INDEXED BY
INDEX MEDICUS
(MEDLINE)
SCIENCE CITATION INDEX
EXPANDED (ISI)

GIORNALE ITALIANO DI

DERMATOLOGIA E VENEREOLOGIA

OFFICIAL JOURNAL OF THE SOCIETÀ ITALIANA DI DERMATOLOGIA MEDICA, CHIRURGICA, ESTETICA E DELLE MALATTIE SESSUALMENTE TRASMESSE (SIDeMaST)

EFFICACY AND LOCAL TOLERABILITY OF DIFFERENT SPRAY PRODUCTS IN THE TREATMENT OF MILD TO MODERATE ACNE OF THE BACK AND CHEST. A CONTROLLED, 3-ARM, ASSESSOR-BLINDED PROSPECTIVE TRIAL

Ada LO SCHIAVO, Rosa V. PUCA, Francesca ROMANO, Massimo MILANI

Società Italiana di Dermatologia
(SIDeMaST)

VOLUME 152 - 2017

EDIZIONI MINERVA MEDICA

Online version at http://www.minervamedica.it
Giornale Italiano di Dermatologia e Venereologia 2017;152

ORIGINAL ARTICLE

Efficacy and local tolerability of different spray products in the treatment of mild to moderate acne of the back and chest. A controlled, 3-arm, assessor-blinded prospective trial

Ada LO SCHIAVO [1], Rosa V. PUCA [1], Francesca ROMANO [1], Massimo MILANI [2]

[1]Clinica Dermatologica, Seconda Università di Napoli, Naples, Italy; [2]Medical Direction Difa Cooper IFC Group, Caronno Pertusella, Varese, Italy

*Corresponding author: Massimo Milani, Via Milano 160, 21042 Caronno Pertusella (VA), Italy. E-mail: massimo.milani@difacooper.com

ABSTRACT

BACKGROUND: A spray formulation containing 2 vitamin-A derivatives (hydroxypinacolone retinoate and retinol) carried in glycospheres (RetinSphere®) combined with an antimicrobial peptide (BIOPEP-15), salicylic acid and vitamin E (Bioretix ultra spray [BR]) has been recently developed for the treatment of truncal acne. We evaluated clinical efficacy of BR in comparison with two commonly used sprays, containing triethylcitrate and ethylinoleate (Aknicare CB [AK]) and containing betaine, glycine and salicylic acid 2% (Salipil spray [SP]). The products were applied twice daily.

METHODS: In a randomized, parallel-groups, assessor-blinded, 6-week trial, we enrolled 75 subjects (38 men, 37 women, mean age 21 years) with mild-to-moderate truncal acne. Twenty-five subjects were randomized to each treatment group (BR, AK or SP). Primary outcome of the study was the evolution of Global Acne Grading System (GAGS) Score in comparison with baseline and within groups at week 6. Secondary outcome was the evaluation of skin irritation.

RESULTS: All but 2 subjects concluded the study. At baseline mean±SD of GAG scores were 9.8±7 in BR, 10.7±7.6 in AK and 10.7±7.0 in SP groups, respectively. At week 6 GAGS Score in BR was statistically significantly lower in comparison with AK and SP (P=0.03). A significant greater percentage reduction of GAGs scores in comparison with baseline was observed in BR group (-72%) in comparison with AK group (-45%) (P=0.05) and with SP group (-36%) (P=0.009). No significant differences between the groups were observed regarding erythema, burning and xerosis scores at week 6. Twelve subjects out of 25(48%) in BR group, 15(60%) in AK group and 14(56%) in SP group reported some grade of erythema, burning or xerosis.

CONCLUSIONS: BR spray showed to be a more effective treatment of mild-to-moderate truncal acne in comparison to AK and SP sprays. This formulation showed also good skin tolerability comparable with anti-acne sprays not containing vitamin-A derivatives.

(*Cite this article as*: Lo Schiavo A, Puca RV, Romano F, Milani M. Efficacy and local tolerability of different spray products in the treatment of mild to moderate acne of the back and chest. A controlled, 3-arm, assessor-blinded prospective trial. G Ital Dermatol Venereol 2017;152)

Key words: Acne vulgaris - Randomized controlled trial - Vitamin A - Analogs and derivatives - Retinoids.

