Symphonic M.D.

RETINOL :: VITAMIN C
& ACNE CLINICAL TRIALS

INTRODUCTION

Acne vulgaris, commonly known as acne, is a chronic inflammatory skin condition that affects the pilosebaceous units of the skin.[1] The clinical features of acne include seborrhoea (excess grease), non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and various degrees of scarring. According to the Global Burden of Disease study in 2010, acne vulgaris was the eighth most common disease among the most prevalent diseases worldwide, with an estimated global prevalence of 9.38%.[2] This condition affects individuals of all ages, with a high incidence observed during adolescence. However, despite its visibility, the impact of acne vulgaris is often underestimated because the condition not only affects the physical appearance of individuals but also has psychological and emotional consequences. These include decreases in self-esteem, body image dissatisfaction, and social withdrawal.[3]

Topical acne treatments such as retinol, a form of vitamin A, and vitamin C (ascorbic acid) are commonly used in skincare products. Retinol has been shown to unclog pores, reduce acne breakouts, and improve overall skin texture.[4] Topical vitamin C has been shown to have anti-oxidative, photoprotective, anti-aging, and anti-pigmentary effects.[5] Studies of retinol plus vitamin C combination have demonstrated significant improvement in the epidermal and dermal compartments of the skin, promoting proliferation of keratinocytes, strengthening the epidermis, and increasing collagen synthesis.[6] However, a key challenge in the use of retinol and vitamin C products is the potential for skin irritation or sensitivity. Skin reactions such as irritant contact dermatitis, resulting in erythema, dryness, burning, and pruritus, can lead to inconsistent use or discontinuation by individuals.[7] These side effects highlight the need to develop new acne topical treatments that can effectively address the underlying causes of acne without resulting in significant skin irritation.

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INTRODUCTION

In the search for more tolerable acne treatments, the use of cannabidiol (CBD) in combination with retinol and vitamin C has been explored. CBD has been shown to have both anti-inflammatory and sebostatic properties when used topically.[8,9] The anti-inflammatory effect of CBD can help reduce inflammation associated with blemishes and acneiform lesions, while its sebostatic properties can address the root cause of acne by reducing excessive sebum production. Furthermore, CBD has been found to have antimicrobial properties, which may help control the growth of acne-causing bacteria.[10,11] In addition to these effects, combining CBD with retinol and vitamin C has shown promise in reducing skin irritation often associated with retinol plus vitamin c alone.[12] To further explore the clinical potential of CBD as an acne treatment, we conducted a prospective clinical trial to test the effectiveness of a new CBD cream on improving the appearance of blemishes and acne-like lesions and the ability to reduce sensitivities known to be associated with the use of topical retinol and vitamin C.

METHODS

STUDY POPULATION

Eligible participants were male and female subjects between the ages of 13 and 35 years, with Fitzpatrick Skin Type I to VI, and could be from any ethnic group. Subjects were eligible for participation if they had mild to moderate global (Score 3-6) appearance of blemishes based upon a 10-point Investigator Global Assessment scale defined as 0=none, 1-3= mild, 4-6 moderate, and 7-9 severe. Furthermore, participants had to have self-reported oily, combination or acne-prone skin, be willing to avoid excessive solar or UV exposure, including minimizing direct sun exposure and be willing to cleanse the face and remove all facial and all eye makeup (if makeup was worn) at least 30 minutes prior to every study visit and use no other topical skincare products on the face for the duration of the study except the assigned test product and the subject's regular brand(s) of non-medicated facial cleanser and color cosmetics/makeup remover (if applicable). Female subjects of childbearing age had to commit to using medically acceptable methods of birth control for the duration of the study. Subjects who had used topical over-the-counter products that contained benzoyl peroxide, sulfur, or salicylic acid in the past two weeks and/or any prescription systemic acne treatment within the prior two months were excluded from study participation. Additionally, subjects who were currently under a physician's care for a medical problem or taking any prescription or over-the-counter medication that, in the opinion of the Investigator, could have affected the subject's treatment response, subjects with a known allergy to CBD, a history of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or those who were currently using immunosuppressive medications were excluded.

