DOI: https://doi.org/10.54393/pjhs.v7i6.4125

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 7, Issue 06 (June 2026)

Original Article

OPEN ACCESS

Efficacy and Safety of Topical Spironolactone Versus Topical Clindamycin in the Treatment of Acne Vulgaris: A Split-Face Study

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ARTICLE INFO

Keywords:
Acne Vulgaris, Topical Spironolactone, Topical Clindamycin, Global Acne Assessment Score

How to Cite:
Khan, A., Hanif, S., Shaukat, R., Hamadani, A., Kausar, I., Chattha, A. A., Nabi, H., Pavin, O., & Rao, B. (2026). Efficacy and Safety of Topical Spironolactone Versus Topical Clindamycin in the Treatment of Acne Vulgaris: A Split-Face Study: Topical Spironolactone Versus Topical Clindamycin in the Treatment of Acne Vulgaris. Pakistan Journal of Health Sciences, 7(6), 99-104. https://doi.org/10.54393/pjhs.v7i6.4125

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Received Date: 23rd February, 2026
1st Revision Received: 3rd April, 2026
2nd Revision Received: 11th April, 2026
Acceptance Date: 16th April, 2026
Published Date: 30th June, 2026

ABSTRACT

This study compares the effectiveness and safety of topical Spironolactone 5% versus topical Clindamycin 2% in treating acne vulgaris in the same patient. **Objective:** To assess the effectiveness and safety of topical spironolactone 5% versus topical clindamycin 2% in the treatment of mild to moderate acne vulgaris in the same patient through a controlled evaluation. **Methods:** A double-blind, split-face comparative study was conducted at the Department of Dermatology, Ghurki Trust Teaching Hospital (October 2023-September 2024). Participants used 5% Spironolactone on one side of the face and 2% Clindamycin on the other for 12 weeks. Both patients and the assessing dermatologist remained blind. Improvement was measured by Total Lesion Count, Acne Severity Index, and Global Acne Assessment Score (GAAS), with a GAAS score of 0 or 1 indicating treatment success. **Results:** Both therapies effectively reduced papules, pustules, and comedones in 42 participants over 12 weeks, achieving Total Lesion Count Reductions of approximately 77.5 % for topical Spironolactone and 79.2% for topical Clindamycin (p=0.877). Clindamycin demonstrated faster initial improvement in total lesion count at week 6 (p=0.043) and week 8 (p=0.012), but Spironolactone showed comparable improvement by Week 12; however, the difference was not statistically significant (p=0.057). Clindamycin reduced pustules more efficiently at Week 12 (p=0.007). **Conclusions:** Both topical spironolactone and clindamycin were effective in treating mild to moderate acne vulgaris. Clindamycin showed a quicker initial improvement, but both treatments had similar results after 12 weeks.

INTRODUCTION

Acne vulgaris is a recurrent inflammatory skin disorder that affects sebaceous glands and hair follicles [1]. Comedones, papules, pustules, nodules, and scars are its prominent features [2]. While the disease is thought to mostly affect adolescents and young adults, it can develop and persist long into adulthood [3, 4]. Around the world, 87% of adults suffer from acne vulgaris. Acne can significantly affect mental health and psychosocial growth [5]. The formation of acne involves a multifaceted process inside the pilosebaceous unit, incorporating numerous factors. These factors encompass hormonal balance alterations, excessive production of sebum, and changes in its composition and follicular hyperkeratinisation. The combination of these complex mechanisms leads to dysfunction in the pilosebaceous unit, facilitating the formation of microcomedones, which subsequently develop into non-inflammatory and inflammatory lesions [6]. Treatment options encompass topical retinoids (Isotretinoin, Tretinoin, Adapalene, Tazarotene), topical antibiotics (Clindamycin, Tetracycline, Erythromycin),