Acne is a chronic inflammatory disease of the pilosebaceous units of the face, neck, chest, and back.[1] It is the most common skin disorder occurring worldwide, with an estimated prevalence of 70-87%.[2] In addition to face, acne lesions commonly involve also back and chest (the so called truncal acne).[3] An epidemiological study shows that prevalence of acne on the chest and back was 45% and 61%, respectively.[4] Truncal acne can cause severe disability.[5] When these areas are involved, the use of topical products like creams and gel could be problematic. Oral treatments (antibiotics or systemic retinoids) are commonly used in subjects with truncal acne. However, both strategies could have some limitations.[6] Despite high prevalence of truncal acne, clinical data regarding its management are so far limited. When large body areas should be

treated formulations that can be applied easily could represent an ideal therapeutic approach. Spray products are considered a more convenient formulation when these body sites should be treated, especially in hairy areas. A new spray formulation containing 0.15% of two vitamin A derivatives (retinol and hydroxypinacolone retinoate) carried in a patented glycospheres system (RetinSphere®), an antimicrobial peptide (BIO-PEP-15), salicylic acid 0.5% and vitamin E has been recently developed (Biretix ultra spray [BR], Difa Cooper, IFC Group, Caronno Pertusella, Italy). The RetinSphere® is an innovative technology which can acts as a penetration enhancer allowing a slow release of the active principles, improving the chemical stability and at the same time the bioavailability.[7] This composition and formulation, from a theoretical point of view, suggests that this product could be effective in the treatment of acne involving chest and back. So far no controlled and comparative data are available evaluating the efficacy and tolerability profile of this product.

We evaluated and compared the clinical efficacy of BR with two commonly used sprays for truncal acne treatment, one containing triethylcitrate and ethylinoleate, GT-peptide-10, salycilic acid 0.5% and Zinc Lattate (Aknicare CB [AK], Synchroline Spa, S. Felice del Benaco, Brescia, Italy), and the other one containing betaine, glycine and salicylic acid 2% (Salipil spray [SP]; Canova Skin Care, Milan, Italy). Efficacy of salicylic acid 2% in lotion and spray formulation was supported by a controlled clinical trial.[8] Several studies have also demonstrated the rationale of the use of GT-peptide 10 and Zinc lactate in acne.[9, 10]

Materials and methods

Study design

The present study was a balanced, randomized, 3-arm, parallel-groups, and observer-masked prospective 6-week trial. The trial registration number was ISRCTN38383374.

Subjects

Study protocol was approved by our IRB Committee. We enrolled a total of 75 subjects (38 men and 37 women, mean age 21 years) after their written informed consent. Main entry criterium was the presence of mild to moderate acne involving back and chest regions (the so called truncal acne). Main exclusion criteria were: severe forms of acne requiring systemic treatments; other severe skin conditions; use of topical acne medications such as tretinoin, benzoyl peroxide or topical antibiotics within 2 weeks prior the enrollment in the trial; use of oral antibiotics within 30 days; use of systemic corticosteroids within 4 weeks and a Body Mass Index >30. A total of 25 subjects were randomly assigned to each treatment group (BR, AK and SP) with a 1:1:1 ratio. Randomization list with a 1:1:1 ratio and with a block of 6 was generated by the mean of statistical software (G-Power®, Düsseldorf, Germany). All the products were applied twice daily (in the morning and in the evening). The total amount of product was 4/5 puffs per application (a total of 1.2/1.5 mL), to cover chest and back areas. Truncal acne was graded using the Global Acne Grading System (GAGS).

Study outcomes

According to Doshi *et al*., the primary outcome of the study was the evolution of GAGS Score,[11] in comparison with baseline and within groups at week 6. Secondary outcome was the evaluation of skin irritation. Safety and tolerability were assessed through evaluations of treated areas tolerability and adverse events. At week 6, the investigator rated erythema (E), burning (b) and xerosis (X), based on a semi-quantitative scale ranging from 0 (none) to 3 (severe). A global skin tolerability score (E+B+X) was also calculated. Study protocol and patient information sheet were approved by the local Investigational Review Board.

Statistical analysis

The trial was designed as a superiority trial. The formulation of BR spray (retinoids plus keratolytic and anti-bacterial compounds) from a theoretical point of view could be considered more efficacious in comparison with spray formulations containing keratolytic and emollient compounds only. The study protocol and the statistical analysis plan specified that comparison of GAGS Score values at week 6 between the three groups should be considered as the primary efficacy outcome of the trial. The power calculation assumed a difference between the BR group and the AK and SP treatments in

the GAGS Score at week 6 of at least 1.0 points with an effect size of 0.6. This assumption provided 90% power at an alpha level of 0.05 (two-tailed test) for a sample size of at least 24 evaluable patients per group. Sample size calculation was performed using G*Power program Ver.3.03 (Kiel, Germany). All statistical analyses were performed using SPSS statistical package Version 13. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. Two-tailed Wilcoxon paired, Mann-Whitney and ANOVA tests were applied to compare treatments and to compare baseline levels with values at the end of study period. The analysis was based on the intention-to-treat principle and involved all patients who were randomly assigned to the three treatments. A P-value <0.05 was considered statistically significant; 95% confidence intervals were calculated for the mean differences of GAGS between treatments.