METHODS

STUDY DESIGN

The efficacy and safety of a novel cannabidiol investigational product (Skincare Product NS-25-1) was evaluated in an 8-week, open-label clinical study conducted at a single site over three visits: baseline, week 4, and week 8. The study was performed between February 2023 and April 2023. Participants received the investigational product at baseline, with additional product dispensed as needed. Subjects were instructed to use the product twice daily (morning and evening) stepwise, washing with a non-medicated cleanser, then applying a dime-sized amount of test product to dry the face and neck, avoiding the eye area. SPF was optional, and participants were permitted to use a product of their choice. The test product and daily diary were inspected for subject compliance at each evaluation time point. Any subject who missed more than two days of applications of the test product in a row or more than six missed applications of the test product (at least 90% compliant) over the course of 30 days resulted in the subject either being re-instructed for proper product use or dropped from the study at the discretion of the investigator.

METHODS

STUDY ASSESSMENTS

Clinical assessment of skin blemishes was performed by the investigator at screening/baseline, 4 and 8-week visits using a 10-point Investigator Global Assessment scale (0=none, 1–3=mild, 4–6=moderate, 7–9=severe) for overall appearance of blemishes, skin texture/roughness (tactile), pore appearance, skin clarity, post-inflammatory hyperpigmentation/post-inflammatory erythema (PIH/PIE), skin tone evenness (redness, blotchiness). All postbaseline scores were compared with the baseline. Improvements based on clinical grading were indicated by a decreased score for each. Facial images were captured at Baseline (all subjects) and Week 8 (up to 30% of responders, n = 10) using a Canfield VISIA imaging system (Canfield Scientific, Inc., Parsippany, NJ). Additionally, all participants completed a self-assessment questionnaire while examining their skin in a mirror at week 8 to evaluate subject satisfaction with skin conditions and study product based upon a scale of 1-strongly agree, 2-agree, 3-neutral, 4-disagree, 5-strongly disagree. Adverse events were recorded throughout the study. To determine product safety, erythema, edema, dryness, and scaling/peeling skin were assessed at each study visit using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

METHODS

STATISTICAL ANALYSIS

For the clinical grading values, mean percent (%) improvement was analyzed from baseline to each time point up to 8 weeks, and paired t-tests were used to compare change from baseline to zero (no change). The per-protocol population was used in analyses and included all subjects who received treatment and completed at least one post-baseline visit. Only the data of subjects who completed each visit was included in the analysis at that time point. Binomial tests were used to evaluate participant self-assessment questionnaires. The level of statistical significance was set at $p \leq .05$ for all analyses.

RESULTS

SUBJECT DEMOGRAPHICS AND DISPOSITION

A total of 33 subjects with mild to moderate blemishes were enrolled, and 30 completed the study. Data collected from 3 participants were not analyzed, one due to noncompliance, one due to failure to maintain the study schedule, and one was lost to follow-up (per-protocol population: n = 30). The majority of participants were Caucasian (85%; n = 28), and 15% (n = 5) were African American. The average age of the participants was 19.4 years. The majority of subjects had Fitzpatrick type III skin (55%, n = 18).

RESULTS

EFFICACY

Investigator Evaluations

Early statistically significant improvements from baseline in the appearance of blemishes were seen in all IGA skin parameters except pore appearance by week 4 and were maintained throughout the 8-week study (Figure 1). Improvements in pore appearance were statistically significant at Week 8. A mean decline in IGA scores by > .5 points (a level considered to be clinically relevant) was achieved for the global appearance of blemishes, skin texture/roughness, skin clarity, and PIE/PIH at both Weeks 4 and 8 (Table 1). Clinical-relevant declines in IGA pore appearance and skin tone evenness were seen by Week 8. A significant improvement in the global appearance of blemishes occurred in 81% of participants at Week 4 and 93% at Week 8. In addition, 71% and 93% of subjects had significant skin texture/roughness responses by weeks 4 and 8, respectively. Overall, statistically significant responses of 80% or better were seen for all parameters by Week 8 except for PIE/PIH, where responses improved from 48% at Week 4 to 63% at Week 8 (Table 1). The clinical grading and self-assessed improvements in overall skin qualities were visualized by the standardized pictures taken at baseline and week 8 in a subset of 10 subjects. Visual assessment showed improvements in the appearance of blemishes after 8 weeks (Figure 1).

