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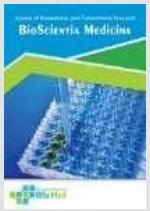

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Cross-Sectional Study of Efficacy, Effectiveness, and Safety of Combination Creams (Tretinoin 0.05%, Clindamycin 3%, and Dexamethasone 0.05%) Anti-Acne – An Online Study

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A B S T R A C T

Background: Acne vulgaris is a common skin condition that causes blackheads, whiteheads, and pimples. It is caused by a number of things, like too much oil, clogged pores, and inflammation. Topical combination creams are an alternative treatment for acne. They can help reduce inflammation, kill bacteria that cause acne, and stop the skin from making too much oil. Topical combination creams like retinoids, antibiotics, and steroids are all mixed together in a single cream or gel. This study talks about the effectiveness and side effects of using combination creams (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) to treat acne in the short and long term (local and systemic). **Methods:** This study is a survey that was done at the Sukma clinic with data from 2022 patients who were diagnosed with acne vulgaris. The survey was done on Google Forms, which is a website. In this study, different factors were looked at, such as demographics, efficacy (like reducing acne severity, making the skin brighter, getting rid of blackheads on the face, getting rid of acne scars, improving skin texture, hiding scars, minimizing facial pores, getting rid of wrinkles and dark spots), local adverse events (like burning, itching, stinging, eruptive papules, hypopigmentation, hyperpigmentation, erythema, scaling, and other), and systemic adverse events. **Results:** The results of this study show that a combination of tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05% is very effective and has minimal side effects. Local symptoms only show up during the first week of taking the drug (the "sensitization phase"), and then they tend to get less common over time. The only exceptions are hyperpigmentation and hypopigmentation, which show up later because they are caused by healing acne lesions. **Conclusion:** There was no direct link between the use of anti-acne combination cream drugs and the number of systemic side effects. This is because the patient had often had this happen before (constipation, GERD, and others).

1. Introduction

Acne is a relatively prevalent skin disorder in teenagers, although it can occur at any age, gender, or skin color. Acne is a skin disorder in which the hair follicles become blocked with oil, dead skin cells, and bacteria, causing inflammation. Acne can arise everywhere on the body, although it most commonly appears on the face, chest, and back.[1,2] Acne is the result of a complex interaction of genetic, hormonal, and environmental factors. The increased synthesis of androgen hormones during puberty might cause the oil glands under the skin to become more active. Overproduction of oil glands promotes oily skin, which can block pores and cause acne. The bacterium *Propionibacterium acnes* (*P. acnes*) may also contribute to acne formation.[3,4] Furthermore, environmental

factors such as pollution and stress can aggravate skin issues and lead to acne. Pollution can clog pores with dust particles and other debris, while stress can disrupt hormone levels and make skin oilier.[1–4]

Acne treatment options include topical combination creams, which can help reduce inflammation, kill acne-causing bacteria, and reduce oil production on the skin. Topical combination creams combine various types of medications, such as retinoids, antibiotics, and steroids, in a single cream or gel.[5,6] Topical retinoids are comedolytic in nature, inhibiting the production of microcomedones, which are the early stages of acne vulgaris. The target of retinoid activity is on aberrant proliferation and differentiation of keratinocytes and has an anti-inflammatory impact. Retinoids, which are vitamin A derivatives, help to prevent the production of comedones by normalizing follicular epithelial desquamation. The main topical retinoids include tretinoin, tazarotene, and adapalene. Tretinoin is the most commonly utilized comedolytic and anti-inflammatory agent.[7–9]

