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SHORT PAPER

Erythema-directed digital photography and colorimeter scores correlate with rosacea erythema evaluation in patients under treatment with topical ivermectin

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Abstract

Inflammatory rosacea is clinically characterized by persistent erythema and inflammatory lesions. Its severity is generally based on clinical observation that may be cumbersome. The aim of this study was to assess if erythema-directed digital photography (EEDP) and colorimeter (COL) correlate and are concordant with clinical evaluation of erythema degree of rosacea under topical treatment. Thirty naïve patients with mild/moderate inflammatory rosacea were instructed to apply ivermectin cream for 8 weeks. Erythema degree was performed at baseline, and at 2, 4, 6, and 8 weeks by clinician erythema assessment based on 5-point severity scale (from 0 = no erythema to 4 = fiery redness), and by instrumental evaluation by EDDP using the same 5-point scale of clinical assessment and by COL using a 5-point scale (from 0 = <1 units = no erythema to 4 > 12 units = fiery redness). Concordance and correlation analysis were performed using Cohen's Kappa coefficient and Correlation Coefficient test respectively. At baseline a statistically significant concordance/correlation value between EDDP and COL was observed. At 2 weeks, the statistical concordance/correlation value between instrumentals were both increased, along with a slight significant concordance between clinical assessment and erythema-directed digital photography. At 4, 6 and 8 weeks, a statistically significant increase of concordance/correlation value among all the considered parameters from baseline was found. The results of our study showed that at baseline and during the early treatment stage both EDDP and COL were able to appreciate more accurately the erythema grade compared to clinical observation supporting the use of non-invasive techniques for a more objective evaluation of erythema in rosacea.

KEYWORDS
inflammatory disorders, therapy-topical

1 | INTRODUCTION

Inflammatory rosacea is a common phenotype of facial rosacea characterized by persistent erythema, inflammatory lesions (papules/pustules) and telangiectasias.[1] Evaluation of its severity is generally based on clinical observation that may have some limits to objectively evaluate the inflammation/erythema grading. Erythema-Directed

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Digital Photography (EDDP) equipped with RBX processing system is a non invasive tool able to provide a detailed evaluation of inflammation/erythema grading in patients affected by erythematous dermatoses of the face including rosacea.[2-7] Colorimeter (COL) is a non invasive handheld device equipped with white LED source and a colorsensor of 4×16 elements that provides a precise evaluation of patient's erythema by a color analysis of a 7 mm in diameter of an inflammatory skin area through the analysis of color differences in terms of trichromatic l^*, a^*, and b^* values as determined by the Commission Internationale de l'Éclairage (CIE).[8-12] The aim of this study was to evaluate if EDDP and COL correlate with the clinical evaluation of erythema of inflammatory rosacea under treatment with ivermectin (IVM) 1% cream.[13]

2 | MATERIAL AND METHODS

Twenty adult subjects (17F/3M; mean age: 46.9 years) affected by mild/moderate inflammatory rosacea were enrolled at the Department of Dermatology of the University of Catania in a 8 week, open-label, prospective clinical trial. The study was performed in accordance with the ethical principles originating from the Declaration of Helsinki 1996 and Good Clinical Practices.

Exclusion criteria were the use of topical and/or systemic treatments for inflammatory rosacea in the previous 2 to 4 weeks, respectively, concurrent exposure to sunlight and/or artificial ultraviolet sources, pregnancy/breastfeeding, and severe underlying diseases.

In order to reduce potential evaluator bias, all subjects were evaluated by clinical and instrumental assessment by an investigator not directly involved in the study at baseline (T0), and at week 2 (T1), 4 (T2), 6 (T3) and 8 (T4).