Subjection Satisfaction

Participant self-assessments demonstrated significant improvements in most attributes related to blemishes and healthy- and younger-looking skin at week 8 (Figure 3). These improvements ranged from being perceived in 65% for firmer-looking skin up to 96% for absorbing easily into the skin. The majority of skin characteristics self-assessed by the study participants were viewed favorably and included skin softness (86%; $p < .001$), the appearance of bumps (75%) and blemishes (95%), swelling (80%), glow (85%), overall skin health (91%) and skin appearance (85%). Overall, 92% of subjects would recommend the product to a friend.

RESULTS

SAFETY

There were no product-related AE's. All AE's reported were mild and transient, with nine subjects experiencing mild intolerance (irritation) during the study: investigator observed erythema (n = 5), edema (n = 1), scaling/peeling (n = 3), and subject reported burning/stinging (n = 3), itching (n=1), and tightness/dryness (n = 9) reported.

DISCUSSION

Acne is one of the most common skin problems in teenagers and young adults and causes significant emotional distress for many. The clinical approach to managing acne often involves retinoid-containing products as a core component of treatment in a patient skincare regime. Clinicians often integrate retinoid-containing products gradually to minimize skin irritation.13 The most common and frequent adverse effect of topical retinoids is known as 'retinoid reaction,' characterized by pruritus, burning sensation at the application site, erythema, and peeling that manifests itself generally within the first few weeks of treatment. It is thought to be initiated by the release of proinflammatory cytokines such as IL-1, TNF-α, IL-6, and IL-8.14,15 Acne is a pro-inflammatory condition with a complex and multifactorial pathogenesis. As such, new treatments should minimize these effects in combination with topical retinoids or seek to develop new treatments that offer the same effectiveness without irritating the skin.

This 8-week study demonstrated that a topical CBD combined with retinol and vitamin C treatment used in subjects with mild to moderate blemish-prone skin led to significant improvements in the overall appearance and condition of the skin. Compliance during the study was high, with only 1 dropout, which reflected the safety profile, tolerability, and fast onset of efficacy shown in the study. The most dramatic improvements involved clinically relevant improvements in IGA appearance of blemishes, skin texture, clarity, and PIE/PIH. Post-inflammatory erythema and PIH are troubling consequences of acne and can reduce the quality of life in patients, and rapid reductions in redness and PIH demonstrated the effectiveness of a topical CBD when added to retinol and vitamin C in treating blemishes. When participants were asked to evaluate their appearance, most of the study participants had favorable responses in attributes commonly related to healthy- and younger-looking skin, such as overall healthy appearance, skin radiance, and clarity. This investigator observed and participants perceived benefits are due to the effects of CBD on skin tone and texture and potentially the effects of CBD on barrier function. Prior studies have identified CBD's anti-inflammatory, anti-pruritic, and epidermal barrier restoration properties, and our results corroborate those findings.16-19

DISCUSSION

The safety and tolerability of oral CBD have been well established, and a CBD-based oral treatment has been proven effective for severe seizure disorders and approved by the U.S. Food and Drug Administration (FDA).[20] However, to our knowledge, limited data exists on the safety profile of topical formulations of CBD.[21] A few subjects in this study experienced transient erythema, stinging or discomfort, and tightness/dryness of skin. None of the nine subjects reporting these symptoms required systemic and/or topical treatment. Stinging was reported in another study of topical CBD used to treat atopic dermatitis but not in another study using the same topical.[22]

The study has several limitations inherent to the single-center open-label study design. First, the open-label design did not allow for a comparison with other regimens. However, it was noteworthy that statistically significant improvements in several attributes were corroborated by clinical grading and participant assessments that collectively confirmed the findings. Second, external validity is an issue inherent to single-center studies. Lastly, the short duration of the study makes it difficult to assess the long-term effects of topical CBD, retinol and vitamin C.

