PROPOSAL PENELITIAN

Tahun Anggaran: 2025

1. **Judul Penelitian:**

   Efficacy, Effectiveness And Safety Of Combination Cream (Clindamycin 3%, Tretinoin 0.05%, And Dexamethasone 0.05%) Over Their Duotherapy (Tretinoin 0.05% and Clindamycin 3%) In Acne Vulgaris Patients: Randomized Controlled Trial

2. **Jenis Penelitian:** Riset Terapan
3. **Lama Penelitian:** 1 Tahun
4. **Skema Penelitian:** Industri Inovatif
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6. **Luaran dan Target Capaian:**

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SUMMARY

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous glands, significantly affecting adolescents both physically and psychologically, but acne vulgaris can persist into adulthood. According to the Indonesian Cosmetics Dermatology Research, the prevalence of acne vulgaris increased between 2006 and 2009, with 83–85% of 14 –17 year old girls and 95–100% of 16–19 year old boys being affected. Accurate treatment of acne vulgaris is crucial for optimal healing and prognosis. Current evidence supports the efficacy of combination therapies incorporating retinoids, antibiotics, and corticosteroids in acne management.

This study was conducted as a randomized controlled trial to evaluate the effectiveness and safety of two anti-acne cream regimens: a duotherapy (tretinoin 0.05% and clindamycin 3%) and a combination cream containing clindamycin 3%, tretinoin 0.05%, and dexamethasone 0.05%. A total of 150 participants aged 15 to 45 years were recruited based on certain inclusion and exclusion criteria. Inclusion criteria required participants to have an ISGA score of 3 or 4, acne vulgaris localized to the facial area, agree to use Combination of Anti-Acne Cream only as subject's daily skin care routine and agree to stop other skin care products minimum of three days. Exclusion criteria included the use of oral steroids, antibiotics, oral tretinoin, or the presence of other dermatological conditions during the monitoring period.

Primary endpoints included the reduction in inflammatory, non-inflammatory, and total lesion counts over two weeks. Secondary endpoints involved changes in the skin parameters such as pigmentation, hydration, and UV damage. Tertiary endpoints involved changes in the Investigator's Static Global Assessment (ISGA) score, Cardiff Acne Disability Index (CADI). Adverse events were monitored throughout the trial.

This study seeks to provide evidence on the comparative efficacy and safety of combination versus duotherapy in acne vulgaris treatment.

Keywords: Acne vulgaris; Randomized controlled trial; Tretinoin; Clindamycin; Dexamethasone; Safety; Effectiveness

INTRODUCTION

The common yet chronic skin disorder, acne vulgaris, is recognized by the inflammation or localized inflammation of the sebaceous glands. [1,2] This skin disorder can manifests in various form, with most cases has a pleomorphic arrangement present. The arrangement could be made of comedones, papules, pustules, or nodules. The manifestation comes early for women than for males, affected by the puberty and hormones. [3] All women of all races can be affected by acne, from Africa and American (37%), Hispanic (32%) , Asian (30%), Caucasian (24%), and Indian (23%). [4] High prevalence (47-90%) is particularly found in adolescents. Prevalence of acne vulgaris is increasing every year, demonstrated by the statistic from Indonesian Cosmetics Dermatology Research where the amount of people with acne vulgaris increased from 60% in 2006, 80% in 2007, to 90% in 2009. [5] Prevalence of 83-85% found in female teenagers (age 14-17) , and high frequency (95-100%) found in male adolescents (age 16-19).[6] Acne vulgaris can persist into adulthood. In women aged 20 to 29 years, the prevalence of AV has been reported to be 50.9%, compared to 26.3% in those aged 40 to 49 years.[7] There are four factors that can cause acne: (1) follicular clogging caused by follicular epidermal hyperproliferation; (2) excessive production of sebum; (3) inflammation; and (4) the activity of *Propionibacterium acnes* (*P. acnes*). [8] It is such a complex condition where many factors are involved, from psychological stress, infection, work, food/diet, climate, environment, skin type, hygiene, cosmetic use, genetics, ethnicity, and race. [9] The predilections for acne are face, shoulders, upper superior extremities, chest, and back. It is not lethal disease but for those affected, for teens in particular, has significant impact both physically and psychologically, causing worry, despair, and low self-confidence. [10]