At baseline, the patients were instructed to apply IVM 1% cream once daily at bedtime for 8 weeks. At all time points clinical assessment included: (a) Clinician Erythema Assessment (CEA) of rosacea using a 5-point severity scale: 0 = no erythema; 1 = slight redness; 2 = definite redness; 3 = marked redness; 4 = fiery redness. Instrumental evaluation of erythema severity was evaluated at all timepoints by: (a) EDDP via VISIA-CRRBX system (Canfield, USA) using the same 5-point scale of CEA, and (b) by COL (ColorMeter DSM II, Cortex Technology, Denmark) performing three measurements on the most erythematosus centrofacial area distant from evident papules and pustules using a 5-point scale: 0 = <1 units (no erythema); 1 = 1-3.9 units (slight redness); 2 = 4-7.9 units (definite redness); 3 = 8-11.9 units (marked redness); 4 > 12 units (fiery redness). Prior to measurement the COL was calibrated according to the manufacturer's instructions and the patient was acclimatized for 15 minutes in a room at 19°C to 23°C and in horizontal position in order to elude an orthostatic effect on facial erythema. Special care was taken not to apply excessive pressure on the head of probe. Unaffected skin of the submental region was used as intra-patient control.

Concordance analysis, by comparing CEA, EDDP and COL scores, was performed by Cohen's Kappa coefficient (κ) as follow: very good = 0.81 to 1.0; good = 0.61 to 0.80; moderate = 0.41 to 0.60; fair = 0.21 to 0.40; poor = <0.20 and by Correlation Coefficient test ($-1 \leq r \leq 1$) as follow: 0.1 to 0.19 = very weak; 0.20 to 0.39 = weak; 0.40 to 0.59 = moderate; 0.60 to 0.79 = strong; 0.80 to 1.0 very strong.

The statistical significance was set at $P \leq .05$.

3 | RESULTS

At baseline (T0), a statistically significant concordance between EDDP and COL (κ = 0.578; $P < .01$) along with a significant correlation value (r = 0.637; $P < .001$) was observed. No concordance or correlation was found between CEA vs EDDP or vs COL (Table 1 [Supplementary File], Tables 1 and 2).

At 2 weeks, the statistical concordance (κ =0.714; $P < .001$) and the correlation value (r = 0.791; $P < .001$) between EDDP and COL were both increased compared to baseline (Table 1 [Supplementary File], Tables 1 and 2). A slight significant concordance between CEA and EDDP (κ =0.497; $P < .01$) was also recorded (Table 1 [Supplementary File], Tables 1 and 2).

At 4, 6 and 8 weeks, a statistically significant increase of concordance and correlation value among all the considered parameters (CEA, EDDP and COL) from baseline was found (Table 1 [Supplementary File], Tables 1 and 2).

TABLE 1 Strength of concordance of CEA, EDDP, and COL data from baseline to week 8 by Cohen's Kappa

	CEA-EDDP		CEA-COL		EDDP-COL	
Time points	Concordance	κ	Concordance	κ	Concordance	κ
Baseline (T0)	57.9%	0.026	37.7%	0.296	84.2%	0.578*
2 weeks (T1)	73.7%	0.497*	68.4%	0.321	84.2%	0.714**
4 weeks (T2)	94.7%	0.923**	78.9%	0.679**	84.2%	0.763**
6 weeks (T3)	84.2%	0.785**	78.9%	0.710**	94.7%	0.928**
8 weeks (T4)	94.7%	0.927**	94.7%	0.925**	89.5%	0.853**

Note: Score of Cohen's Kappa test (κ): 0 = no concordance; 0-0.4 = slight; 0.4-0.6 = moderate; 0.6-0.8 = substantial; 0.8-1 almost perfect concordance.
Abbreviations: CEA, Clinician Erythema Assessment; COL, Colorimeter; EDDP, Erythema-Directed Digital Photography.
*$P < .01$.
**$P < .001$.

