Simplifying Regimens Promotes Greater Adherence and Outcomes With Topical Acne Medications: A Randomized Controlled Trial

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New combination topical formulations for the treatment of acne may improve outcomes by increasing adherence. We assessed adherence to and efficacy of a combination topical medication for acne applied once daily compared with daily applications of 2 separate generic subcomponents. Twenty-six participants with mild to moderate acne vulgaris were randomized to 12 weeks of once daily application of clindamycin phosphate 1.2%–tretinoin 0.025% gel (CTG) combination product or separate daily applications of clindamycin phosphate gel 1% and tretinoin cream 0.025% (C gel + T cream) for a total of 2 applications daily. Disease severity was measured at baseline and weeks 4, 8, and 12. Adherence was monitored using electronic monitoring caps on the medication tubes. Of the 26 participants enrolled, 21 completed the 12-week study. Median adherence in the CTG group was 88% compared with 61% in the C gel + T cream group. There was a 51% mean reduction in total lesions for the CTG group versus a 32% mean reduction for the C gel + T cream group by the end of the study. Both CTG and separate applications of C gel + T cream improved mild to moderate acne. The use of a once daily combination product has the advantage of promoting better adherence and clinical outcomes.

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Acne is a widely prevalent chronic condition, and topical agents can be effective in both acute treatment and long-term management. However, many patients with chronic skin diseases are nonadherent to topical medications, and poor medication adherence is a major contributor to unresponsiveness to topical acne treatments.[1-3] Patients with acne that are resistant to topical therapies may be treated with oral antibiotics or isotretinoin, which have a potentially greater risk for adverse effects.[4] To improve treatment outcomes, it may be valuable to optimize use of topical acne treatments.

Combinations of topical therapies, such as clindamycin and tretinoin, are effective in the treatment of patients with mild to moderate acne.[5] However, applying topical medications can be messy and inconvenient, and the need for multiple applications daily may discourage patients from regularly

using their medications.[3] Adherence may be improved by decreasing the complexity of the regimen with topical formulations that contain multiple active ingredients. Using electronic monitors, we sought to test this hypothesis by investigating adherence among patients with acne randomized to 2 study groups: one group using a combination gel applied once daily and the other group using the 2 separate medications each day.

Methods

After obtaining approval from the Wake Forest University School of Medicine Institutional Review Board, 26 participants with mild to moderate acne vulgaris were enrolled in this 12-week, investigator-blinded, prospective, single center, randomized, controlled trial. Participants were 12 years and older with an investigator global assessment (IGA) of mild to moderate acne vulgaris (score of 2 or 3). Individuals were excluded from the study if they were pregnant or planning to become pregnant; breastfeeding; using oral retinoids within 2 months of enrollment; or using topical retinoids, oral antibiotics, nicotinamide, oral steroids, or any other medication determined to have potentially confounding effects on the results of the study within 1 month prior to the start of the trial. Other exclusion criteria included the use of topical medications for acne, such as cosmetics containing retinol, within 2 weeks prior to study entry; any skin condition or disease requiring concurrent therapy or confounding evaluation; history of hypersensitivity to the medications or their components; facial skin cancer or actinic keratoses; use of photosensitizing agents; use of isotretinoin in the last 6 months; use of chemical peels, microdermabrasion, or laser resurfacing within 3 months of study entry; Crohn disease; ulcerative colitis; or colitis with prior antibiotic use.