The key factors for patient's recovery and prognosis are accuracy and speed in treating acne vulgaris.[11] The best acne treatments are antibiotics to suppress the growth of bacteria, corticosteroid to reduce the inflammation, and retinoids to reduce the formation of microcomedones.[12] Since all the components can be incorporated into a single cream, combination of anti-acne cream is one of the best way to treat acne. Being reasonably inexpensive, non-invasive, practical, and has less adverse effects than other treatments made the researchers favor the combination of anti-acne creams.[13]

This is a randomized controlled trial research comparing the efficacy of a duotherapy (tretinoin 0.05% and clindamycin 3%) to that of a combination cream containing Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%. On the other hand, this study will also examine clinical improvements, side effects, and patient satisfaction with the two treatment options.

LITERATURE REVIEW

Acne vulgaris is disease of the pilosebaceous, which is chronic inflammatory illness. Pilosebaceous unit is an immunocompetent organ that can respond to threats of infection. In acne vulgaris, hypercornification, sloughed keratinocyts and other debris block the follicular opening, make comedo, excess production of sebum, abnormal proliferation of Propionibacterium acnes and infiltrate leukocyte in repons to the inflamatory.[14–18]

Inflammarry phase is start when sebaceous follicle become sensitive to any alteration. Microcomedone "lesions" in which an abnormal number of keratinized cells are formed are believed to be the earliest indicator of subclinical acne, although not being fully understood.

Keratinocytes and sebocytes secreate chemokines and proinflammatory cytokines, stimulate and recruiting lymphocytes and T-helper cell, into infected site. These earliest events appear to be the commencement of intracellular communication/signaling mechanisms, as well as the determination of subsequent protective immunological measures. In the case of inflammatory acne, both innate (nonspecific) and acquired (antibody-mediated) immune responses will be triggered.[19]

The subsequent proliferation of P. acnes within the blocked follicle causes this organism to discharge extracellular foreign material. Lipase is one of the proinflammatory that produce cytotoxic free factty acid, protease, hyluronidase and nueroamindade that come from sebum that can break follicular wall, leaking to dermis and induce inflammation. P. acnes is capable of creating highly immunogenic proteins, porphyrins that combine with oxygen, generate hazardous oxygen species and free radicals, that highly comedogenic squalene peroxide.[20–28]

P. acnes releases powerful low molecular weight chemoactive factors and chemotactic lipases into the dermis and follicles during the first stages of pre-inflammatory and inflammatory acne. This process can draw diverse white blood cells, including neutrophils, lymphocytes, and monocytes, to the site of an infection. During early infection, P. acnes also increases the synthesis of proinflammatory small polypeptide cytokines, including, granulocyte-macrophage colony-stimulating factor (GMCSF), interferon-gamma (IFN), tumor necrosis factor alpha (TNF), and interleukin (IL) IL-1α, IL-1β, IL-6, IL-8, and IL-12. These messenger molecure are produce in and around the damage follicle, as part to defence the skin and prevent infection to spread.[29–32]

In addition to the inflammatory challenge described above, additional innate and acquired immune responses are produced within the host, which exacerbates inflammation in the follicle. T lymphocytes (T-cells) that are immunoreactive, CD4+ cells, and CD14+ cells infiltrate the inflammatory lesion. Active monocytes change into macrophages and begin to encircle and ingest pathogen-associated foreign substances.

Intracellular neutrophil/macrophage phagocytosis produces enzymes and toxic compounds, such as reactive oxygen species, which help prevent destruction and elimination of P. acnes and its damaging extracellular products. When persistently and excessively produced, these

substances can harm the follicle, enter the surrounding dermis, and inflame the host.[33,34,43,35–42]

Leukotriene B4 (LTB4) and C5-derived neutrophil chemotactic factor are take part in pathogenic acne, since they can induce neutrophils, monocytes, and eosinophils, to make inflammation. Some proinflammatory that also can aggravate the inflammation include Toll-like receptor (TLR), transcription factor activator protein 1 (AP-1), vascular cell adhesion, macrophage degranulation, growth factors, transglutaminase and lipoxygenase expression, cytokine modulation metalloproteinase activity in the dermis, prostaglandin synthesis, and possibly IL-5.[44–51]

