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Is Spironolactone an Effective Method for Reducing Lesion Count in Individuals With Acne Vulgaris?

Alana M. Waters
Philadelphia College of Osteopathic Medicine

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Alana M. Waters, PA-S

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Is spironolactone an effective method for reducing lesion count in individuals with acne vulgaris?"

STUDY DESIGN: A systematic review of three English language studies published after 2009 in peer-reviewed journals, including two randomized, controlled trials and one retrospective cohort study.

DATA SOURCES: Two randomized, controlled trials and one retrospective cohort study that evaluated spironolactone as a treatment for acne vulgaris were found using PubMed.

OUTCOMES MEASURED: Reductions in total lesion counts (TLC).

RESULTS: All three studies supported the efficacy of spironolactone in reducing lesion counts in individuals with acne vulgaris. Kelidari et al. (*Colloid Surface B*. 2016;146:47-53. doi:10.1016/j.colsurfb.2016.05.042) demonstrated a significant reduction in total lesion counts in both groups treated with spironolactone between baseline and week 8, with a p-value < 0.001. Afzali et al. (*J Dermatol Treat*. 2012;23(1):21-25. doi:10.3109/09546634.2010.488260) showed a significant difference between the case and control groups with p-value = 0.007, reflecting the efficacy of spironolactone in reducing total lesion count. The retrospective cohort study by Isvy-Joubert et al. (*Eur J Dermatol*. 2017;27(4):393-398. doi:10.1684/ejd.2017.3062) exhibited that 71% of patients treated with spironolactone for acne vulgaris experienced reduction in lesion counts.

CONCLUSIONS: The results of the randomized, controlled trials and retrospective cohort study indicate that spironolactone is effective in reducing lesion counts in individuals with acne.

KEY WORDS: Acne, Spironolactone, Aldactone.

INTRODUCTION

Acne vulgaris is a very common dermatologic condition affecting individuals of all ages. It is a disease process of the pilosebaceous gland, characterized by hyperseborrhea, noninflammatory lesions (comedones), and inflammatory lesions, which include papules, pustules, nodules, and cysts. The chronic nature of acne vulgaris poses physical, psychological, and economic implications, both to the individual suffering and society at large.

Acne vulgaris is the most common skin condition diagnosed by dermatologists and is frequently encountered in other areas of medicine such as pediatrics and primary care.[1] Extensive data reflect the universality of acne, revealing that 40-50 million people in the U.S. and 80% of individuals between the ages of 11 and 30 suffer with acne.[2,3] In addition to being widespread in society, acne often persists into late adolescence and adulthood: 64% and 42% of individuals have unremitting acne into their 20s and 30s, respectively.[1] Furthermore, the prevalence of both early onset and late adult acne is increasing, likely due to earlier onset of puberty.[2,4]

This condition has grave socioeconomic and psychological consequences. Severe acne is associated with rising rates of anxiety, suicidal ideation and unemployment.[2,3] A particular study concluded that acne patients were two to three times more likely to experience depression, reporting an 8.8% prevalence of clinically diagnosed depression in the sample population of acne patients.[3] It is estimated that over 2 billion dollars and over 5 million health care visits are dedicated to the management of acne each year in the U.S.[1]

The pathophysiology of acne is complex and multifactorial, involving both genetic and environmental factors. Acne is the result of the interactions between bacteria, inflammation, and a rise in hormones during puberty.[1,5] This surge of androgens provokes abnormal differentiation of follicular cells, development of hyperkeratotic plugs, and increased sebum production,

followed by the overgrowth of the bacteria *Propionibacterium acnes (P. acnes)*.[1] It is well known that acne is genetically inherited, occurring more commonly and more severely in those who have first-degree relatives with a history of acne.[1,2] While studies link dairy intake and cigarettes with increased acne risk, they fail to identify the highly debated roles of UV light and chocolate.[1]