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systemic antibiotics (Azithromycin, Minocycline, Doxycycline, Tetracycline), systemic retinoids, and hormone therapy, based upon the degree of severity [7]. Resistance to antibiotics in acne presents a significant concern [8]. Anti-androgens appear to be an acceptable approach to the treatment of acne vulgaris because androgen hormones cause sebaceous gland hyperplasia and increased sebum production [9, 10]. As a result, several anti-androgen medications have been used for acne vulgaris, including Androgen Receptor Blockers (spironolactone, combined oral contraceptive pills, and topical clascoterone), Non-steroidal anti-androgens (flutamide), and 5 alpha reductase inhibitors (finasteride, dutasteride) [11]. Spironolactone exerts its effects via the following mechanisms: Androgen Receptor blockade acts as a competitive inhibitor of testosterone and dihydrotestosterone (DHT), blocking their binding. Suppression of 5 alpha reductase leads to reduced DHT formation, resulting in decreased size and activity of sebaceous glands. Side effects include menstrual irregularities, postural hypotension, and hyperkalaemia. Breast enlargement and alterations in libido are specific to males. Topical preparations can be utilized to obtain the benefits of their action while minimising significant side effects [12]. Clindamycin diminishes the development of acne lesions by inhibiting the growth of Cutibacterium acnes and preventing the synthesis of bacterial proteins [13].

Direct comparative studies between topical spironolactone and topical clindamycin in acne vulgaris are limited. While randomized controlled trials (RCTs) are the standard design for clinical trials, ethical and practical considerations make a non-randomized split-face design more achievable. This approach minimizes inter-individual variability, allows for direct within-patient comparisons, and ensures no patient is deprived of standard therapy. The current study used double-blinding and standardized application to limit biases that will improve clinical decision-making and acne management protocols. This study aimed to assess the effectiveness and safety of topical spironolactone 5% versus topical clindamycin 2% in the treatment of mild to moderate acne vulgaris in the same patient through a controlled evaluation.

METHODS

A double-blind split-face comparative study was conducted at the Department of Dermatology, Ghurki Trust Teaching Hospital, from October 2023 to September 2024 after taking ethical approval from the Institutional Review Board (LMDC/16989/23; dated 9th October 2023). A third party made both formulations and made sure they had the same color, texture, and smell. The participants and the dermatologist who was judging the treatment did not know which treatment was given to each person. The study protocol followed the Declaration of Helsinki's ethical guidelines and Good Clinical Practice (GCP) guidelines. Participants were selected using consecutive sampling from patients presenting to the department during the study duration. The study included 42 patients, aged 12-39 years, with mild to moderate acne vulgaris. Patients who had hypersensitivity to either clindamycin or spironolactone, Individuals who had used systemic or topical acne medications during the month before beginning therapy, pregnant or lactating women, and patients with nodulocystic acne were excluded from the study. All patients provided written informed consent before participating in the trial. The sample size was calculated by the WHO sample size calculator using a 95% confidence interval and 80% power of the study. The mean Acne severity index of the cases was taken from a previous study with (Group A) = 5.1 ± 5.3, the mean Acne severity index of the controls (Group B) = 7.7 ± 6.2 [14]. Acne lesions were evaluated by type (comedones, papules, pustules), number, and severity using the Global Acne Assessment Score (GAAS) and Acne Severity Index (ASI). Acne severity was assessed using the Global Acne Assessment Score (GAAS), a validated and widely used clinical grading tool with demonstrated reliability and applicability across different populations [15, 16]. Based on GAAS scores, patients were classified into mild, moderate, and severe. Photographic evaluation of the lesion was carried out at each visit with the patient's consent. The effectiveness of both treatments was determined by Total Lesion Count, GAAS, and ASI, and it was evaluated biweekly at 2,4,6,8 and 12 weeks by a single investigator who is blinded to the treatment allocation. The formulations of the study creams were as follows: 5% Spironolactne Cream: Spironolactone 5%, cetyl alcohol 1.5%, croda wax 10%, polawax 3%, glycerine 5%, propylene glycol 5%, white soft paraffin 10%, phenoxyethanol 1%, lactic acid 2%, methylparaben 0.2%, propyl paraben 0.02%, reverse osmosis water to 100g. 2% Clindamycin Cream: Clindamycin phosphate 2%, cetostearyl alcohol 2%, pola wax 5%, 2-phenoxy ethanol 1%, liquid paraffin 5%, white soft paraffin 20%, reverse osmosis water to 100g. To ensure blinding, both study formulations were prepared by a third party that was independent and standardized to match in colour, texture, and Odor. The creams were poured into identical coded containers, which allowed neither the participants nor the assessing dermatologist to identify which cream was used. The outcome assessor was not aware of treatment assignment during the study period. A simple randomization method (a coin toss) was used to decide which side of the face would get treatment. Spironolactone went to one side and clindamycin went to the other. Patients were directed to cleanse their face with a mild