Topical retinoids (adapalene 0.1% and 0.3%; tazarotene 0.1%; tretinoin 0.01%, 0.025%, 0.038%, 0.04%, 0.05%, 0.08%, and 0,1% in the United States; isotretinoin 0.05% and 0.1% in other regions of the world) used in acne therapy. Topical retinoid has been shown to reduce visible lesions as well as inhibit the growth of microcomedone. Retinoids correct desquamation by inhibiting keratinocyte growth and encouraging differentiation.[47,52,53] Many significant inflammatory mechanisms like, Toll-like receptors, leukocyte migration, and the AP-1 pathway get activated. Its molecular activity has been proven to be dose-dependent for adapalenes. Base on evident that isotretinoin, tretinoin, and tazarotene decrease the expression of Toll-like receptors as well. Blocking this route decrease inflammation by reducing the inflammatory cytokines and nitric oxide.[54–56]

The efficacy of topical retinoids increase as the concentration gets higher. Tretinoin is an example that shown to have a dose-dependent effect in an animal model.[57] In two different ultrastructural trials, 0.1% and 0.025 % tretinoin reduced microcomedones by 80% and 35%, after 12 weeks of treatment.[53] Registration studies of 0.3% adapalene gel demonstrate greater dose-related effectiveness compared to adapalene gel. 0.1% across all effectiveness metrics, with tolerability at both dosages being satisfactory. Examination of the phase III trial of 0.3% adapalene gel revealed that patients with a greater number of lesions at the beginning of the trial saw the best efficacy.[58,59]

Due to their method of action in the dermis, topical retinoids have been proven to affect on scarring and pigmentation, in addition to the main acne lesion. Acne scarring is caused by dermal remodeling and an imbalance between matrix degradation and matrix synthesis, both of which are regulated by matrix metalloproteinases (MMPs).[60] During week 24, participants in an open-label pilot study using 0.3% adapalene for scarring demonstrated an improvement of one or two levels on a scar assessment, as well as an overall improvement in skin texture. In addition, 0.3% adapalene was related with activation of the procollagen gene as well as enhanced procollagen-1 and collagen-3 staining.[61]

In pigmentation disorders, retinoids diminish epidermal pigmentation by increasing epidermal turnover and lighten hyperpigmented lesions by preventing melanosome to keratinocytes.[62] Grimes et al. observed that tazarotene 0.1% cream is helpful for acne-related post-inflammatory hyperpigmentation, lowering the intensity and area of pigmentation considerably over 18 weeks than the placebo (P 0.05).[63] In a study 0.1% tazarotene cream compare to 0.3% adapalene gel, Tanghetti et al. shows that 16 weeks of tazarotene significantly lowered post-inflammatory hyperpigmentation in acne patients, whereas adapalene did not achieve a significant difference from baseline. Moreover, in 25% (10/40) of the participants treated with tazarotene, post-inflammatory hyperpigmentation resolved completely.[64] Griffiths et al. discovered that 0.1% tretinoin cream significantly reduced pigmentation in melasma patients compared to the placebo ($P = 0.0006$).[65] In an open-label study with dark skin and acne from South Africa, 0.1% adapalene gel reduced the frequency of pigmented macules and density of hyperpigmentation to levels "similar to those reported with topical tretinoin."[66] Research from Bulengo-Ransby et al. In a 40-week discovered thatnhyperpigmentation lesions in patients treated with tretinoin were substantially lighter than patients treated with a placebo ($P < 0.001$).[67]

The prevailing consensus, show retinoids should be prescribed for acne. Substantial evidence provided by previous randomized controlled trials that monotherapy with topical retinoids dramatically reduces inflammatory lesions with effects comparable to noninflammatory lesions. The therapeutic effects on topical lesions of topical retinoid were demonstrated by

patients' photos taken before and after having topical retinoid monotherapy. Leyden et al. evaluated the effect of topical retinoids on inflammatory lesions by analyzing high-resolution digital images of 577 patients enrolled in an enrollment study and treated with topical retinoids. Five blinded researchers evaluated the severity of acne prior to and afterward 12–15 weeks of topical retinoids monotherapy (tazarotene, adapalene, or tretinoin). All retinoids demonstrated an clinical improvement in inflammatory acne; additionally, the rate of improvement increased as acne severity increased. Jacobs et al. revealed in a recent comprehensive study that BPO and adapalene both exhibit a rapid beginning of effect (measured as a 25% time decrease mean number of inflammatory lesions) in contras to other retinoids (tretinoin, topical isotretinoin).[61,68–72]