Topical antibiotics are commonly used as an effective acne therapy. Clindamycin is a semi-synthetic antibiotic derived from lincomycin. Clindamycin has a mode of action, notably reducing the proportion of free fatty acids, anti-inflammatory actions, and reducing the amount of propionibacteria. Specifically, the anti-inflammatory characteristics of clindamycin limit proliferation, protein synthesis, lipase production, follicular generation of free fatty acids, and leukocyte chemotaxis molecules in *Proprioninbacterum acnes*.[7–9] Corticosteroids permeate past the stratum corneum barrier and through cell membranes to reach the cytoplasmic keratinocytes and other cells in the epidermis and dermis. Corticosteroids have anti-inflammatory, immunomodulatory, antiproliferative, and vasoconstrictive properties. Corticosteroids work as an anti-inflammatory by decreasing the release of phospholipase A2, an enzyme responsible for the synthesis of prostaglandins, leukotrienes, and other arachidonic acid derivatives. Administering steroids in the aforesaid mixture aims specifically to avoid inflammation and inflammation that leads to scar formation / scar tissue production.[7–9]

Nonetheless, topical combination creams must be used with caution and in accordance with the doctor's instructions. Dry skin, redness, inflammation, and skin peeling are some of the possible adverse effects. Also, the use of topical combination creams might make the skin more susceptible to sunlight, so it is critical to use sunscreen when going outside. In addition to using topical combination creams, self-care measures such as bathing the skin with mild soap and warm water on a regular basis, avoiding popping or scratching pimples, and keeping the skin moisturized with a moisturizer are essential. The efficacy and adverse effects of employing combination creams (Tretinoin 0.05%, Clindamycin 3%, and Dexamethasone 0.05%) for anti-acne treatment in the short and long term are described in this study (local and systemic).

2. Methods

This is a cross-sectional study that will be done at the Sukma Clinic in January 2023. This study included all acne vulgaris patients who received a combination anti-acne cream Tretinoin 0.05%, (clindamycin 3%, and dexamethasone 0.05%). This study's sample is drawn from the population that fits the inclusion criteria. Patients who arrived for treatment in 2022 and had used a combination anti-acne cream were eligible for this trial. Patients who refused to participate in the survey were excluded from this study. The minimum sample size in this study was 97 participants according to the Slovin method (Type 1 error of 5 percent and Research Power of 80%). The non-random purposive sampling technique was used in this investigation. Surveys using Google Forms that are submitted online were employed as research instruments in this study. Age, gender, duration of acne, duration of use of combination creams, reasons for discontinuing use of combination creams, efficacy parameters, parameters of local adverse effects, and systemic side effects were all evaluated in this study.

This study's data analysis method is descriptive data presentation. Qualitative data will be displayed as proportions (%), while quantitative data will be given as centralized data distribution.

The study was conducted out in compliance with the Declaration of Helsinki's ethical principles, the International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and applicable regulatory requirements. The Tarumanagara University Human Research Ethics Committee Institute of Research and Community Engagement approved this study for ethical reasons (Registration Number: PPZ20192057 and Letter Number: 1681-Int-DIR-KLPPM/Untar/X/2019). This research has been submitted to ClinicalTrials.gov.

3. Results

This study included 547 respondents who met the inclusion criteria. The distribution of the basic data of respondents which includes gender, age, duration of acne disease, duration of drug use, and causes of drug discontinuation, is presented in Table 1.

Table 1. Data distribution of respondents using combination cream (clindamycin 3%, tretinoin 0.05%, and dexamethasone 0.05%) anti-acne period 2022.

Parameter	Results
Gender, n (%)	
Male	296 (54,1%)
Female	251 (45,9%)
Age, (years) (median, minimum, maximum)	20 (12, 44)
Duration of acne (months), n (%)	
<1	105 (19,2%)
1-6	156 (28,5%)
7-12	159 (29,1%)
13-24	127 (23,2%)
Long time using anti-acne combination cream (weeks)	
< 1	11 (2,0%)
1-2	13 (2,4%)
2-4	176 (32,2%)
4-8	185 (33,8%)
8-12	87 (15,9%)
> 12	75 (13,7%)
Causes of stopping using anti-acne combination cream, n (%)	
Already recovered	317 (57,9%)
Substitution of drugs according to doctor's recommendations (Dose reduction because it has improved)	169 (30,9%)
Substitution of drugs according to doctor's recommendations (replacing more potent ones)	42 (7,7%)
Dropping treatment without consulting a doctor	8 (1,5%)
Allergic reaction (mild)	11 (2,0%)

The efficacy of using combination cream (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) for anti-acne is presented in Table 2. The parameters assessed to assess efficacy are drug efficacy in reducing acne severity, brightening effect, remove blackheads on the face, removes acne scars, improves skin texture, disguise scars, minimize facial pores, fades facial wrinkles, fades dark spots.