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cleanser, gently pat it dry, and apply an equal number of designated creams to each side of the face twice daily. To minimize cross-contamination, participants were given directions to clean their hands between applications. Treatment adherence was assessed through patient self-reporting and verification of medication usage at each follow-up visit. Clinical evaluations were conducted biweekly over the 12 weeks. The patients were instructed to discontinue medication after 12 weeks and undergo re-evaluation after one month to check for relapse. Acne Severity Index (ASI) was calculated using the following formula: ASI=papules+(2×pustules)+(comedones/2)[16]. Participants with a GAAS score of 0 (none) or 1 (minimal) will be classified as having achieved "success". Side effects were also noted at each follow-up visit. At the conclusion of the follow-up period, participants rated their satisfaction level by using a 4-point scale: 1 = Excellent (very satisfied), 2 = Good (moderately satisfied), 3 = Fair (slightly satisfied), and 4 = Poor (not satisfied). The Global Acne Grading System (GAGS) was initially created in 19973. The GAGS breaks the face (forehead, each cheek, nose, and chin) into six parts, and the severity of each area is rated on a scale of 0 to 4 (0, there are no lesions; 1, comedones; 2, papules; 3, pustules; and 4, nodules). The sum of the six zones is then added, and the severity of acne is determined as mild (118), moderate (1930), severe (3138), and very severe (>39) [15]. The primary outcome of the study was a reduction in total lesion count, while secondary outcomes included changes in Acne Severity Index (ASI), Global Acne Assessment Score (GAAS), patient satisfaction, side effects, and relapse.

Data were analysed using SPSS version 27.0. Qualitative variables were represented as numbers and percentages, whereas quantitative data were presented as mean ± standard deviation (SD). The Wilcoxon signed rank test was used for comparison between the spironolactone-treated side and the clindamycin-treated side at each follow-up visit. The Kolmogorov-Smirnov test was applied to check the normality of data and found that p-values were <0.005, so non-parametric testing was applied. As it was a split-face study, the Wilcoxon test was used for comparison. All p-values less than 0.005 were considered statistically significant.

RESULTS

In this study with 42 participants, 85.7% were female, 90.5% were between the ages of 18 and 29, and 71.4% were unmarried. All participants were non-smokers, with 14.3% having comorbidities. Disease duration exhibited variability: 45.2% experienced it for 6 to 12 months, 35.7% for three to six months, and 19% for more than one year. All participants completed the study and were included in the final analysis, with no dropouts reported. At baseline, there was no statistically significant difference between the two treatment groups regarding papules, pustules, comedones, total lesion count, and Acne Severity Index ($p>0.005$), indicating similar initial conditions. By week 12, no significant difference in total lesion count (TLC) was observed between the treatments ($p=0.877$), suggesting comparable long-term effectiveness. The comparison of lesion counts and ASI between the two treatments. The Acne Severity Index ASI was comparable between the groups (spironolactone 17.06 ± 2.66 versus clindamycin: 18.02 ± 2.68, $p=0.103$). Both treatments resulted in a decrease in ASI over time, with clindamycin demonstrating significantly greater reductions starting from week 6 ($p<0.005$). However, at week 12, clindamycin demonstrated a lower ASI (3.43 ± 2.26) in comparison to spironolactone (4.50 ± 1.63, $p=0.014$). The magnitude of this difference was small, suggesting limited clinical significance despite statistical significance (Table 1).

Table 1: Comparative Clinical Profile of Patients from Baseline to 12 weeks Between Treatment with Topical Spironolactone and Topical Clindamycin (Split face n=42)