Results

Table I shows the subjects' baseline characteristics. The three groups were well balanced for all the main clinical characteristics. All but 2 subjects (one in AK and one in SP groups respectively) concluded the study. Analysis was conducted based on Intention-To-Treat principle. At baseline mean±SD of GAG scores were 9.8±7 in BR, 10.7±7.2 in AK and 10.1±5.5 in SP groups, respectively. In comparison with baseline, GAG Score was reduced significantly in the BR group (from 9.8 to 3.6; P=0.0001; Wilcoxon matched paired test). The reduction in AK and SP in comparison with baseline were also statistically significant (P=0.001; Wilcoxon test). At day 45 GAGS Score in BR was statistically significantly lower in comparison with AK (6.3) and SP (6.9) (P=0.03; ANOVA Test). A significant greater percentage

TABLE I.—*Subjects' characteristics at baseline.*

	BR group	AK group	SP group
Number	25	25	25
Men/women	13/12	14/11	11/14
Age, years, mean (SD)	22 (6)	21 (5)	21 (6)
Acne severity			
Mild, N. (%)	21 (84%)	21 (84%)	22 (88%)
Moderate, N. (%)	4 (16%)	4 (16%)	3 (12%)
GAGS Score, mean (SD)	9.8 (6.9)	10.7 (7.2)	10.1 (5.5)

Mild acne, GAGS Score: from 1 to 18; moderate acne, GAGS Score: from 19 to 30.

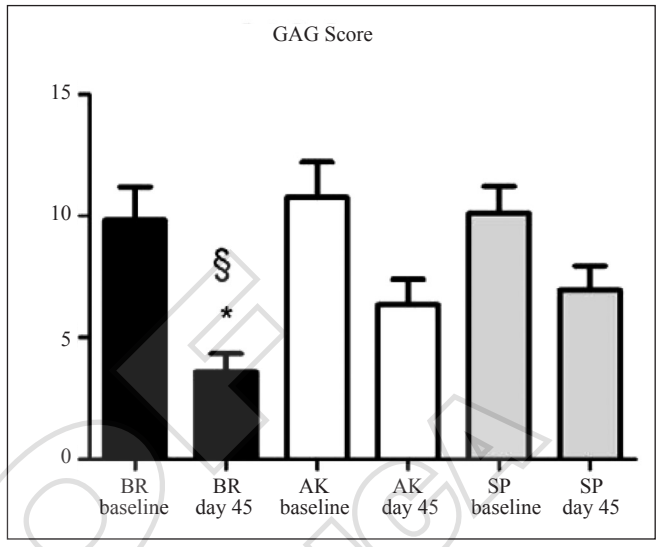

Figure 1.—Evolution of GAG scores in the three groups from baseline to day 45 (week 6).
BR day45 *vs*. AK day45 *P=0.03; BR day45 *vs*. SP day45 §P=0.006; BRd ay45 *vs*. BR baseline, AK baseline *vs*. AK day45 and SP baseline *vs*. SP day45: P=0.0001.

reduction of GAG scores in comparison with baseline was observed in BR group (-72%; 95% CI from 62% to 83%) in comparison with AK group (-45%; 95%CI from 32% to 57%) (P=0.05) and in comparison, with SP group (-36%; 95%CI from 25% to 47%) (P=0.009) (Mann-Whitney Test). Figure 1 shows the evolution of GAGS scores in the three groups, from baseline to week 6.—No significant differences between the three study groups were observed regarding erythema, burning and xerosis scores at week 6. At the end of the study the mean global skin tolerability score (range from 0 to 9) was 1.2 in BR, 1.1 in AK and 0.8 in SP group (P=0.57; ANOVA Test). Twelve subjects out of 25 (48%) in BR group, 15 (60%) in AK group and 14 (56%) in SP group reported some grade of erythema, or burning or xerosis. The reasons for the two drop out subjects were a lack of efficacy (one subject in SP) and a reduced compliance to the treatment (one subject in AK).