Topical antimicrobials currently available include clindamycin, erythromycin, tetracycline, dapsone, benzoyl peroxide, and azelaic acid. Those compounds have local adverse effects (AE) like erythema, desquamation, dryness, and burning. Benzoyl peroxide also bleaches hair, clothing, and bed linens.[73]

Randomized controlled trials show the evidence essential to justify usage topical acne vulgaris. When inflammatory lesions (papules/pustules) are present, the Global Alliance recommends adding topical antimicrobials to topical retinoids as a first-line treatment for all kinds of acne. The preferred treatment for mild comedo acne (whiteheads/blackheads) is topical retinoids. The most effective treatment for moderate comedonal acne and mild to moderate inflammation is a combination of topical benzoyl peroxide or retinoids and a topical antibacterial. The correct evaluation of a treatment's efficacy involves trials spanning 6 to 8 weeks or 8 to 12 weeks. Topical retinoid and topical antimicrobial is preferred that benzoyl peroside and topical antimicrobial. In case moderate to severe acne, using systemic medication are suggested (oral tetracyclines, isotretinoin, hormonal contraceptives, etc.).[73–75]

Topical antibacterial monotherapy is not suggested due to the slow onset of action and the potential for the formation of bacterial resistance. According to the medicine label, topical application of dapsone is not advised excpet glucose-6-phosphate dehydrogenase (G6PD) levels have been determined. Foam, gel, solution, and lotion formulations of 1% clindamycin are available in the United States, with two combination products: clindamycin phosphate 1.2% andtretinoin gel 0.025%, benzoyl peroxide 5% with clindamycin 1% gel/lotion. Under investigation is a gel formulation containing 0.025% tretinoin and 1% clindamycin. Except for topical foams, benzoyl peroxide/clindamycin combinations, and clindamycin/tretinoin combinations, these treatments should normally be administered twice daily. This review focuses solely on the use of clindamycin in the treatment of acne vulgaris.[75,76] In all 18 trials, topical clindamycin was statistically better than placebo in terms of reducing the number of lesions and investigator/patient assessment. [77,78,87–92,79–86]

The vehicle and salt form (hydrochloride versus phosphate) had no effect on the effectiveness. [81,83,87]. When clindamycin was given once or twice a day, the findings were identical in both studies. [86]. The kind of formulation (gel versus lotion, for example) had no significant in efficacy. [93], compare gel to solution [84,85], gel versus foam [79] and lotions versus solutions [94]). Topical clindamycin seems to be as effective as or more effective than oral tetracycline or minocycline. [87], topical tetracycline [95], topical benzoyl peroxide [96] and topical erythromycin with/without zinc [94,97].

Combination therapies were statistically more superior than their constituent monotherapies on all efficacy metrics (e.g., topical clindamycin was lesser compare to topical benzoyl peroxide/clindamycin). [88–92], tretinoin/clindamycin [91], and adapalene/clindamycin [98,99]; Topical benzoyl peroxide is lower than topical benzoyl peroxide/clindamycin [90–92]; topical tretinoin is less effective than topical tretinoin/clindamycin.[91] Also, topical clindamycin was less effective than topical benzoyl peroxide/erythromycin.[100] On the other hand, the effectiveness of benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin is comparable. [101]. In only three studies (topical clindamycin versus benzoyl peroxide/clindamycin) were combination therapy and monotherapy similarly efficacious (clindamycin against benzoyl peroxide/clindamycin)[102] or tretinoin/klindamisin [103] and tazarotene versus clindamycin/tazarotene [104].