Parameters	Visit (Weeks)	Spironolactone, (Mean ± SD)	Clindamycin, (Mean ± SD)	p-value
Papules	0	6.71 ± 2.08	7.07 ± 1.80	0.398
	2	5.50 ± 1.77	5.24 ± 1.39	0.456
	4	4.24 ± 1.72	3.12 ± 1.02	<0.001
	6	3.29 ± 1.64	1.98 ± 0.84	<0.001
	8	2.60 ± 1.71	1.36 ± 1.08	<0.001
	12	1.50 ± 1.37	0.98 ± 1.09	0.058
Pustules	0	1.93 ± 1.20	2.19 ± 1.19	0.322
	2	1.86 ± 1.16	2.05 ± 1.25	0.468
	4	1.55 ± 0.99	1.60 ± 1.01	0.819
	6	1.40 ± 0.99	1.31 ± 0.98	0.677
	8	1.17 ± 0.88	0.76 ± 0.82	0.030
	12	0.88 ± 0.74	0.38 ± 0.54	<0.001
Comedones	0	12.98 ± 2.91	13.14 ± 2.51	0.788
	2	10.90 ± 3.09	10.45 ± 3.27	0.519
	4	8.98 ± 3.65	8.83 ± 3.20	0.842
	6	7.12 ± 3.26	7.00 ± 3.16	0.884
	8	4.93 ± 3.11	4.74 ± 3.06	0.779
	12	2.48 ± 2.55	3.38 ± 2.58	0.112
Total Lesion Count	0	21.62 ± 3.41	22.40 ± 2.34	0.225
	2	18.26 ± 3.40	17.74 ± 3.53	0.494
	4	14.76 ± 3.41	13.55 ± 3.39	0.107
	6	11.81 ± 3.30	10.29 ± 3.47	0.043
	8	8.69 ± 2.92	6.86 ± 3.59	0.012
	12	4.83 ± 2.34	4.74 ± 2.95	0.877
Acne Severity Index (ASI)	0	17.06 ± 2.66	18.02 ± 2.68	0.103
	2	14.67 ± 2.67	14.56 ± 3.19	0.864
	4	11.82 ± 2.19	10.73 ± 2.85	0.053
	6	9.65 ± 2.26	8.10 ± 2.83	0.007
	8	7.39 ± 2.02	5.25 ± 5.06	0.014
	12	4.50 ± 1.63	3.43 ± 2.26	0.015

Both spironolactone and clindamycin therapies

DOI: https://doi.org/10.54393/pjhs.v7i6.4125

significantly decreased the presence of papules, pustules, and comedones; however, Clindamycin demonstrated faster initial improvement in total lesion count at week 6 (p=0.043) and week 8 (p=0.012). The reduction in lesion count over time for both treatments is shown (Figure 1).

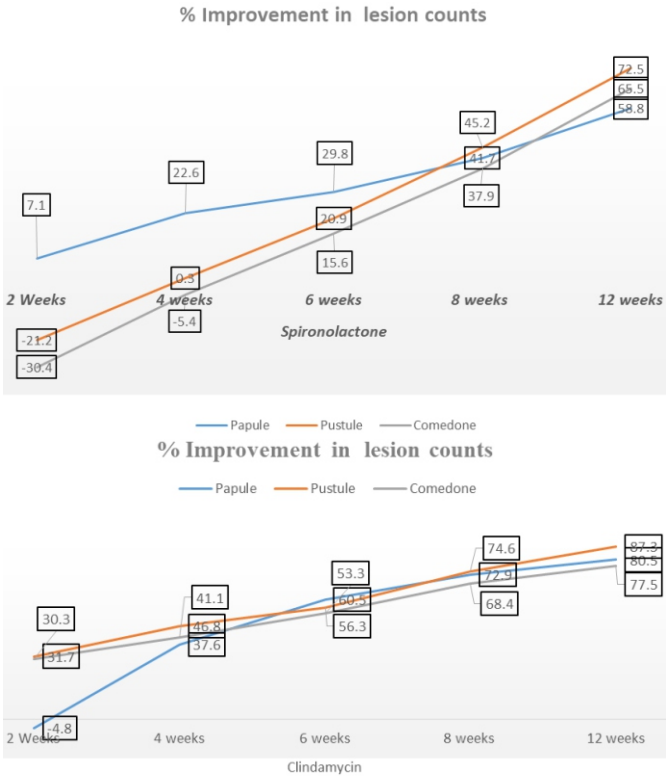

Figure 1: Improvement in Lesion Count in the Spironolactone Side and Clindamycin Side from Baseline to 12 Weeks

The two treatments demonstrated progressive improvements. None of the patients succeeded during baseline and week 2. By week 6, there were equal success rates (7.1% each). Clindamycin demonstrated a quicker response at week 8 (45.2% vs 19.0%). But by week 12, the two treatments showed similar effectiveness, with clindamycin and spironolactone success rates of 81.0 and 78.6, respectively (Table 2).