CONCLUSION

Topical CBD combined with retinol and vitamin C treatment improved skin characteristics and the appearance of blemished skin. To the best of our knowledge, this is the first clinical study of an explicitly formulated CBD topical treatment that has demonstrated statistically significant clinical improvements when combined with retinol and vitamin C. The formulation was well tolerated, with only mild transient AE's reported, and subjects reported high satisfaction with treatment. Results of this study show that CBD has beneficial effects on improving blemished skin, mitigates the effects commonly seen with topical retinol and vitamin C, and warrants further study as a treatment for acne.

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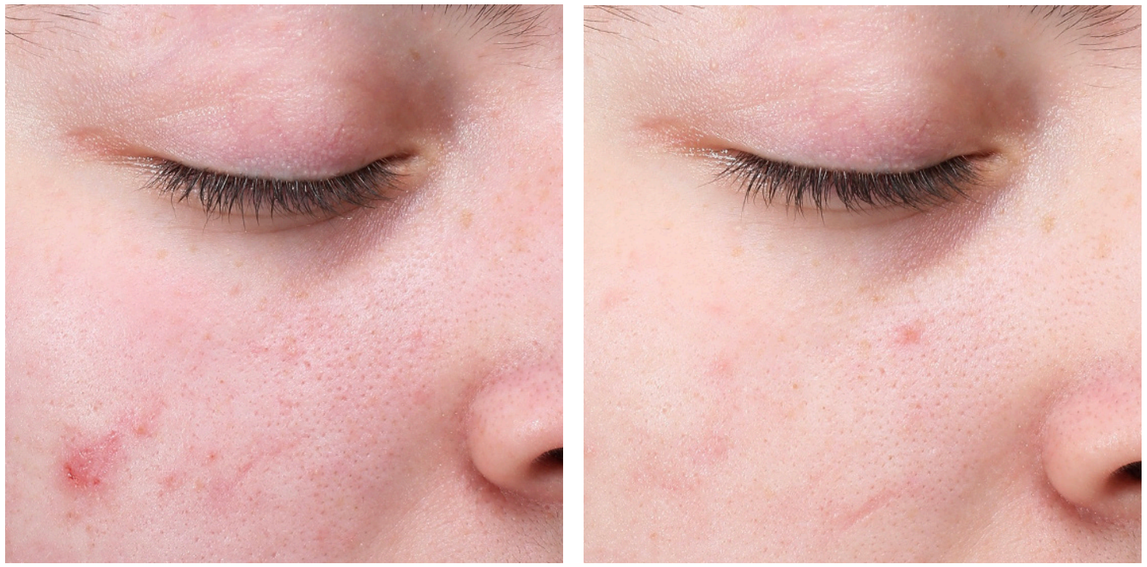

FIGURE 1: Visual improvements from baseline to week 8.