In 1976, there are study that compare efficacy of the basic and phosphate salt versions of hydroalcoholic and N-methyl-2-pyrrolidone (NMP) medicines and vehicles was examined in a study involving 60 patients. At week 2/8, phosphate salts in NMP carrier, phosphate salts in hydroalcoholic carrier, base in NMP carrier, and base in hydroalcoholic carrier reduced the number of inflammatory papules by 44/80%, 32/55%, 41/75%, and 22/50%, respectively. At week 8, the proportions corresponding to no P. acnes growth in open comedones were 79, 46, 40, and 42%. In an experiment involving 45 patients, topical clindamycin phosphate 1% in NMP and hydroalcoholic vehicle was compared to 'standard' regimens, such as oral tetracycline. At week 2/8, the number of inflammatory papules decreased by 44/80%, 32/55%, and 18/27% respectively. Regrettably, in the same city, beneficiaries of topical clindamycin and conventional oral antimicrobials are treated at separate clinics.[105]

Study that form in 1985, include 45 non-inflammatory acne case (mainly women aged 14–15 years) that treated with four different therapy (A = vitamin A 0.025% daily [n = 9]; B = benzoyl peroxide 5%/2% sulfur daily [n = 8]; C = clindamycin 1% once daily [n = 8]; and D = vitamin A acid 0.025% 3 days/week alternating with clindamycin 1% 4 days/week [n = 20]). The proportions of increase (where increase was defined as a reduction in the number of comedones exceeding 50% after 3 months) were 64, 60, 48 and 65%.[106]

In 1998, the results of three comparative clinical trials using previously unreported data-on-file were published. Once-daily of clindamycin gel 1.2%/tretinoin 0.025% is superior than twice-daily of clindamycin gel 1% and clindamycin lotion 1%. There were no significant differences between treatments in the percentage of reduction in inflammatory lesions. In two of the three investigations, the combination product was considerably more effective than clindamycin gel (64 vs. 51%; p = 0.04) and clindamycin lotion (69 vs. 61%; p = 0.05) at reducing the number of noninflammatory lesions. In two of the three investigations, the combination product outperformed clindamycin gel (2.5 against 1.6; p 0.001) and clindamycin lotion (2.9 versus 2.1; p = 0.007) in terms of the amount of Cook grade enhancement. Scaling and erythema are more prevalent in combination product receivers compared to clindamycin monotherapy because tretinoin, a keratolytic, is present in combination products.[107]

In the treatment of numerous dermatological disorders, topical corticosteroids play a pivotal role. They are FDA-approved and suggested for the treatment of inflammatory and pruritic skin disorders. Indications using topical corticosteroid are psoriasis, vitiligo, eczema, atopic dermatitis, phimosis, acute dermatitis, lichen planus, lichen simplex chronicus, discoid lupus erythematosus, and lichen sclerosis.[108] They are beneficial for hyperproliferative, immunological, and inflammatory disorders.[109,110]

The mode of action of topical corticosteroids are use for anti-inflammatory, antimitotic, and immunosuppressive actions. Topical corticosteroid have anti-inflammatory action by vasoconstriction, suppresiton of phospholipase A2, and inhibit effect on DNA and inflammatory factor directly.[111,112] Vasocontriction in upper dermis decrease the inflammatory mediation in affected region.[111]. Formation lipocortin, inhibitis phospholipase A2 and decrease prostaglandins and leukotriends, giving anti-inflammatory effect. 157 In addition to acting directly at the DNA level to boost anti-inflammatory gene expression, topical corticosteroids indirectly block inflammatory factors, such as NFkb, to reduce proinflammatory gene expression.[111]

The anti-mitotic in the topical corticosteroids plays a significant role for psoriasis; it has been postulated that decrease epidermal mitosis happened by increase in lipocortin, a protein regulated by endogenous glucocorticoids. The dermis possesses an anti-mitotic action that suppresses cell proliferation and collagen formation.[113] Topical corticosteroids decrease humoral components as one of function as immusuppressive agent, inhibit the maturation, differentiation, and proliferation of all immune cells.[113]

