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Effectiveness of a combination of salicylic acid-based products for the treatment of mild comedonal-papular acne: a multicenter prospective observational study

Running title: salicylic acid-based products for acne

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ABSTRACT

Background

The most common therapeutic approach to acne is a combined treatment of retinoid and benzoyl peroxide, with oral antibiotics recommended for moderate-to-severe cases. These kinds of therapies often lead to adverse reactions, leading to the request for new therapeutic options. Recently, the combined use of three salicylic acid-based products for the topical treatment of acne has been related to a significant improvement in acne lesions.

Methods

To provide new evidence on the clinical effectiveness, tolerability and acceptability of three salicylic acid-based products for the topical treatment of acne in the daily clinical practice, a multicenter prospective observational study was carried out on patients with a diagnosis of mild comedonal-papular facial acne. Clinical effectiveness on lesions improvement, the evaluation of personal discomfort related to acne and the assessment of overall clinical outcome were the primary endpoints. Treatment acceptability and tolerability were also evaluated.

Results

The treatment with the three salicylic acid-based products has been related to a significant improvement on acne lesions over 8 weeks of treatment, along with a reduction of personal discomfort related to acne and an improvement on lesions appearance. The products have also shown good acceptability and tolerability.

Conclusion

The results of this observational study support the effective and well-tolerated use of a combined treatment with three salicylic acid-based products for the topical treatment of acne.

KEYWORDS

Acne, topical therapy, salicylic acid, combined treatment.

INTRODUCTION

Acne is the most common chronic inflammatory disease of the skin worldwide and,[1,2] although is not a life-threatening or physically debilitating disease, it can cause substantial discomfort and pain, impacting patient's quality of life.[3,4]

Acne requires prolonged therapy for a satisfactory outcome. The main goal of acne treatment is to control and treat existing acne lesions, prevent permanent scarring, limit the duration of the disorder and minimize morbidity.[5] Current therapeutic approaches depend on the severity of acne lesions and usually vary from topical treatments to systemic therapy (oral administration).[6] The most common therapy for inflammatory acne is a combined treatment of a retinoid and benzoyl peroxide. For moderate-to-severe cases, an oral antibiotic is also recommended and whenever ineffective, oral isotretinoin finds an indication.[7]

Unfortunately, these kinds of therapies can cause adverse reactions.[8,9] In addition, considering the importance of minimizing the risk of community antibiotic resistance, the development of non-antibiotic therapies is preferable.[10] These aspects lead to the request for new therapeutic options, particularly for patients with long-term disease and during periods of relapse.

Thanks to an increase in research that elucidates the mechanisms of action of different non-pharmacological compounds in the pathogenesis of acne, growing attention is given to their use as alternatives to the common therapies.[11]

The authors have accumulated their experience on three salicylic acid-based products for the topical treatment of acne: 1) salicylic acid, nicotinamide, saccharide isomerate and vitamin E (moisturizing gel, class I medical device); 2) salicylic acid, zinc/taurine, urea peroxide and vitamin E (purifying gel, class I medical device); and 3) salicylic acid, urea peroxide, glycolic acid and hydrogenated starch hydrolysate (cleanser gel). Thanks to their formulations, the combined use of these products creates a synergistic effect against the pathogenic pathways that characterize acne. In particular, the

salicylic acid has anti-inflammatory properties and is useful to contrast abnormal keratinization.[11,12] Nicotinamide can regulate the sebum production[13] and, along with the zinc/taurine association, confers an anti-inflammatory effect to the treatment;[14,15] urea peroxide and zinc have an antiseptic activity against the bacterial colonization by *Propionibacterium* acnes.[16] Glycolic acid and saccharide isomerate add purifying and moisturizing properties to the combined treatment.

In a clinical observational study conducted in 200 volunteers affected with mild-to-moderate acne, the safety and the clinical effectiveness of the three products were shown. After 30 days of treatment, in combination with also oral antibiotics and estro-progestinics, the use of the three products was associated to a significant improvement in acne lesions. A high tolerability and pleasantness of use were also reported.[17]

To obtain further evidence of the effectiveness of these products in the daily clinical practice, used for the skin care without concomitant adjunctive therapies, a multicenter prospective observational study was carried out. The aim of the study was to assess their clinical effectiveness. Tolerability and patients' acceptability of treatment were also reported.