TABLE 2 Strength of correlation of CEA, EDDP, and COL by Correlation Coefficient Test from baseline to week 8

Time points	CEA/EDDP r	CEA/COL r	EDDP/COL r
Baseline (T0)	0.026	0.327	0.637**
2 weeks (T1)	0.760**	0.555*	0.791**
4 weeks (T2)	0.955**	0.857**	0.914**
6 weeks (T3)	0.931**	0.895**	0.974**
8 weeks (T4)	0.974**	0.962**	0.934**

Note: Score of correlation coefficient test ($-1 \leq r \leq 1$): 0.00-0.019 = very weak; 0.20-0.39 = weak; 0.40-0.59 = moderate; 0.60-0.79 = strong; 0.80-1.0 very strong.
Abbreviations: CEA, Clinician Erythema Assessment; COL, Colorimeter; EDDP, Erythema-Directed Digital Photography.
*$P < .05$.
**$P < .001$.

4 | DISCUSSION

A precise evaluation of erythema in rosacea may be challenging. Facial erythema may include different clinical components such as background erythema, telangiectasias, and perilesional erythema that may complicate the clinical presentation and its severity rating. This is particularly observed in clinical trials in which, however, the evaluation is mostly done on clinical ground. Numerous non-invasive techniques are currently investigating erythema in rosacea the most common being EDDP and COL. A recent inter-observer study on the reliability of standard photography vs EDDP for the assessment of erythema and telangiectasias in rosacea showed that advanced digital photography was able to provide a better strength of agreement and higher reliability among independent observers compared to standard photography suggesting new horizons for digital appraisal of skin inflammatory diseases.[2] Colorimeter represents a low-cost, simple, and objective in vivo tool, as supported by several clinical evidences.[8] Its principal advantage includes the possibility to obtain reproducible and accurate erythema index values from the same skin area over time, without causing any local change that might potentially interfere with the diagnosis or therapy. However, validation studies are necessary, as well as standardization and erythema index estimation algorithms shared from the scientific community.

In our study, some interesting findings deserve to be discussed. In particular, at baseline both EDDP and COL measurements were able to appreciate more accurately the erythema grade compared to clinical observation. In the early stages of treatment, at week 2, clinical observation did not show any change compared to baseline, as shown by the unmodified CEA (Table 1. Supplementary file). In contrast, both EDDP and COL recorded a statistical significant reduction of erythema, thus confirming that instrumental evaluation by EDDP and COL may detect early changes in erythema not visible yet at naked eye thus indicating also that treatment was starting to be effective. At 4, 6, 8 weeks data match on correlation between COL and EDDP showed consensual results. Considering that data derived from COL analysis are objective, an explanation for such could be that with advancing treatment the erythema improvement is more evident and possible confounding factors related to observer-related clinical EDDP evaluation (ie, inter-observer individual visual perception and personal interpretation) become negligible. Moreover, at the end of the study the significant concordance between all evaluation data suggest that, as patient improvement progresses, the differences between clinical and instrumental examination become minimal. Our study further supports the use of non-invasive techniques such EDDP and COL for a more objective evaluation of erythema in rosacea, as demonstrated by a significant strength of correlation and concordance observed at all time points. Interestingly, two recent clinical trials on rosacea-associated erythema are based on clinical and COL evaluation (https://clinicaltrials.gov).[14,15] Our clinical results confirm the efficacy of IVM 1% cream in mild to moderate inflammatory rosacea through its acaricide and anti-inflammatory effects, the latter being related to a decrease in neutrophil phagocytosis and chemotaxis, inhibition of proinflammatory cytokines (TNF-α, IL-1β) and upregulation of the antinflammatory ones (IL-10).[16]

5 | CONCLUSIONS

Our results strengthen the notion that the use of non-invasive techniques for an accurate erythema severity assessment may represent a valuable tool especially in the early treatment stages of rosacea. We are aware that our study has some restrictions: it was an open prospective study and the number of patients was limited. However, the number of time points along with EDDP/COL evaluations data processing were considerably time and cost consuming. Finally, the study was not sponsored and was a single institution trial. Further studies on larger series are necessary to confirm our results.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ETHICS STATEMENT

All subjects were informed about the conditions related to the study and gave their consent for publication.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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