Table 2: Comparison of the Number of Patients Who Achieved Success on the Global Acne Assessment Score

Visit (Weeks)	Spironolactone Success, n (%)	Spironolactone Failure, n (%)	Clindamycin Success, n (%)	Clindamycin Failure, n (%)
0	0 (0%)	42 (100%)	0 (0%)	42 (100%)
2	0 (0%)	42 (100%)	0 (0%)	42 (100%)
4	0 (0%)	42 (100%)	1 (2.4%)	41 (97.6%)
6	3 (7.1%)	39 (92.9%)	3 (7.1%)	39 (92.9%)
8	8 (19.0%)	34 (81.0%)	19 (45.2%)	23 (54.8%)
12	33 (78.6%)	9 (21.4%)	34 (81.0%)	8 (19.0%)

The Global Acne Assessment Score indicates that the success rates for both groups were similar at week 12. The treatment success based on GAAS at each follow-up visit is presented, with 33 of 42 individuals in the spironolactone group attaining success (78.6%) and 34 of 42 participants in the clindamycin group achieving success (81.0%). This shows that both therapies were equally successful in reaching success by the conclusion of the study even though clindamycin exhibited faster improvement early. Both treatments were generally well tolerated, with only mild side effects reported during the study period. The difference in treatment success between the two sides was minimal and appeared comparable at week 12 (Figure 2).

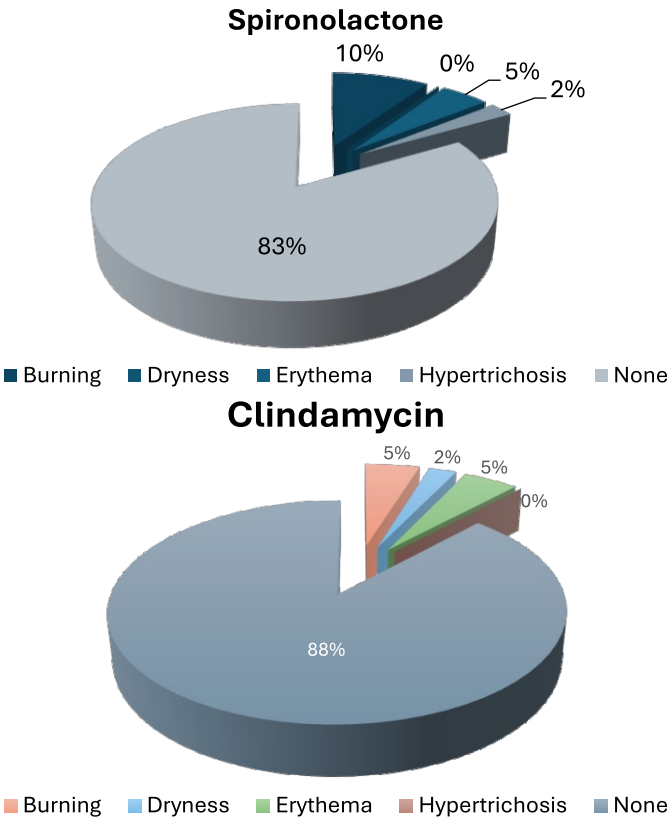

Figure 2: Side Effects Observed During Study

Patient satisfaction was high in both treatment groups, with most participants reporting good to excellent outcomes. The distribution of patient satisfaction scores is presented (Figure 3).

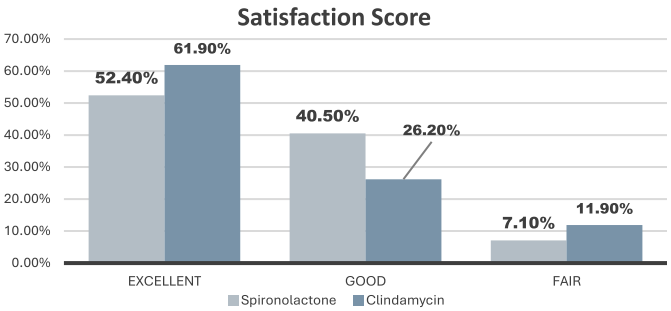

Figure 3: Patient Satisfaction Score of Spironolactone and Clindamycin

Before and after, the picture of the spironolactone side effects was shown (Figure 4).