Table 2. Efficacy of using combination creams (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) for anti-acne.

Parameter	Survey answers	
	Yes	No
Reducing acne severity, n (%)	499 (91,2%)	48 (8,8%)
Brightening effect, n (%)	369 (67,5%)	178 (32,5%)
Remove blackheads on the face, n (%)	423 (77,3%)	124 (22,7%)
Removes acne scars, n (%)	213 (38,9%)	334 (61,1%)
Improves skin texture, n (%)	203 (37,1%)	344 (62,9%)
Disguise scars, n (%)	267 (48,8%)	280 (51,2%)
Minimize facial pores, n (%)	278 (50,8%)	269 (49,2%)
Fades facial wrinkles, n (%)	223 (40,8%)	324 (59,2%)
Fades dark spots, n (%)	235 (43,0%)	312 (57,0%)

Local side effects and their onset due to the use of combination creams (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) anti-acne are presented in Table 3. the parameters for local side effects that were assessed were incidents of burning, itchy, stinging, eruptive papules, hypopigmentation, hyperpigmentation, erythema, scaling, urticaria and angioedema, atrophy, and striae. as in the table presented, generally local symptoms only appear in the first week of drug use (sensitization phase) and gradually the incidence tends to decrease, except for the hyperpigmentation and hypopigmentation variables which appear at a late onset due to the effect of healing acne lesions.

Table 3. Local side effects and their onset due to the use of combination creams (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) anti-acne.

Parameter	Onset of local adverse events				
	Never happen	1-7 days	1 – 2 weeks	2 – 4 weeks	> 4 weeks
Burning	510 (93,2%)	3 (0,5%)	3 (0,5%)	-	-
Itchy	508 (92,8%)	1 (0,2%)	-	-	-
Dry skin	373 (68,2%)	1 (0,2%)	-	-	-
Stinging	450 (82,2%)	3 (0,5%)	-	-	-
Eruptive papules	545 (99,6%)	-	-	-	-
Hypopigmentation	524 (95,8%)		-	-	-
Hyperpigmentation	445 (81,3%)	-	-	-	-
Erythema	524 (95,8%)	3 (0,5%)	-	-	-
Scaling	532 (97,3%)	1 (0,2%)	-	-	-
Urticaria and angioedema	547 (100%)	-	-	-	-
Atrophy	547 (100%)	-	-	-	-
Striae	547 (100%)	-	-	-	-

Systemic side effects and their onset due to the use of combination creams (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) anti-acne are presented in Table 4. Further investigations revealed that there was no direct correlation between the incidence of systemic side effects and exposure to anti-acne combination cream drugs. This is because previously the patient had often experienced this (constipation, GERD, and others).

Table 4. Systemic side effects and their onset due to the use of combination creams (tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%) anti-acne.

Parameter	Onset of systemic adverse events				
	Never happen	**1-7 days**	**1 – 2 weeks**	**2 – 4 weeks**	**> 4 weeks**
Constipation	542 (99,1%)	-	-	-	2 (0,4%)
Diare	544 (99,4%)	-	-	-	
Gastroesophageal reflux disorder	538 (98,3%)			7 (1,3%)	2 (0,4%)
Increased blood glucose	547 (100%)	-	-	-	-
Pyrexia	541 (99,0%)	-	-	-	3 (0,5%)
Urinary tract infection	538 (98,4%)	-	-	-	6 (1,1%)
Jaundice (Increase Bilirubin)	547 (100%)	-	-	-	-
Allergies	544 (99,5%)	-	-	-	-
Moon face	547 (100%)	-	-	-	-