Discussion

Acne is a chronic inflammatory disease of the pilosebaceous unit resulting from hormon-induced increased sebum production associated with altered keratinisation, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back

by *Propionibacterium acnes*.[12] Acne is a common skin condition.[13] Back and chest localization (truncal acne) represents a therapeutic challenge.[14] Although not as noticeable as facial acne, truncal acne may affect a person's self-esteem and body image and reduce one's participation in sports because of the need to undress in a shared locker room.[15] In general acne studies focus on facial acne and ignore treatment outcomes in the chest and back. For this reason, information is limited on the management of truncal acne vulgaris. Epidemiological studies suggest that dermatologists commonly prescribe oral antibiotic or oral retinoid therapies when acne involves also chest and back.[16] Effective treatment of truncal acne is an important goal since atrophic scarring is quite common in this condition and may represent a significant cosmetic issue.[17] In truncal acne scarring evolution of acne lesions could be observed in up to 11% of subjects. In the present study, we compare the clinical efficacy of a spray formulation containing two vitamin A derivatives (hydroxypinacolone retinoate and retinol) carried in glycospheres (RetinShpere®), an antimicrobial compound (Biopep-15) and a keratolytic agent with two other commonly prescribed spray formulations containing mainly keratolytic substances only, in mild to moderate truncal acne. Hydroxypinacolone retinoate is a retinoic acid ester and thus carries out retinoid activity while at the same time ensuring greater skin tolerability. Glycospheres help enhance delivery of the retinol. Vitamin A derivatives are commonly used in the treatment of acne, both topically and orally.[18] Oral treatment with retinoid is in general limited for severe forms of acne.[19] Topical retinoids are commonly used in mild and moderate acne.[20] Retinoids are the core of topical therapy for acne in view of their potent comedolytic and anti-inflammatory actions.[21] However their use in acne could be limited by side effects.[22] The use of topical retinoids is commonly associated with skin dryness peeling, erythema and irritation.[23] In addition, some formulations of retinoids are not photostable and should be applied in the evening, avoiding sun exposure. Hydroxypinacolone retinoate is a new synthetic ester of 9-cis-retinoic acid. Retinol is one of the best known cosmeceutical forms of vitamin A.[24] The Retinsphere technology is capable to act as a penetration enhancer allowing a slow release of the active principles, improving the chemical stability and at the same time the bioavailability. BIOPEP-15 is a polypeptide with an anti *P. acnes* activity.[25] Salicylic acid is a comedolytic agent that could be used in 0.5% to 2% strengths as an over the counter product. This product is commonly used in the therapeutic strategies of mild to moderate acne in general combined with other products.[26] Vitamin E is the major naturally occurring lipid-soluble non-enzymatic antioxidant protecting skin from the adverse effects of oxidative stress.[27] The spray product we have evaluated in this trial is therefore formulated with 4 different active principles which could act at different levels of the pathogenesis of acne. The spray formulation is particularly indicated when large body area should be treated. In our trial, we have also shown that this formulation has a good local tolerability. This could be due to characteristics of the specific composition of the spray (presence of vitamin E, the combination of retinoids and the delivery system).

Limitations of the study

Some limitations should be considered in evaluating our results. First, this study was not double-blind. We decided to perform an assessor-blinded evaluation of the primary endpoint of the study to increase the internal validity of our results. A second limitation could be the relative short (*i.e*. 6 weeks) observation and treatment period. Finally, data from controlled studies may differ from clinical practice. However we believe that the external validity of the present study could be considered good in consideration that inclusion and exclusion criteria were not particularly strict, offering therefore a significative generalization of the results obtained.

Conclusions

BR spray containing vitamin A derivatives, an antimicrobial peptide, salicylic acid and vitamin E has shown to be a more effective treatment of mild to moderate acne of the back and chest in comparison to sprays containing keratolytic and exfoliating agents only. This formulation has also good skin tolerability comparable with anti-acne sprays not containing vitamin A derivatives.