Participants enrolled in the study were assigned to 1 of 2 treatment groups. Participants in group 1 were given clindamycin phosphate 1.2%–tretinoin 0.025% gel (CTG) and instructed to apply it to the entire face once daily at bedtime. Participants in group 2 were given both generic clindamycin phosphate gel 1% as well as tretinoin cream 0.025% to apply to the entire face (C gel + T cream). To help minimize any potential dilution effects of simultaneous application as well as mimic the prescribing pattern of some dermatologists, the participants in group 2 were instructed to apply the clindamycin in the morning and the tretinoin at bedtime. All participants were allowed to continue to use their own nonmedicated facial wash and moisturizer for the entire study. Participants were evaluated at baseline and weeks 4, 8, and 12 (or end of the study) via acne lesion counts and IGA of acne (0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe; 5=very severe). At weeks 4, 8, and 12, participants were evaluated on their disease improvement using the investigator global assessment of improvement from baseline (0=clear; 1=excellent

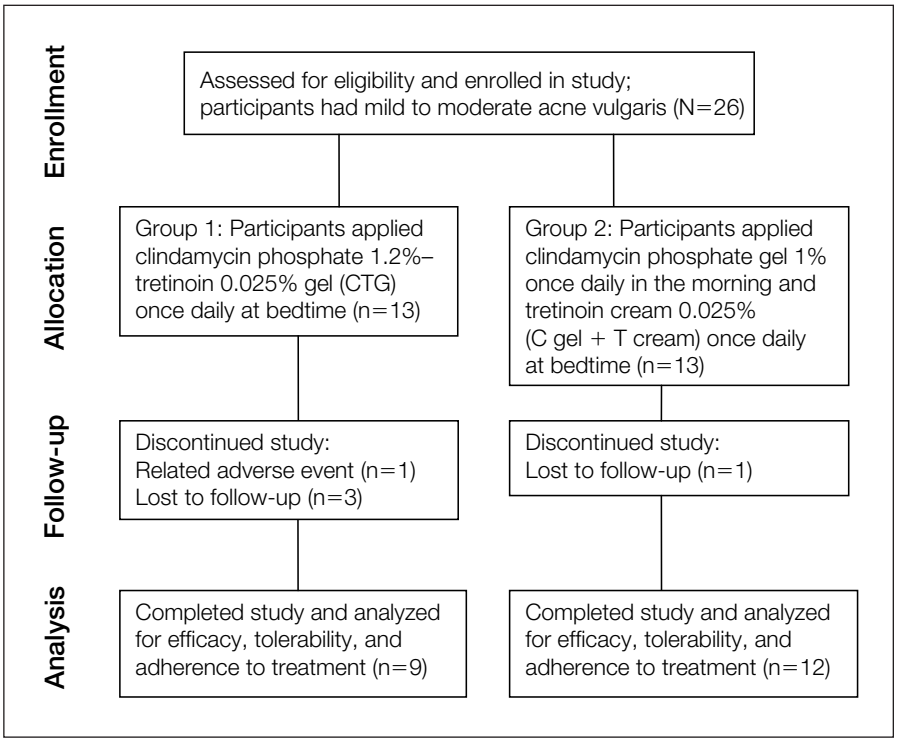

Figure 1. Consort flow diagram.