Treatment regimens are individualized to each patient, usually consisting of some combination of topical or oral antimicrobials, topical retinoids, salicylic acid, benzoyl peroxide, oral contraceptives, and isotretinoin in severe and refractory cases.[1] Treatment should also incorporate patient counseling in proper hygiene and recommendation of skincare products, such as cleansers, moisturizers, and makeup.[1]

Although its specific role in acne remains unclear, *P. acnes* is often the target of acne treatment, through the use of antimicrobials such as sulfonamides, macrolides, tetracyclines, and dapsone.[1] However, the development of bacterial resistance via biofilms threatens the efficacy of this treatment option.[2] Although highly effective in reducing sebum production and treating acne, isotretinoin poses the risks of teratogenicity, altered mood, and hypertriglyceridemia.[2] These issues with current treatment options propose a need for further research into alternative acne treatments.

The aforementioned treatment options are supported only by limited scientific evidence and often require numerous adjustments to achieve success.[2] Several research studies have demonstrated the efficacy of spironolactone, which targets the excess of androgens associated with acne by competitively inhibiting dihydrotestosterone at the androgen receptor.[4] This paper evaluates two randomized control trials (RCT) and one retrospective cohort study evaluating the efficacy of spironolactone as a method for reducing lesion counts in patients with acne vulgaris.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is spironolactone an effective method for reducing lesion count in individuals with acne vulgaris?"

METHODS

The three studies in this review were researched through PubMed using keywords "acne," "spironolactone," and "Aldactone." All articles were published in English in peer-reviewed journals after 2009. Articles were selected by the author based on relevance to the clinical question and patient-centered outcomes, including studies published after 2009 with a primary research design. Studies published prior to 2009 were excluded from this systematic review. Statistics utilized in the three studies to evaluate outcomes include p-values and mean change from baseline. Table 1 illustrates the demographics and characteristics of each study.

Two double-blind, randomized controlled trials and one retrospective cohort study were included in this systematic review. Selection criteria included population, intervention, comparison, and patient-centered outcomes measured. The population studied consisted of both male and female patients over the age of 8 years with acne vulgaris. The intervention studied was spironolactone, either oral or topical preparation, compared to the control group who received either placebo or a different dose of spironolactone. Isvy-Joubert et al. investigated outcomes in a sample of women treated with low dose spironolactone (< 150 mg/day) for six months through a retrospective cohort study.[4] The subjects of Kelidari et al. were treated for 8 weeks with either 10 mg spironolactone in a nanostructured lipid carrier (SP-NLC 1%) or 50 mg spironolactone in an alcohol gel (SP-ALC 5%).[5] The participants in the study conducted by Afzali et al. either received topical 5% spironolactone gel or a placebo gel, applied twice a day for 6 weeks.[6] The efficacy of spironolactone was measured based on the reduction in total lesion counts.

Table 1. Demographics & Characteristics of included studies

Study	Type	# Pts.	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Isvy-Joubert[4] (2017)	Retrospective Cohort Study	70	> 20	-Adult women with acne on the face or back -Minimum age of 20 years -Treated with spironolactone (<150 mg/day) between January 2010 and January 2015	-Women with hidradenitis suppurativa and rosacea who concomitantly received anti-androgens.	0	Low dose (<150 mg/day) oral spironolactone
Kelidari[5] (2016)	RCT	76	8-38	-Patients with mild to moderate acne, 8 years or older, defined as a score of 1-30 on the Global Acne Grading System (GAGS) scale who were not satisfied with their previous acne therapy	-Pregnant patients, patients planning to become pregnant, lactating patients, patients with skin diseases that might interfere with diagnosis or evaluation of their hyperpigmentation.	16	10 mg spironolactone loaded nanostructured lipid carrier gel VS. 50 mg spironolactone loaded alcohol gel
Afzali[6] (2012)	RCT	78	11-30	-Patients with mild to moderate acne vulgaris	-Patients with a background of systemic disease, pregnant or lactating, or who had taken anti-acne antibiotics or hormone medications in the last 3 months.	16	5% spironolactone topical gel vs. topical placebo gel

