] and/or retinoids [6–8].

They are physical, self-managed and noninvasive treatments; however, they can be poorly effective when used alone, especially in advanced and diffused forms of photoaging [9].

Physical treatments (cryotherapy, CO\textsubscript{2} and q-switched lasers, pulsed light, chemical peels e.g. trichloroacetic acid), while being more effective, are not completely free from side effects, including posttreatment hyperchromia, especially in patients with a high-grade phototype [10, 11]. Correct counseling of the patient with solar lentigi-
nes is crucial in order to prevent the use of inappropriate or ineffective therapies [2].

In this study, we evaluated two main points: whether a lipogel containing pidobenzone 4% is able to increase the therapeutic action of physical treatments (laser or cryotherapy) on solar lentigines and whether it is effective in preventing postlesional hyperpigmentation – not an uncommon complication of physical treatments. Pidobenzone: [C_{11}H_{11}NO_{4} – (4-hydroxyphenyl) [2S]-5-oxopyrrolidine-2-carboxylate], an amino acid ester of hydroquinone, is a second-generation worldwide patented depigmenting agent, reliable and free of collateral risks, which has already demonstrated a clear efficacy on melasma [12].

**Materials and Methods**

For further details, see the supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000447356) [13] (fig. 1).

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**Results**

All the enrolled patients completed the study. Among them, 49 were female and 23 male, aged between 29 and 80 years (median age 56.34), and all were Caucasians. Of the 72 patients, 43 belonged to skin phototype III, 25 to phototype II, and 4 to phototype IV. The two groups of patients did not differ in sex, mean age, or phototype.

In the patients included in arm 1 (cryotherapy plus pidobenzone 4%), a marked improvement of solar lentigines was obtained (fig. 2a, b). The mean chromatic variation (Δv) was 1.92 ± 0.15 in the treated patients, and the chromatic intensity (v) significantly changed from a baseline mean value of 4.82 ± 0.64 to a T12 mean value of 6.73 ± 0.79 (p < 0.0001) (fig. 3a).

Also, according to the patients’ perspective, a significant improvement in the hyperpigmentation of solar lentigines (Visual Analog Scale, VAS) was detected in arm 1: a mean value of 6.11 ± 1.71 at T0 moved to a mean value of 2.78 ± 0.42 at T12 (p < 0.0001) (fig. 3b).
Patients from arm 2 (fractional CO₂ laser plus pido-benzone 4%) showed a moderate improvement of solar lentigines (Δv) of 0.89 ± 0.10 (from a T0 mean value of 6.70 ± 0.34 to a T12 mean value of 7.34 ± 0.30), and the difference across the time points was statistically significant (p < 0.0001) (fig. 4a). The patients also reported a significant variation of VAS from a pretreatment mean value of 6.39 ± 0.77 to a T12 mean value of 3.44 ± 1.33 (p < 0.0001) (fig. 4b).

Patients from arm 3 (cryotherapy alone) experienced only a moderate improvement of solar lentigines (Δv = 1.05 ± 0.11): the chromatic intensity of skin lesions significantly changed from a T0 mean value of 6.43 ± 0.37 to a T12 mean value of 7.48 ± 0.48 (p < 0.0001) (fig. 5a). The patients also reported a significant change in VAS: from a T0 mean VAS value of 6.50 ± 1.20 to a T12 mean VAS value of 2.33 ± 0.90. The difference between the two time points was statistically significant (p < 0.0001) (fig. 5b).

Results from arm 4 (fractional CO₂ laser alone) showed a moderate improvement of solar lentigines with Δv = 1.43 ± 0.31: a T0 mean value of 6.43 ± 0.74 and a T12 mean value of 7.86 ± 0.33 (p < 0.0001) (fig. 6a) and a significant improvement in VAS: VAS mean value at T0 of 5.33 ± 1.02 and VAS mean value at T12 of 2.33 ± 0.84 (p < 0.0001) (fig. 6b).
Moreover, according to the clinicians, the association of pidobenzone 4% to physical treatments implied a significant improvement of therapeutic results compared with physical therapy alone, independently from the type of physical treatment received by the patients: the chromatic intensity of solar lentigines (ν) at T12 was in fact significantly different between patients in arm 1 and arm 3: ν mean value of 6.73 ± 0.79 versus 7.48 ± 0.48 (p = 0.01) (fig. 7) and also between patients in arm 2 and arm 4: ν mean value of 7.34 ± 0.30 versus 7.86 ± 0.33 (p < 0.001) (fig. 8b).