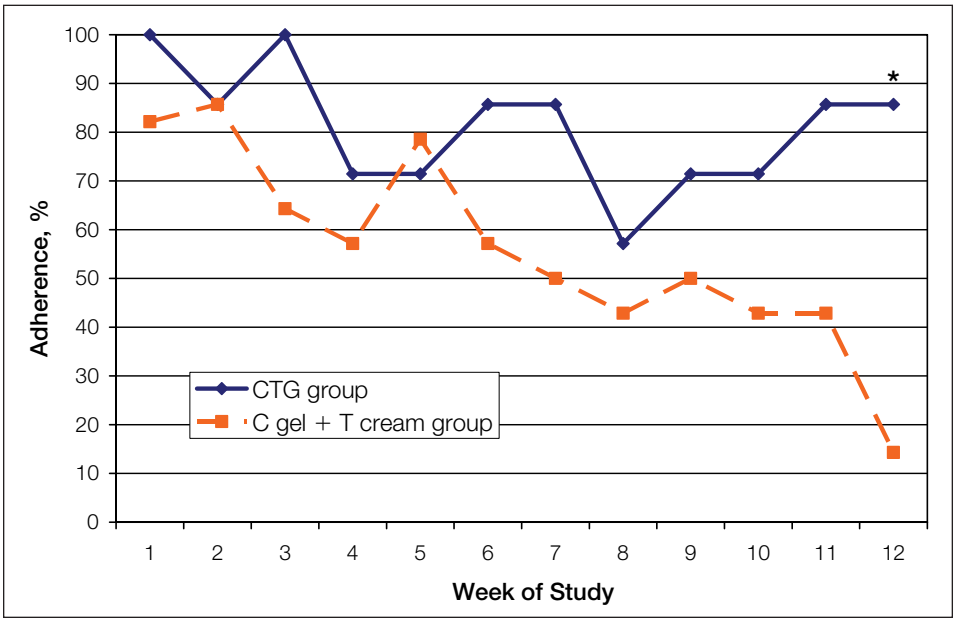

Figure 2. Median adherence over time. The median adherence in the clindamycin phosphate gel 1% and tretinoin cream 0.025% group (C gel + T cream) dropped significantly from week 1 to week 12 (P=.003). There was no statistically significant change in adherence in the clindamycin phosphate 1.2%–tretinoin 0.025% gel (CTG) group (P=.24). Asterisk indicates the difference in adherence between the 2 groups reached statistical significance at week 12 (P=.02).

improvement; 2=moderate improvement; 3=mild improvement; 4=no improvement; 5=worse).

Adherence to treatment was electronically monitored with Medication Event Monitoring System® (MEMS) caps that utilized a concealed microprocessor to record the dates and times when the medication was opened. Participants were not specifically informed about the use of the MEMS caps until the end of the study but were told to bring back medication tubes at each visit for the tubes to be "checked and redispensed." While the participants in group 2 were encouraged to apply the clindamycin in the morning and the tretinoin in the evening, all topical applications recorded by the MEMS cap each day were included in the adherence analysis (ie, 2 applications anytime during the day is equivalent to 100% adherence for that day).

All statistics were performed using SAS 9.1 software. Wilcoxon signed rank test was used to test for improvements in objective assessments from baseline to each return visit. Kruskal-Wallis and Wilcoxon rank sum tests were used to compare differences in outcomes between the groups.

Results

Of 26 participants who were enrolled, a total of 21 participants completed the 12-week study (Figure 1). Adherence ranged from 13% to 115% in the CTG group, and 8% to 95% in the C gel + T cream group. Median and mean adherence in the CTG group was 88% and 67%, respectively. Median and mean adherence in the C gel + T cream group was 61% and 53%, respectively. The difference in overall adherence between the study groups did not reach statistical significance (P=.12). However, at the week 12 assessment, a statistically significant difference in adherence was demonstrated (P=.02). Compliance with treatment was defined as 80% or more adherence; 6 of 9 (67%) participants in the CTG group were compliant, while only 1 of 12 (8%) participants in the C gel + T cream group were compliant.

The median adherence in the C gel + T cream group dropped from 82% at week 1 to 14% at week 12 (Figure 2); this change in adherence over time was statistically significant (P=.003). There was no statistically significant change in adherence in the CTG group (P=.24), with a median adherence of 100% at week 1 and 86% at week 12. While the CTG group appeared to have better adherence and outcomes compared with the C gel + T cream group, no statistically significant correlation was identified between adherence and outcome using linear regression models with percentage adherence as the independent variable and percentage improvement in clinical assessments as the dependent variable (P>.1).

Baseline severity (lesion count and IGA) was similar between the 2 study groups (Kruskal-Wallis test, P>.1). Only the CTG group had significant improvements from baseline to week 4 (noninflammatory and total lesion counts, P≤.05). With the exception of noninflammatory lesion counts in the C gel + T cream group, both groups had significant improvement from baseline in all assessments by week 12 (all P<.05).