According to ophthalmology research, topical steroids are used to treat inflammation of the conjunctiva, cornea, and anterior segment. Steroids may also be beneficial in treating uveitic or postoperative macular edema in specific conditions. Diffusion over the cornea allows penetration into the aqueous fluid.[114] Dexamethasone is intrinsically about 25 to 30 times stronger than hydrocortisone.[115] Efficacy in any preparation is determined not just by the

drug's intrinsic potency, but also by its penetration and staying power. More liphophilic like acetate preparation more likely penetrate deeper into the cornea compare to less liphophilic like phosphate preparation.[116] Even though prednisolone acetate is six times more potent on a molar basis compare to dexamethasone or betamethasone, 1% prednisolone acetate has a stronger anti-inflammatory impact than 0.1% dexamethasone or betamethasone phosphate due to topical prednisolone acetate. Since preservatives impair the tight connections between the corneal epithelial cells, solutions with preservatives have more penetration than those without.[117] Frequency of applicationa also increase the anti-inflammatory effect. A study of ocular inflammation found that applying topical prednisolone acetate every 15 minutes (or five doses at 1-minute hourly intervals) had a stronger anti-inflammatory impact than applying it hourly. It is critical to shake the suspension promptly before using it, or otherwise the dose will vary.[118]

Ophthalmology research even indicates long-term use of dexamethasone with continuous release formulations. A biodegradable intravitreal implant containing 0.7 mg dexamethasone, OZURDEX, in the solid rod-shaped polymer drug delivery system NOVADUR. It is intended to release a greater dose in the first 6 weeks with lower dose following over 3 to 6 months. Steroids are injected in a stepwise manner using a single-use intravitreal applicator. It is used for the treatment of DMO, central or branch retinal vein occlusion (CRVO, BRVO) that causes macular edema, and non-infectious posterior uveitis.[119–121]

Acne is influence by many factor, including hyperkeratosis and blackheads, production of sebum, inflammation, and a rise in the quantity and activity of Propionibacterium acnes. Hyperkeratosis and comedones choke hair follicles, particularly those with big sebaceous glands (on the face, neck, chest and back). This increases the amount of comedogenic and inflammatory components that produce acne lesions. The development of the free fatty acid component in the sebum induces irritation of the follicles and thickens the sebum. Propionibacterium acnes is a follicular flora that participates in the inflammatory chemotactic process as well as the synthesis of lipolytic enzymes that alter the lipid portion of sebum.[122–124]

Acne manifests as open or closed comedones (non-inflammatory lesions) and as papules, pustules, or nodules (inflammatory lesions). Severe acne can result in systemic symptoms known as acne fulminans, as well as non-systemic symptoms known as acne conglobata. In most cases, severe acne resolves with scar tissue. Acne can have a negative impact on the patient's mentality in varying degrees.[122–124]

Acne management should focus on the elements that contribute to its pathogenesis. Acne treatment is currently depending on severity, according to current agreement. Retinoids (topical tretinoin, adapalene, tazarotene, isotretinoin), antibiotics (tetracycline, minoxycycline, doxycycline, trimethoprim/sulfamethoxazole, clindamycin, erythromycin, daptomycin), selective aldosterone antagonists, estrogen/progestin combos, and other acne treatments are utilized. Diet is another nonpharmacological therapy to explore. Patients are recommended to avoid low glycemic index diets and greasy meals. Comedone extraction, intralesional steroid injections, and glycolic acid or salicylic acid peels are common acne treatments. Blue light treatment can be utilized to kill Proprionibacterium acnes by eliminating porphyrins in bacterial cells. Scar tissue caused by acne should be treated with skin surgery. [122–124]

Topical retinoids are comedolytic in nature, inhibiting the production of microcomedones, the early stages that seen in acne vulgaris. The target of retinoid activity is aberrant keratinocyte proliferation and differentiation, and it has an anti-inflammatory effect. Retinoids, which are vitamin A derivatives, help to avoid the production of comedones by normalizing follicular epithelial desquamation. Tretinoin, tazarotene, and adapalene are the most common topical retinoids. Tretinoin is the most commonly utilized comedolytic and anti-inflammatory agent. [122–124]

Topical antibiotics are commonly used as an effective acne therapy. Clindamycin is a semi-synthetic chemical derived from the antibiotic Lincomycin. Clindamycin works by decrease the amount of free fatty acids, reducing inflammation, and decreasing the number of propionibacteria. Clindamycin's anti-inflammatory characteristics specifically suppress

Proprioninbacterum acnes development, protein synthesis, lipase production, follicular production of free fatty acids, and leukocyte chemotaxis molecules.[122–124]

Corticosteroids enter cytoplasmic keratinocytes and other epidermal and dermal cells via the stratum corneum barrier and cell membranes. Corticosteroids are anti-inflammatory, immunomodulatory, anti-proliferative, and vasoconstrictive. Corticosteroids work as anti-inflammatory agents by inhibiting the activity of phospholipase A2, an enzyme that is responsible for the creation 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. [122–124]