OUTCOMES MEASURED

The three studies measured the outcome of the intervention based on the total lesion counts, which is the summary of comedones, papules, and pustules.[6] Kelidari et al. assessed changes in facial lesion counts based on number, type, and distribution at 0, 2, 4, and 8 weeks.[5] Afzali et al. also evaluated changes in total lesion counts at 2-week intervals up to 6 weeks.[6] Both Kelidari et al. and Afzali et al. calculated change in lesion counts from baseline in order to evaluate the efficacy of spironolactone, using a p-value < 0.05 to establish clinical significance.[5,6]

Isvy-Joubert et al. examined data of women treated with spironolactone between January 2010 and 2015, measuring outcomes based on the lesion count of superficial inflammatory lesions (papules and pustules) and retentional lesions (open and closed comedones) on the face, back, neck, and breast after six months of treatment.[4] Good clinical response was defined as ≤ 2 superficial inflammatory lesions on the face and ≤ 5 retentional lesions after six months of treatment.[4]

RESULTS

This systematic review analyzed two randomized, double-blind, controlled trials and one retrospective cohort study to determine the efficacy of spironolactone in reducing lesion counts in individuals with acne vulgaris. Both Kelidari et al. and Afzali et al. studied patients of all ages with mild to moderate acne, excluding patients who were pregnant, lactating, or planning to become pregnant.[5,6] Kelidari et al. excluded patients suffering from any other skin disease that might interfere with the biweekly skin assessments completed to measure the effect of spironolactone on acne.[5] Afzali et al. excluded individuals who had taken antibiotics or hormone medications in the last 3 months, as these may have had an impact on their acne.[6] Isvy-Joubert et

al. studied adult women over the age of 20 with mild to severe acne, excluding those with hidradenitis suppurativa or rosacea, as they may have been treated with anti-androgens for those conditions.[4]

Isvy-Joubert et al. analyzed the data of 70 adult women aged 20-34 years with acne who were treated with low dose (<150 mg/day) spironolactone between January 2010 and 2015.[4] At the initiation of spironolactone, the participants' acne was classified by the number of inflammatory lesions: 76% had mild acne (<10 lesions), 17% had moderate acne (10-20 lesions), and 7% had severe acne (>20 lesions).[4] Lesion counts were assessed at initial prescription of spironolactone and at routine follow-up visits at 3-4 months, 6-8 months, and then every 6 months.[4] Remission was characterized by the presence of ≤ 2 superficial inflammatory lesions and ≤ 5 retentional lesions after six months of treatment.[4] Based on the collected data, a remission analysis was conducted on 52 women to evaluate the efficacy of spironolactone in reducing their lesion counts.[4] Of these women, 71% (n=47) were characterized as successful treatments based on the remission criteria previously mentioned.[4]

Table 2. Mean lesion counts from baseline to 6 months.[4]

	Baseline	6 Months	% Reduction
Facial Inflammatory Superficial Lesions	8	2.5	68.75%
Facial Retentional Lesions	8.5	2.75	67.65%

Kelidari et al. conducted a randomized, double-blind, controlled trial on 76 patients aged 8-38 years with mild to moderate acne.[5] Group A received 10 mg spironolactone-loaded nanostructured lipid carrier gel (SP-NLC 1%), while group B received 50 mg spironolactone loaded alcohol gel (SP-ALC 5%).[5] Both groups were instructed to wash their face, apply a 2 cm amount of the gel each morning and evening, then massage for two minutes, and finally wash the

gel off after 2-3 hours.[5] Facial lesion counts were assessed based on number, type, and distribution at 0, 2, 4 and 8 weeks.[5] In total, 16 patients withdrew from the study due to personal reasons or allergies.[5] There was a statistically significant decrease in total lesion counts between baseline and week 8 for both groups A and B, with $p < 0.001$.[5] The administration of SP-NLC 1% in group A yielded a 47.18% reduction in TLC with p-value = 0.003.[5] For group B, who received SP-ALC 5%, there was a 43.77% reduction in TLC with p-value = 0.022.[5] These data are illustrated in further detail in Table 3 below.