Percentage Reduction in Lesion Counts From Baseline

	CTG Group				C Gel + T Cream Group				
Lesion Counts	No. of Participants	Mean	Median	95% CI	No. of Participants	Mean	Median	95% CI	Test Statistic[a]
Week 4									
Noninflammatory	9[b]	14%	14%	−11 to 40	13	−16%	19%	−60 to 27	.57
Inflammatory	9[b]	9%	36%	−60 to 79	13	−5%	25%	−57 to 47	.66
Total	9[b]	23%	19%	2 to 43	13	−9%	6%	−48 to 30	.42
Week 8									
Noninflammatory	8	17%	45%	−43 to 78	11	21%	35%	−32 to 74	1.0
Inflammatory	8	61%	71%	24 to 99	11	40%	56%	4 to 77	.41
Total	8	43%	54%	17 to 70	11	31%	46%	−2 to 65	.84
Week 12									
Noninflammatory	9	24%	52%	−48 to 96	12	8%	30%	−53 to 69	.52
Inflammatory	9	61%	73%	29 to 94	12	56%	63%	23 to 89	.97
Total	9	51%	47%	23 to 80	12	32%	41%	−2 to 66	.43

Abbreviations: CTG, clindamcyin phosphate 1.2%–tretinoin 0.025% gel; C gel + T cream, clindamycin phosphate gel 1% and tretinoin cream 0.025%; CI, confidence interval.
[a]Kruskal-Wallis test for difference between groups.
[b]All assessments for week 4 for the CTG group were done on 9 participants; 4 participants were lost to follow-up or dropped before the return visit.

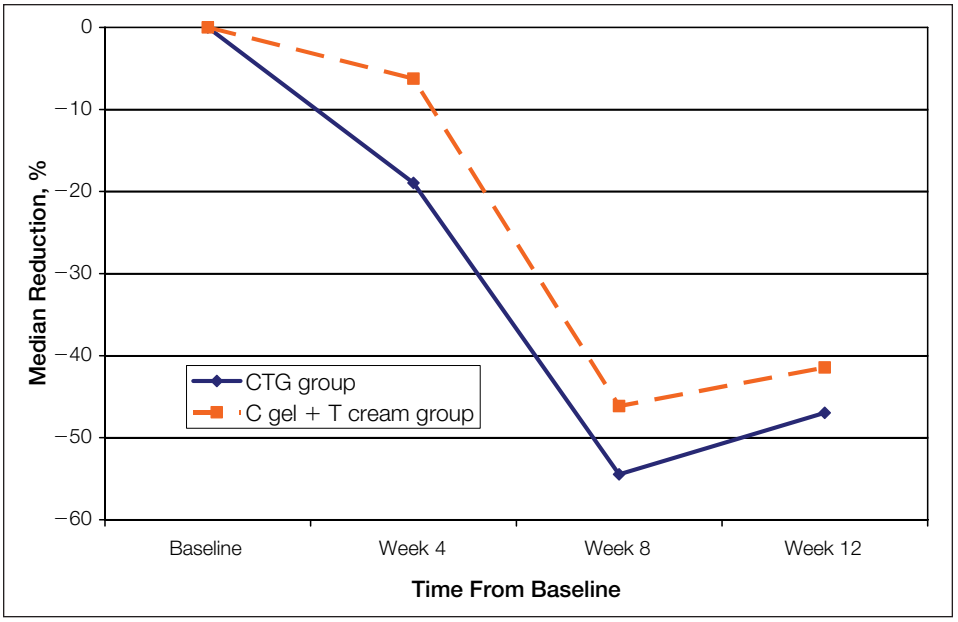

Figure 3. Median percentage reduction in total lesion counts over 12 weeks. There was a dramatic improvement in lesion counts for both study groups and a slightly better improvement with clindamycin phosphate 1.2%–tretinoin 0.025% gel (CTG). There was no statistically significant difference between the 2 groups. C gel + T cream indicates clindamycin phosphate gel 1% and tretinoin cream 0.025%.