4. Discussion

Acne is thought to be caused by a number of molecular pathways, with four major pathophysiological processes, namely:[10,11] Abnormal desquamation within the sebaceous follicle, resulting in pilosebaceous canal occlusion. Excess sebum production as a result of androgen hormones. *Propionibacterium acnes* proliferation within the follicle, resulting in a proinflammatory stimulation. Changes in immune system activity and inflammation. Even though there are many factors that can cause acne, improper desquamation and sebaceous hyperplasia are the most important. This is because they cause microcomedones to form, which are the source of all acne lesions.[12–16] Topical retinoids are an important part of acne treatment because they have been shown to reduce visible lesions and stop the growth of new microcomedones and lesions. Desquamation is fixed by retinoids, which stop keratinocyte growth and encourage differentiation.[12,17,18] Topical retinoids inhibit toll-like receptors, leukocyte migration, and the AP-1 pathway, which activate acne. Adapalenes have dosage-dependent molecular action. Isotretinoin, tretinoin, and tazarotene, on the other hand, clearly diminish the expression of Toll-like receptors. Blocking this pathway reduces cellular inflammation by decreasing cytokines and nitric oxide production.[19–21]

Topical retinoid therapy can cause skin irritation, such as peeling, redness, itching, or dry skin. This usually happens in the first few weeks of treatment and goes away after that. During the process of normalizing desquamation, the arrangement of the corneocytes can get messed up and lose their ability to stick together. After being treated for a few weeks, the corneocytes reset, the desquamation returned to normal, and the irritation went away. In clinical trials of retinoids, the most irritating effect on the skin usually happened in the first two to four weeks and then went away. So, the anti-inflammatory and microcomedone effects of retinoids have become well-known.[22–29] Retinoids connect to core hormone receptors (retinoic acid or retinoid X receptor) and cellular retinoic acid binding protein II (CRABP II) in distinct ways. Differences in tolerance may stem from these variations.[12,29] In 34 clinical studies with face-to-face comparisons and parallel designs, all three topical retinoids (tretinoin, tazarotene, adapalene) caused little clinically significant irritation. In statistically significant studies, 0.1% and 0.3% adapalene gel were best tolerated. Tazarotene 0.1% and tretinoin 0.025% creams were easy to use. Notably, sensitive skin (a history of facial product irritation) was the best predictor of irritation, more so than the specific retinoid, concentration, or formulation.[28] Leyden et al. looked at how well topical

retinoids worked on the faces of 253 healthy volunteers in a randomized, split-face, investigator-blind study with the same researchers. The study looked at how the amount of retinoid, how it was mixed with the vehicle, how sensitive the skin was, and what kind of retinoid it was. The results show that the vehicle (cream vs gel) affects how well it is tolerated, but whether gel or cream is better depends on the retinoid. People with normal skin and lower levels of retinoid can usually handle it better than those with sensitive skin and higher levels. For skin that is normal to sensitive, the best cream is tazarotene, and the best gel is adapalene. The results of this study agree with a systematic review that found the sensitivity of facial skin has less of an effect on tolerability than the choice of retinoid and more of an effect on how the retinoid is made or how much of it is used.[30]