Table 3. Mean change in TLC from baseline to 8 weeks.[5]

	Mean TLC at Baseline (± SD)	Mean TLC at Week 8 (±SD)	Mean Change from Baseline	% Reduction in TLC	p-values
Group A	37.165 ± 9.28	19.63 ± 6.36	17.54	47.18%	P = 0.003
Group B	32.60 ± 9.32	18.33 ± 5.56	14.27	43.77%	P = 0.022

Afzali et al. conducted a randomized, double-blind, placebo controlled trial on 78 patients aged 11-30 years with mild to moderate acne.[6] The case group received a topical gel containing 5% spironolactone, while the control group received a topical placebo gel of similar formulation without spironolactone.[6] Both groups were instructed to apply the gel twice per day and wash off after 2-3 hours.[6] Total lesion counts were assessed every 2 weeks up to 6 weeks, based on number, type, and distribution.[6] There was a statistically significant difference in total lesion counts between the two groups at week 6, with p-value = 0.007.[6] There was a 71% reduction in the TLC from baseline in the case group, with a $p\text{-value} < 0.01$.[6] The control group experienced a 36.02% reduction in the TLC from baseline, with a $p\text{-value} < 0.01$.[6] These results are displayed below in Table 4 in more detail.

Table 4. Mean change in TLC from baseline to 6 weeks.[6]

	Mean TLC at Baseline (±SD)	Mean TLC at Week 6 (±SD)	Mean Change from Baseline	% Reduction in TLC	p-values
Case Group	17.5 ± 11.4	5.1 ± 4.7	12.4	71.0%	P < 0.01
Control Group	15.7 ± 12.9	10.0 ± 6.5	5.7	36.02%	P < 0.01

In the retrospective cohort study conducted by Isvy-Joubert et al., 24% of patients reported treatment-related side effects, including menstrual irregularities, cramps, and low blood pressure.[4] While Kelidari et al. reported that there were no serious adverse events related to treatment with spironolactone, they documented complaints of dryness and itchiness from participants.[5] Among the control group in Afzali et al., 11.1% of patients complained of pigmentation at the treatment site and 8.3% showed scaling, while none of the patients in the case group reported either of these side effects.[6] Additionally, 9.1% of the case group and 13.9% of the control group developed erythema during this trial.[6]

DISCUSSION

Spironolactone, known by the brand name Aldactone, is approved by the FDA for use in primary aldosteronism, congestive heart failure, cirrhosis of the liver, nephrotic syndrome, essential hypertension, and hypokalemia.[7] Off-label uses include acne vulgaris, hirsutism, and hormone therapy for transgender females.[8] Although spironolactone has been increasingly used in the treatment of acne for the past 30 years, the limited number of existing controlled trials as well as the small sample size of published studies provide insufficient data supporting its clinical efficacy.[9,10] Despite this, the American Academy of Dermatology states: "the work group supports the use of spironolactone in the management of acne in select women."[10] Furthermore, the severe side effects associated with isotretinoin and the growing development of antibiotic resistance justify the urgent need for further research of alternative acne treatments.[9]

The reluctance of the FDA to approve spironolactone for the treatment of acne is warranted by the black box warning, which states "Aldactone has been shown to be a tumorigen in chronic toxicity studies in rats. Aldactone should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided." [7] However,

researchers question the authority and validity of this warning, arguing that the rats in the studies were given a dose of spironolactone 100-150 times greater than doses given in clinical practice to treat individuals for acne.[9] Additionally, a recent retrospective cohort study published confounding evidence, establishing that there was no association found between spironolactone and breast cancer among the 1.29 million women who participated in the study.[10] These findings are crucial in the recognition of spironolactone as a viable and safe treatment option for acne vulgaris.