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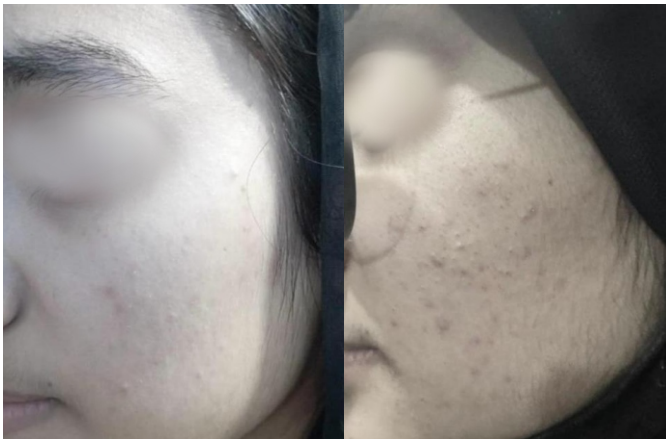

Figure 4: Before and After Pictures of the Patient (Spironolactone Side)

DISCUSSION

This study demonstrated that both topical spironolactone 5% and clindamycin 2% are effective in reducing acne severity, with comparable outcomes at 12 weeks, although clindamycin showed a relatively faster onset of action. These results are in line with the emerging evidence of the topical spironolactone being an effective anti-androgen therapy. The clinical efficacy of topical spironolactone formulations has been recently documented by significant decreases in the Acnes Severity Index (ASI) and total lesion count (TLC), which validates its use [17]. But these comparisons are to be approached with caution because of variations in formulation, study design, and severity of baseline. The effectiveness of topical clindamycin we observed is in line with the previous literature showing that it is effective in the treatment of inflammatory lesions, especially papules and pustules [18]. But its slower and less prolonged action in later weeks than spironolactone may indicate its dominance as an antibacterial agent and not an action on the hormonal part of acne. Importantly, comparisons in this discussion are restricted to topical therapies with similar routes of administration to ensure methodological consistency. Although oral spironolactone is effective in moderate-severe acne, these results cannot be directly compared because they vary in systemic exposure and pharmacokinetics [19]. Conversely, topical spironolactone, with its localized anti-androgenic effect and low systemic absorption, is a factor in its good safety profile. The growing importance of topical antiandrogenic treatments, such as spironolactone and clascoterone, in the management of acne has also been noted in the recent literature. These agents have shown considerable decreases in inflammatory and non-inflammatory lesions, and are better tolerated than systemic treatments [20]. This justifies the topical spironolactone use over prolonged use of antibiotics, especially given the current trend of increasing antimicrobial resistance. In terms of safety, the localized adverse effects that were mild and registered in our study are in line with other reports that suggest that topical spironolactone is well tolerated [17]. On the contrary, adverse effects of systemic spironolactone have been reported to include menstrual abnormalities and dizziness, further highlighting the safety benefit of topical preparations [19].

This research has a number of weaknesses. Small sample size and single-center design could limit generalizability. The use of mild to moderate acne only limits the generalizability to severe cases, and the duration of the follow-up does not allow evaluation of long-term effectiveness and relapse. Though the split-face design minimizes inter-individual variability, there is still a risk of cross-contamination. Also, possible confounders like hormonal status, diet, use of cosmetic and menstrual variations were not controlled, and no subgrouping based on age or gender was done. According to these gaps, future research ought to be performed on larger multicenter randomized trials with longer follow-up and including severe acne.

CONCLUSIONS

Both topical spironolactone 5% and clindamycin 2% showed considerable clinical improvement over 12 weeks in the severity of acne. Clindamycin exhibited a more rapid action and was more successful in weeks 6 and 8, but at week 12, the two treatments had similar efficacy. Spironolactone was found to have significant decreases in both lesion counts and severity indices, suggesting the agent as an effective topical antandrogen agent. Both interventions were tolerated well, and there were minimal localized adverse effects noted.

Authors' Contribution

Conceptualization: AK
Methodology: SH, RS, AH
Formal analysis: AH, HN
Writing and Drafting: AK, SH, RS, AH, IK, AAC, HN, OP, BR
Review and Editing: AK, SH, RS, AH, IK, AAC, HN, OP, BR

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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