Clindamycin is thought to help acne because of both its antimicrobial and non-antimicrobial effects. For example, *P. acnes* can stop the production of polymorphonuclear chemotactic factors, lipases, and neutrophil chemotactic factors (biotypes 1, 2, 3, 5, but not 4). This effect on inflammatory mediators is stronger in sensitive bacterial strains than in resistant ones, and it can happen at drug concentrations below those that inhibit.[31–35] Topical antimicrobial monotherapy is not recommended because it takes a while for the medicine to work and bacteria could become resistant to it. According to the drug label, you shouldn't use dapsone on your skin until your glucose-6-phosphate-dehydrogenase (G6PD) levels have been checked. Topical clindamycin products available in the US include 1% foam, gel, solution, and lotion, as well as two combination products: clindamycin phosphate 1.2%/tretinoin gel 0.025% and benzoyl peroxide 5%/clindamycin 1% gel/lotion. Researchers are looking into making a gel that has 0.025% tretinoin and 1% clindamycin. Most of these products should be given twice a day, except for combinations of topical foams, benzoyl peroxide and clindamycin, and clindamycin and tretinoin, which should only be given once a day. This review only talks about clindamycin in terms of how it is used to treat acne vulgaris.[31,36]

Two studies have looked at how irritating topical retinoids are when used with either a single antibiotic or a combination of antibiotics. In the first study, 0.1% adapalene gel, 0.05% tazarotene cream, and 0.04% tretinoin microsphere gel were used as retinoids. Two brands of 5% benzoyl peroxide/1% clindamycin gel were used as antimicrobials. In the second study, the antimicrobials were 1% clindamycin lotion and benzoyl peroxide/erythromycin. The retinoids were 0.1% adapalene gel, 0.025% tretinoin cream, and 0.1% tretinoin microsphere gel. In both studies, adapalene was significantly less irritating than the control retinoids for all antimicrobial combinations that were tested using the mean cumulative irritant index parameter (range: p-value 0.001 to 0.01). No matter which retinoid was used, clindamycin lotion therapy caused less irritation than 5% benzoyl peroxide gel, 2% erythromycin gel, or 5% benzoyl peroxide/2% erythromycin gel. Since these data were not put through a statistical analysis, there is no way to come to any official conclusions. Based on these results, it seems that 0.1% adapalene gel is the best topical retinoid and that clindamycin may be the best topical antimicrobial when used with topical retinoids.[37,38]

There is no evidence that taking clindamycin by mouth or putting it on the skin during pregnancy is harmful to the baby. Clindamycin had no significant effect on the immunomodulatory effects of tretinoin, such as reducing the release of IL-6 when phorbol myristate acetate was given, reducing the release of IFN-γ, and increasing the release of IL-5 when superantigens were given. Clindamycin's ability to kill germs is not changed by tretinoin.[39,40] Topical dexamethasone is a medicine used to treat eczema, psoriasis, and contact dermatitis, among other skin conditions. It is a type of corticosteroid that works by reducing inflammation and slowing down the immune response. Several studies have looked at how well topical dexamethasone works for treating different skin conditions, and the results have been positive.[41] Corticosteroids can get into the cytoplasm of

keratinocytes and other cells in the epidermis and dermis by getting through the stratum corneum barrier and cell membranes. Corticosteroids narrow blood vessels, suppress the immune system, reduce inflammation, and stop cells from multiplying. Corticosteroids help treat acne vulgaris by stopping the release of phospholipase A2, an enzyme that makes leukotrienes, prostaglandins, and other arachidonic acid derivatives. This stops inflammation. Several studies show that Dexamethasone is the corticosteroid that is used most often and is safe to use. Because it can reduce inflammation locally, which is pretty good, and because it doesn't soak into the skin very well.[42]

5. Conclusion

The pathophysiology of acne vulgaris has changed from what was thought in the past to what is known now. At first, acne vulgaris was thought to be caused by poor hygiene, and antibiotics were used to kill the bacteria that caused it. Now, it is known that acne vulgaris is caused by a number of different things. When a disease happens, the causes are often many and interconnected. This growing knowledge encourages doctors to keep coming up with new ways to treat acne to get the best results and stop it from coming back. Different treatment plans have been made, ranging from retinoids, antioxidants, antibiotics, and steroids used alone to retinoids, antioxidants, antibiotics, and steroids used together. But before combination creams for acne can be made, they need to be proven to work through studies. This study shows that a combination of tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05% works well and has few (tolerable) side effects on the body as a whole.

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