PATIENTS AND METHODS

Subjects and study design

A multicenter, prospective, observational study was conducted at four study centers (Ferrara, Milan, Naples and Catania) between December 2018 and March 2019. The observation time per patient was 8 weeks. Inclusion criteria for patients of either gender were consecutive patients with a diagnosis of mild comedonal-papular facial acne, suspension of oral antibiotic and topical pharmacological treatment from at least 1 month, and suspension of oral isotretinoin from at least 3 months.

Included patients used the three products for the topical treatment of acne as follows: the moisturizing gel every morning, the purifying gel every evening and the cleanser gel twice daily (this protocol is termed hereafter as combined treatment).

The local ethics committees of participating centers were properly informed about the present study. All patients provided their written informed consent prior to enrollment.

Clinical measures

Clinical assessments were performed at three time points: baseline (T0), after 4 weeks of treatment (T1) and at the end of the study (after 8 weeks of treatment; T2). The primary objective of the study was to evaluate the effectiveness of the combined treatment. Clinical evaluations were the number of lesions (blackheads, papules and pustules). The personal discomfort related to acne was reported at T0, T1 and T2 by a patient-centered acne severity scale, created using a visual analogue scale (VAS) format for acne discomfort (0–10 rating scale, where 0 represents minimum discomfort and 10 represents the maximum discomfort). The overall assessment of the treatment effectiveness was also registered at the end of the study, by the use of the following descriptors, that best describe the overall appearance of the lesions: unchanged, great improvement, improvement, mild improvement and worsening.

As secondary objective of the study, tolerability (combination of redness, desquamation, stinging and burning) and acceptability/pleasantness (combination of percentage and rapidity of absorption, oily residue, ability to spread, stickiness, perfuming and general feeling toward the product) of the combined treatment were evaluated at the end of the study, on a numerical scale as: poor (0), mild (1), moderate (2) and excellent (3).

Statistical analysis

Descriptive statistics were used for the present study. The comparison among different time points was performed with the paired T-test with an explorative intent only. $p \leq 0.05$ was considered statistically significant.

RESULTS

Participants

A total of 41 patients that met the inclusion criteria were evaluated for each time-point of the study. A total of 68% of patients were female. The mean age was 20±5 years. At baseline, the mean number of papules was 7.9 (standard deviation [SD] = 4.6), the mean number of pustules was 0.9 (SD = 2.5) and the mean number of blackheads was 16.1 (SD = 16.6) (Table 1).

Clinical Effectiveness on Lesions Improvement

A significant reduction of the mean number of papules after 4 weeks of combined treatment was reported (T1: mean±standard deviation [SD] = 6.4±4.1; p=0.0057) if compared to baseline evaluation (T0: mean±SD = 7.9±4.6). At T2, after 8 weeks of combined treatment, the mean number of papules is further decreased (T2: mean±SD = 4.4±5.0; p<0.0001) (Figure 1A).

The mean number of pustules is also significantly decreased at T1 (T1: mean±SD = 0.6±2.0; p=0.04) and T2 (T2: mean±SD = 0.34±1.2; p=0.01), when compared to baseline T0 measurement (T0: mean±SD = 0.9±2.5) (Figure 1B).

The combined treatment is also associated with the significant reduction of the mean number of open comedones (blackheads) at T1 (T1: mean±SD = 14.0±14.6; p=0.007) and T2 (T2: mean±SD = 8.1±8.4; p<0.0001), compared to T0 baseline count (T0: mean±SD = 16.1±16.6) (Figure 1C).

Evaluating the global skin appearance, at the end of the study a relevant reduction of inflammatory and non-inflammatory lesions was observed (Figure 2).

Personal Discomfort Related to Acne

At the baseline, the mean VAS score was 6.2 (SD = 3.1, n=30). At T1 and T2, the mean VAS scores were significantly reduced to 5.2 and 4.3, respectively (T1: SD = 3.3; p=0.005; T2: SD = 3.1; n=30, p<0.0001) (Figure 3).