The apprehension associated with spironolactone due to the black box warning is only intensified by the potential teratogenicity and contraindications of this drug. Spironolactone is contraindicated for patients with hyperkalemia, acute renal insufficiency, severe renal impairment, Addison disease, anuria, pregnancy, breastfeeding, and concurrent use of eplerenone or heparin.[7,8] Spironolactone is pregnancy category C, which indicates that despite the existence of animal studies showing adverse effects on the fetus, the potential benefit of spironolactone may warrant use in pregnant women.[7] Animal reproduction studies yielded variable results: no teratogenicity or embryotoxicity was found in mice, while feminization of male fetuses was seen in rats.[7] While there is also possibility of sex differentiation of male embryos in humans due to anti-androgenic activity, the FDA maintains that spironolactone may be used in pregnant women if the benefit outweighs the risk to the fetus.[7]

The studies included in this systemic review demonstrated the efficacy of spironolactone in reducing total lesion counts in acne vulgaris, as well as the relative safety of this treatment option. Isvy-Joubert et al. concluded that 71% of patients treated with spironolactone for acne vulgaris displayed a good clinical response based on established criteria.[4] Kelidari et al. exhibited a statistically significant reduction in total lesion counts in both groups treated with

spironolactone compared to baseline.[5] The case group in the study conducted by Afzali et al. displayed a significant improvement in total lesion count compared to the control group.[6] Isvy-Joubert et al. focuses on the population of adult women who experience hormone-related acne that is persistent through adulthood and flares up prior to menstruation, attributing the efficacy of spironolactone in these women to the hypersensitivity of their androgen receptors.[4] However, research by Barbieri et al. emphasizes the effectiveness of spironolactone in women of all ages, while Afzali et al. and Kelidari et al. demonstrate the value of spironolactone in both males and females.[5,6,9] Isvy-Joubert et al. published data identifying the number of inflammatory superficial lesions and the concurrent usage of third and fourth generation oral contraceptives as positive predictors of successful treatment response with spironolactone.[4] This new information may aid clinicians when selecting candidates suitable for spironolactone therapy in the future.

The limited inventory of recent research on the treatment of acne with spironolactone made the compilation of this systematic review slightly challenging. The lack of randomization, blinding, and control group in the retrospective cohort study conducted by Isvy-Joubert partially discounts the credibility of the research, establishing only associations rather than cause and effect. Although Kelidari et al. utilized double-blind procedures, the limited sample size of 76 participants and the considerable dropout rate of 16 participants reduce the overall generalizability of this study.[5] Another factor that may have influenced the outcome of the study was the permitted use of non-medicated cosmetics throughout the trial, which may have affected the participants' skin condition.[5] There was also reason to question the generalizability of Afzali et al., with a sample size of only 78, a short duration of 6 weeks, and 16 patients lost to follow up.[6] Additionally, the alcohol content of both the placebo and spironolactone gel formulations administered to participants of this trial should be acknowledged as a possible contributor to the

reduced lesion counts.[6] Although these studies have limited generalizability due to low sample sizes and high dropout rates, the research is clinically relevant due to the diverse populations studied, including both females and males ranging in age from 8 to 52 years. Isvy-Joubert et al. identified multiple factors that may predict clinical response to spironolactone, such as concurrent use of oral contraceptives and number of inflammatory lesions at baseline.[4] Additionally, this research supports the efficacy of spironolactone as an alternative treatment option, specifically for patients who have failed other treatments such as antimicrobials, zinc, and isotretinoin.[4]

CONCLUSION

The three studies analyzed in this systematic review confirm that spironolactone is an effective method for reducing lesion counts in individuals with acne vulgaris. Despite small sample sizes and large dropout rates, the significant evidence established by Kelidari, Afzali, and Isvy-Joubert opens a window of opportunity to initiate further research into the approval and use of spironolactone as a first line agent for acne vulgaris. Future research is needed in the form of long-term, randomized, controlled trials studying the effects of both oral and topical spironolactone. Populations should consist of larger sample sizes including both females and males of all ages. With additional research into safety and efficacy, spironolactone could possibly replace oral antibiotics, which remain the most common systemic agent prescribed for acne treatment despite negative effects on the gut microbiome and the growing concern of antimicrobial resistance. [9]

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