References

1. Thiboutot DM. Overview of acne and its treatment. Cutis 2008;81(1 Suppl):3-7.
2. Katsambas AD, Stefanaki C, Cunliffe WJ. Guidelines for treating acne. Clin Dermatol 2004;22:439-44.
3. Del Rosso JQ. A closer look at truncal acne vulgaris: prevalence, severity, and clinical significance. J Drugs Dermatol 2007;6:597-600.
4. Tan JK, Tang J, Fung K, Gupta AK, Thomas DR, Sapra S, *et al*. Prevalence and severity of facial and truncal acne in a referral cohort. J Drugs Dermatol 2008;7:551-6.
5. Motley RJ, Finlay AY. How much disability is caused by acne? Clin Exp Dermatol 1989;14:194-8.
6. Ross JI, Snelling AM, Carnegie E, Coates P, Cunliffe WJ, Bettoli V, *et al*. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003;148:467-78.
7. Truchuelo MT, Jiménez N, Mavura D, Jaén P. Assessment of the Efficacy and Safety of a Combination of 2 Topical Retinoids (RetinSphere) in Maintaining Post-Treatment Response of Acne to Oral Isotretinoin. Actas Dermo-Sifiliográficas (English Edition) 2015;106:126-32.
8. Eady EA, Burke BM, Pulling K, Cunliffe WJ. The benefit of 2% salicylic acid lotion in acne a placebo-controlled study. J Dermatolog Treat 1996;7:93-6.
9. Eilers H, Alexeyev OA. Effect of GT-Peptide 10 and Triethyl Citrate on P. acnes Biofilm Formation, Viability, and Dispersion. J Drugs Dermatol 2016;15:778.
10. Kircik LH. Evolving Concepts in the Pathogenesis of Acne Vulgaris open access articles. J Drugs Dermatol 2014;13:s56.
11. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol 1997;38:416-8.
12. Hywel WC, Dellavalle RP, Garner S. Acne vulgaris. The Lancet 2012;379:361-72.
13. Cordain L. Acne vulgaris: a disease of Western civilization. Arch Dermatol 2002;138:1584-90.
14. Cunliffe WJ. Evolution of a strategy for the treatment of acne. J Am Acad Dermatol 1987;16:591-9.
15. Bowe WP, Leyden JJ, Crerand CE, Sarwer DB, Margolis DJ. Body dysmorphic disorder symptoms among patients with acne vulgaris. J Am Acad Dermatol 2007;57:222-30.
16. Del Rosso JQ. Management of truncal acne vulgaris: current perspectives on treatment. Cutis 2006;77:285-9.
17. Del Rosso JQ, Bikowski J, Baum E. Prevalence of truncal acne vulgaris: a population study based on private practice experience. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2–6, 2007; Washington, DC.
18. Orfanos CE, Zouboulis CC. Oral retinoids in the treatment of seborrhoea and acne. Dermatology 1998;196:140-7.
19. Peck GL, Olsen TG, Butkus D, Pandya M, Arnaud-Battandier J, Gross EG, *et al*. Isotretinoin versus placebo in the treatment of cystic acne: a randomized double-blind study. J Am Acad Dermatol 1982;6:735-45.
20. Czernielewski J, Michel S, Bouclier M, Baker M, Hensby JC. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. J Eur Acad Dermatol Venereol 2001;15(s3):5-12.
21. Leyden JJ. Retinoids and acne J Am Acad Dermatol 1988;19:164-8.
22. Saurat JH. Side effects of systemic retinoids and their clinical management. J Am Acad Dermatol 1992;27:S23-S28.
23. Healy E, Simpson N. Acne vulgaris. Br Med J 1994;308:831.
24. Rossetti D, Kielmanowicz MG, Vigodman S, Hu YP, Chen N, Nkengne A, *et al*. A novel anti-ageing mechanism for retinol: induction of dermal elastin synthesis and elastin fibre formation. Int J Cosmet Sci 2011; 33:62-9.
25. Bojar R, Fitzgerald DJ. Efficacia anti-microbica di BIOPEP·15 valutata su 24 ceppi di Propionibacterium acnes. Evocutis plc, EVO-0406 Oct 2012
26. Zander E, Weisman S. Treatment of acne vulgaris with salicylic acid pads. Clin Ther 1991;14:247-53.
27. Nachbar F, Korting HC. The role of vitamin E in normal and damaged skin. J Mol Med 1995;73:7.

Authors' contributions.—Ada Lo Schiavo and Francesca Romano had the original study idea and participated in its design and coordination. Massimo Milani helped regarding study design, protocol definition, data collection and analysis and manuscript preparation. Francesca Romano and Rosa V. Puca carried out the patients selection and follow up visits. All authors read and approved the final manuscript.

Funding.—The study was partially supported by a grant of Difa Cooper.

Conflicts of interest.—MM is an employee of Difa Cooper. All others authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: November 16, 2016. - Manuscript revised: November 8, 2016. - Manuscript received: September 21, 2016.