Overall Assessment of Clinical Outcome

In the majority of the patients, an improvement in lesion appearance was observed. In particular, in 40% of cases (12/30) a "great improvement" was reported, an "improvement" was observed in the 26.6% of cases (8/30), and a "mild improvement" in the 20% of cases (6/30). A "worsening" of lesions was reported in 3.3% of patients (1/30) and in 10% of patients (3/30) the acne condition was "unchanged" at the end of the study.

Patient Evaluation of Treatment Acceptability and Tolerability

Among 41 patients, 97.5% (40/41) reported a score of 3 to describe the acceptability of the treatment (Table 2). Among 41 patients, 90% (37/41) reported a score of 3, related to an opinion of excellent tolerability of the treatment (Table 2).

DISCUSSION

Acne is a chronic inflammatory disease of the skin, which requires long periods of treatment to obtain a satisfactory outcome.[18] In addition, the most common therapies for acne treatment can reveal adverse reactions and are limited by the risk of antibiotic resistance. On this basis, the implementation of different therapeutic strategies is necessary.

The studied line of products is composed of three salicylic acid-based ones for the topical treatment of acne. In a previous study, these products were used by patients affected with mild-to-moderate facial acne and were associated with a clinical effectiveness, a high tolerability and pleasantness of use.[17]

The present multicenter observational study was designed to provide new evidence about the clinical effectiveness of the products, with not-stringent inclusion criteria to best reflect the daily clinical practice. Patients who have suspended any other therapy for the treatment of acne, used the three products for their acne management and skin daily care and were evaluated for 8 weeks. Even if the study is limited by its observational design, along with a reduced number of enrolled patients, the combined use of all three products was associated with a significant improvement of acne lesions, with a reduction of papules, pustules and comedones. These data are also supported by a significant reduction of personal discomfort related to acne, evaluated by VAS score. In addition, an improvement of overall acne condition at the end of the study was reported by most of the patients; in 40% of cases, this is classified as “great improvement”.

These products have also shown a good acceptability and tolerability, evaluated as secondary outcomes: the majority of patients (acceptability: 97.5% and tolerability: 90%) described these parameters as excellent.

Taken together, these data suggest a satisfactory outcome of the combined use of the studied products in the management of acne.

This effect could be a result of the synergistic mechanisms of different agents in combination (salicylic acid, urea peroxide, zinc/taurine and niacinamide), which enables simultaneous targeting of multiple pathogenic factors of acne.[19] This suggests how a multitarget therapy could be a promising strategy to treat and control existing acne lesions.

Moreover, these results have been obtained without the concomitant assumption of other anti-acne therapies, increasing the value of non-pharmacological treatments and, on the other hand, suggesting that this combination treatment associated to other pharmacological interventions could improve their efficacy.

In conclusion, the results of this observational study support the effective and well-tolerated use of a combined treatment with salicylic acid-based products for the topical treatment of acne and as a maintenance therapy.

Funding and Conflicts of Interest

No conflicts of interest to declare

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Authors' contributions

All authors contributed to the conception of the study, the acquisition and the interpretation of the data and revised and approved the final version of the manuscript before submission.