Finally, the patients agreed that the use of a combined therapy improves therapeutic results regardless of the treatment received: the subjective evaluation of hyperchromia at T12 was significantly different between patients in arm 1 and arm 3: VAS mean value of 2.78 ± 0.42 versus 2.33 ± 0.90 (p < 0.05) and also between patients in arm 2 and arm 4: VAS mean value of 3.44 ± 1.34 versus 2.33 ± 0.84 (p = 0.005) (fig. 8).

**Discussion**

Solar lentigines belong to the group of skin problems which are still a therapeutic challenge for clinicians [14–16]. Several chemical or physical treatments are currently available (lightening gel, cryotherapy, CO₂ and q-switched lasers, pulsed light, and chemical peels e.g. trichloroacetic acid).
However, the US Preventive Services Task Force (USPSTF) on health care provided a consensus paper where they stated that the first-line therapy for solar lentigines is ablative therapy with cryotherapy [2]. Although no large-scale studies have been conducted, the authors reported that there is also good evidence to suggest that laser treatments can be also effective [2]. However, both laser and cryotherapy are not completely free from side effects like temporary postinflammatory hyperpigmentations [17, 18]. Among patients treated with cryotherapy or CO₂ laser, approximately half of them report a postlesional hyperpigmentation lasting for 1 month or less and 9% a postlesional hyperpigmentation lasting less than 3 months [19].

The results from our study indicate that both clinicians and patients agreed that patients receiving combined therapy (chemical plus physical therapy) reported a greater improvement compared with patients who received physical therapy alone. The application of a topical product containing 4% pidobenzone produces a 2-fold result: on the one hand it promotes active depigmentation synergistic to physical therapy, and on the other it prevents postiatrogenic hyperpigmentation caused by ablative therapy. The combined treatment also demonstrated a good safety profile, as none of the patients reported any side effects despite the use of ablative treatments that reduce the natural effectiveness of the skin barrier. Unfortunately, no data are available regarding the efficacy of pidobenzone as monotherapy for solar lentigines.

The study has some limitations. First of all, its short-term design did not allow the clinicians to evaluate the long-term efficacy and safety of treatments and the risk of incidence of local recurrence over time. Secondly, its small sample size made it impossible to stratify the enrolled patients according to age, sex, and phototype, and this limited the spectrum of surveys applicable to the study.

In conclusion, although it is a preliminary study which requires validation on larger samples and longer observation periods, the results seem to indicate the existence of benefit related to the topical application of pidobenzone 4% in addition to ablative therapy (cryotherapy with liquid nitrogen and fractional CO₂ laser therapy) in the treatment of solar lentigines. The effect of the topical application of pidobenzone alone on solar lentigines still remains undetermined, and further investigations are required. Finally, the STCS can be considered as a promising tool for quantifying the improvement of solar lentigines in Caucasian patients. Even if STCS has been

Fig. 7. Efficacy comparison between cryotherapy (a) or fractional CO₂ laser (b) and combined treatment according to clinicians. * p = 0.01; *** p < 0.001.

Fig. 8. Efficacy comparison between cryotherapy (a) or fractional CO₂ laser (b) and combined treatment according to patients. * p = 0.05; ** p = 0.005.
introduced for Asian skin types, until a specific scale for assessing chromatic changes in Caucasians is validated it could be taken into consideration for standardizing results in clinical trials.

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Statement of Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and those of the International Conference on Harmonization – Good Clinical Practice. The local Ethics Committee approved the study protocol, and all patients provided written informed consent to participate.

Disclosure Statement

The authors have no conflicts of interest to declare.