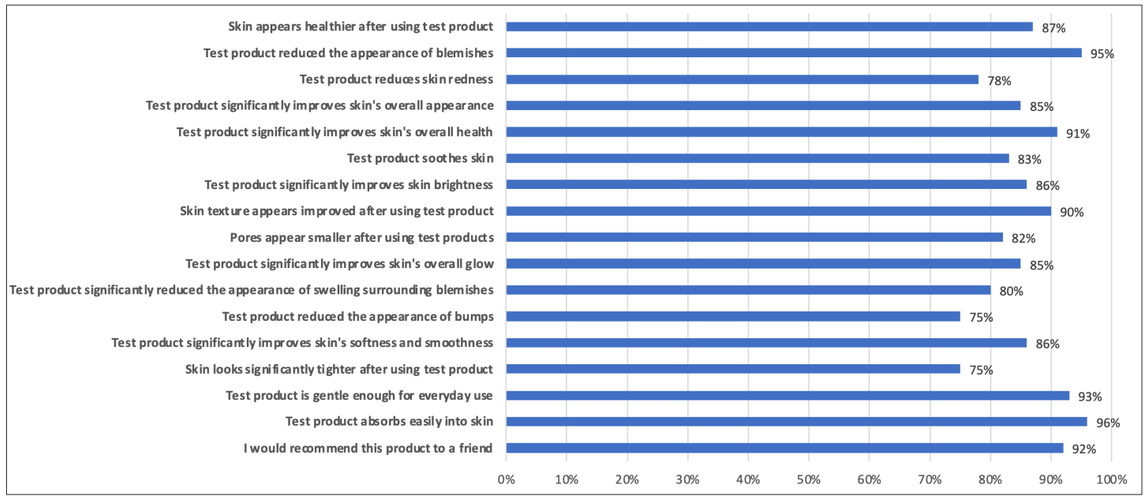

FIGURE 3: Self-assessed improvements in skin attributes expressed as a percentage of participants in agreement at week 8 compared with baseline.

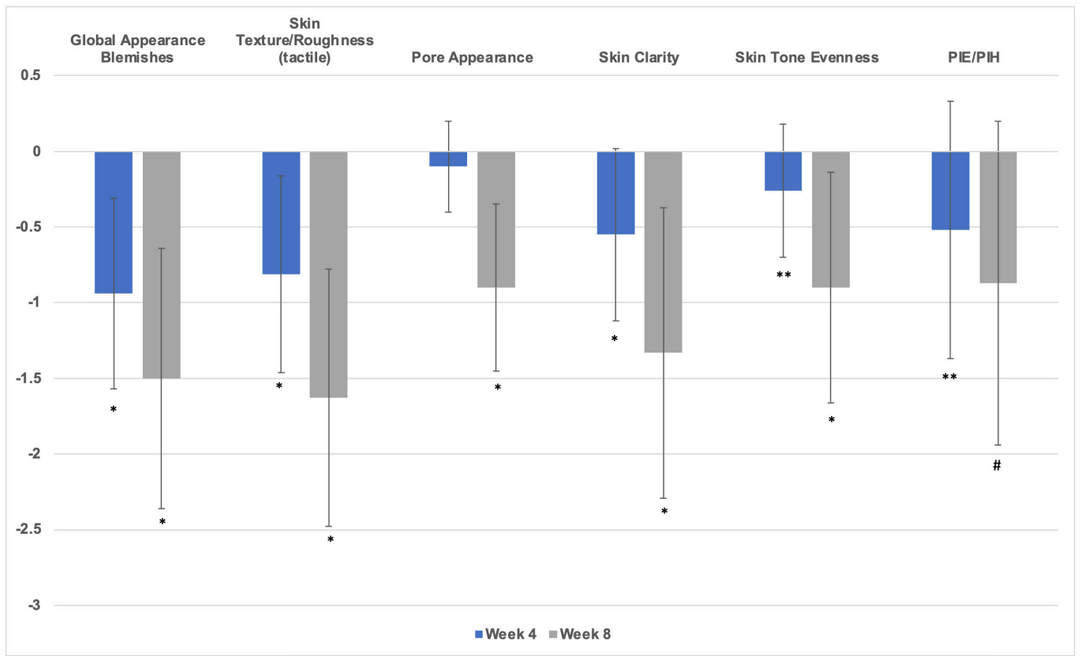

FIGURE 2: Changes from baseline in skin attributes related to blemishes assessed by clinical grading over 8 weeks of topical treatment. Values are mean ± sd. * P<0.0001; **P<0.01; #P=0.0001

TABLE 1: Percent of subjects showing improvement in clinical assessment of blemish skin parameters after 8 weeks of treatment.

	Week 4	Week 8
Global Appearance Blemishes	81%	93%
Skin Texture/Roughness (tactile)	71%	93%
Pore Appearance	10%	80%
Skin Clarity	52%	80%
Skin Tone Evenness	26%	80%

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