REFERENCES

1. Zouboulis CC. Acne vulgaris. Der Hautarzt 2014;65:733–750. https://doi.org/10.1007/s00105-014-2853-9
2. Sevimli Dikicier B. Topical treatment of acne vulgaris: efficiency, side effects, and adherence rate. J Int Med Res 2019;47:2987–2992. https://doi.org/10.1177/0300060519847367
3. Marron SE, Chernyshov PV, Tomas-Aragones L. Quality-of-life research in acne vulgaris: current status and future directions. Am J Clin Dermatol 2019;20:527–538. https://doi.org/10.1007/s40257-019-00438-6
4. Vilar GN, dos Santos LA, Sobral Filho JF. Quality of life, self-esteem and psychosocial factors in adolescents with acne vulgaris. An Bras Dermatol 2015;90:622–629. https://doi.org/10.1590/abd1806-4841.201533726
5. Fox L, Csongradi C, Aucamp M, du Plessis J, Gerber M. Treatment modalities for acne. Molecules 2016;21:1063. https://doi.org/10.3390/molecules21081063
6. Ogè LK, Broussard A, Marshall MD. Acne vulgaris: diagnosis and treatment. Am Fam Physician 2019;100:475–484.
7. Zaenglein AL. Acne vulgaris. N Engl J Med 2018;379:1343–1352. https://doi.org/10.1056/NEJMcp1702493
8. Reilly BK, Ritsema TS. Managing nonteratogenic adverse reactions to isotretinoin treatment for acne vulgaris. JAAPA 2015;28:34–39. https://doi.org/10.1097/01.JAA.0000459815.24908.02
9. Erdemir U, Okan G, Gungor S, Tekin B, Yildiz SO, Yildiz E. The oral adverse effects of isotretinoin treatment in acne vulgaris patients: A prospective, case-control study. Niger J Clin Pract 2017;20:860–866. https://doi.org/10.4103/1119-3077.183248
10. Ingram JR, Grindlay DJC, Williams HC. Management of acne vulgaris: an evidence-based update. Clin Exp Dermatol 2010;35:351–354. https://doi.org/10.1111/j.1365-2230.2009.03683.x
11. Araviiskaia E, Dréno B. The role of topical dermocosmetics in acne vulgaris. J Eur Acad Dermatol Venereol 2016;30:926–935. https://doi.org/10.1111/jdv.13579

12. Lu J, Cong T, Wen X, Li X, Du D, He G, Jiang X. Salicylic acid treats acne vulgaris by suppressing AMPK/SREBP1 pathway in sebocytes. Exp. Dermatol. 2019;28:786–794. https://doi.org/10.1111/exd.13934
13. Draelos ZD, Matsubara A, Smiles K. The effect of 2% niacinamide on facial sebum production. J Cosmet Laser Ther 2006;8:96–101. https://doi.org/10.1080/14764170600717704
14. Shahmoradi Z, Iraji F, Siadat AH, Ghorbaini A. Comparison of topical 5% nicotinamid gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris: A double-blinded randomized clinical trial. J Res Med Sci 2013;18:115–117.
15. Jarrousse V, Castex-Rizzi N, Khammari A, Charveron M, Dréno B. Zinc salts inhibit in vitro Toll-like receptor 2 surface expression by keratinocytes. Eur J Dermatol 2007;17:492–496. https://doi.org/10.1684/ejd.2007.0263
16. Sandeep Varma R, Shamsia S, Thiyagarajan OS, Vidyashankar S, Patki PS. Yashada bhasma (Zinc calx) and Tankana (Borax) inhibit Propionibacterium acne and suppresses acne induced inflammation in vitro. Int J Cosmet Sci 2014;36:361–368. https://doi.org/10.1111/ics.12134
17. Rigoni C, Cantù AM, Barba A, Belloli C, Cameli N, Capasso C, Capezzera R, Demichelis P, Di Lella E, Falconi Klein E, Farina S, Forgione P, Guareschi MG, Mariano M, Mazzola G, Melino M, Pabisch S, Praticò M, Rescigno O, Sorbellini R, Villa L, Vincenzi C. Clinical observational study of the topical treatment of mild to moderate acne. Journal of Plastic Dermatology 2016; 12, 1
18. Serup J, Lindblad K, Maroti M, Kjellgren K, Niklasson E, Ring L, Ahlner J. To follow or not to follow dermatological treatment. Acta Dermato-Venereologica 2006;86:193–197. https://doi.org/10.2340/00015555-0073
19. Cooper AJ, Harris VR. Modern management of acne. Med J Aust. 2017;206(1):41-45.

Table 1. Patient Baseline Characteristics

Characteristics	**Patients (n=41)**
Gender (N): • Female • Male	 28 13
Age (years); mean (SD)	20 (5)
Inflammatory lesions at baseline; mean (SD): • Papules • Pustules • Blackheads	 7.9 (4.6) 0.9 (2.5) 16.1 (16.6)

Table 2. Acceptability and tolerability scores.

Score (descriptor)	Patients, N (%)
Acceptability	
0 (poor)	0
1 (mild)	0
2 (moderate)	1 (2.5)
3 (excellent)	40 (97.5)
Tolerability	
0 (poor)	0
1 (mild)	0
2 (moderate)	4 (10)
3 (excellent)	37 (90)