Greater improvement was seen in participants in the CTG group compared with the C gel + T cream group in lesion counts from baseline to each time point (Figure 3). There was a 51% mean reduction in total lesions for the CTG group versus a 32% mean reduction for the C gel + T cream group by the end of the study (Table). Participants in the CTG group had greater mean and median percentage reduction in lesion counts; however, statistical significance was not reached when comparing the 2 groups. Both groups demonstrated moderate improvement (median investigator global assessment of improvement score of 2) by the end of the study.

Treatment in both groups was generally well-tolerated. One participant in the CTG group withdrew from the study because of burning on the face related to the medication. Other adverse events reported during the study included irritant contact dermatitis, gastroenteritis, shingles, and a staphylococcal infection, all of which were deemed by the investigators to be unrelated to treatment.

Comment

In the treatment of mild to moderate acne, topical therapy avoids the risks associated with systemic drug exposure. Although patients may be dissuaded from using topical tretinoin because of local irritation, tretinoin is an effective agent and first-line therapy for acne vulgaris.[6] Decreased irritation can be achieved by combining the use of clindamycin with tretinoin versus tretinoin alone.[5] Topical clindamycin has anti-inflammatory properties that may be responsible for the improved tolerability seen in combination with tretinoin.[7,8] Informing patients of potential side effects of topical retinoids also may help improve patient compliance, especially when patients understand the temporary nature of those side effects.[9,10]

Combination therapy for acne is more effective than monotherapy, and the evidence strongly supports the simultaneous use of topical clindamycin and tretinoin versus either therapy alone.[5,8,11,12] In the present study, the use of CTG once daily had greater efficacy and adherence in the treatment of mild to moderate acne versus the individual applications of clindamycin and tretinoin. The potential advantage of a topical combination formulation compared to the same 2 medications used concomitantly is two-fold: potentially greater adherence because of greater ease of use, and potentially greater efficacy because of greater adherence with both monotherapy agents.

While it may be possible to have patients mix the 2 generic monotherapy agents and use them in once daily applications, the efficacy and tolerability of this regimen is unknown. By mixing the generics in such a way, one may increase adherence to 2 active agents but also may dilute the concentration of each agent. Furthermore, data on the stability of each active ingredient after mixing with another vehicle are limited.

Poor adherence is a major factor in the lack of improvement seen in patients undergoing acne treatment.[1] A number of factors affect poor adherence;

they can be social or psychological, or relate to the therapy itself.[10] Most commonly, patients attribute their failure to use medication to frustration and forgetfulness.[13] A potential advantage of using a combination therapy for acne is the convenience of once daily application, which can improve medication use in patients who may not remember to apply it more than once daily.

Adherence to oral medications can be improved by reducing the complexity of treatment by decreasing the frequency of doses and administering fewer pills.[14,15] The same principle of simplifying treatment may be applied to topical medications. Correlation between poor adherence and medication responsiveness in patients treated for chronic skin conditions is becoming more apparent.[16] While our study was not designed to demonstrate a direct correlation of compliance and efficacy, it provides additional data to support the simplification of treatment regimens to encourage better adherence. While we did see a greater reduction of lesions with the use of CTG and an improved adherence to therapy, the correlation between the two did not reach statistical significance. However, the lack of a statistically significant correlation can be attributed to the small sample size and the tendency for patients whose disease has improved to reduce their use of treatment. Despite the limitation of small sample size, trends of greater improvement from baseline as well as superior adherence in the CTG group were large enough to be demonstrated.

This study provides valuable insight into the use of combined formulations of medication and how simplified regimens affect the actual use of the medication and the resulting efficacy. Increasing patient knowledge about the therapy and providing support is crucial to getting patients to comply with treatment. Expectation levels of patients often exceed what is clinically possible and physicians should be honest as to what results can be achieved with topical therapy, though our own expectations may be based on experiences in which patients were not fully adherent to treatment. Having patients participate in the decision-making process may reveal barriers to therapy, such as a busy lifestyle, that can be addressed by using combinations of agents in a single application medication.[3] By acknowledging factors that may inhibit consistent medication application, physicians may have greater success in the treatment of mild to moderate acne with topical medications.

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