As is well known, treating scar tissue caused by acne is still tough and expensive. In general, invasive therapy takes a long healing time since it involves the synthesis of epidermal tissue again (difficult), as well as the formation of collagen tissue in the skin. If the scar forms are ice pick and box, all processes such as laser therapy, subsection scar, and needling are ineffective. The point is that all scar therapies are still difficult, expensive, take a long time to heal, interfere with the activities of patients who are usually of productive age, and the results are still unsatisfactory. As a result, preventing the formation of scars is preferable to treating scars after they have formed.[122–124]

The steroid utilized topically in this combination is of the Dexamethasone type. We have heard that Dexamethasone is a steroid with very low absorption; hence, dexamethasone is rarely employed in topical steroid therapy for various types of skin conditions that require topical steroids.[122]

Because Dexamethasone's absorption is poor in the skin's layers, we use it as an advantage in acne therapy. This may be why no one has ever used Dexamethasone in acne therapy until now, but we discovered that because absorption into the epidermis layer is poor, it actually has the advantage that this Dexamethasone "only" works on the surface of the skin and will only enter into the pores that are open. Minoxcidil, for example, was originally a vasodilating medicine for heart illness, but it was discovered to have side effects for growing hair, and its side effects are now being utilized to grow hair, which is used for alopecia therapy to this day.[122–124]

There has been a paradigm change from the pathophysiological idea (acne causes) to therapy management, necessitating the formulation of this cream from the three medications or active ingredients listed above. Biofilms, bacteria, toxins, and dysbiosis events from the microbiome are some of the components (interactions between numerous variables) that, according to the most recent theory, contribute to the development of acne. All of these activities will result in the release of several metabolites that, individually and collectively, will induce irritation or serve as the basis for acne. Due to the multifactorial nature of acne's etiopathogenesis, it would be prudent to employ a combination therapy as opposed to a single treatment. [122–124]

Night cream formulas are intended to keep the skin moist, encourage skin regeneration, and function so that it appears bright. Night cream also stimulates collagen formation, which improves skin suppleness. Night creams are typically made up of components that cannot be exposed to sunlight, resulting in thicker and thicker formulations.[122–124]

This night cream formulation is used as an anti-inflammatory, antibacterial, and comedolytic, which is the key component in the pathogenesis of acne, and it is manufactured in the form of a night cream to have an additional effect on skin regeneration. Apart from eradicating acne, this invention will make the facial skin brighter and its function will be preserved, which is especially crucial in preventing scars, which are tough to cure and the results have not been satisfying so far.[122–124]

METHOD AND MATERIAL

Study Population

All patients with acne vulgaris as the clinical diagnosis and aged 15 to 45 years included as the sample population for this study. Patient sampling will be conducted at Mayapada Hospital Tangerang, Precious Me Clinic, Indra Pharmacy and Clinic, and Citra Semanan

Clinic. The severity of acne vulgaris is based on the number of lesions, with mild cases having fewer than 20 comedones or 15 inflammatory lesions or fewer than 30 total lessions, moderate cases having between 20 and 100 comedones or 15 to 50 inflammatory lesions or fewer than 30 to 125 total lessions, and severe cases having more than 5 cysts, or more than 100 comedones, or more than 50 inflammatory lesions, or more than 125 total lesions.

Age requirement 15 – 45 years old, acne vulgaris in the face region, independent of skin tone, consenting to therapy with informed consent, Investigator's Static Global Assessment (ISGA) score of 3 (moderate) or 4 (severe), agree to use Combination of Anti-Acne Cream only as subject's daily skin care routine and agree to stop other skin care products minimum of three days. Patient with any skin disease on the face, including rosacea, impetigo, viral and fungal infections, atopic or contact dermatitis, acneform eruptions, or any usage of oral tretinoin and steroids within 4 weeks, and any respondents whom suspected allergic to the active ingredients in the anti-acne cream combination, were excluded in this study.

The study was carried out in accordance with the Declaration of Helsinki's ethical principles, the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice, and applicable regulatory requirements. This study was granted ethical clearance by the Universitas Tarumanagara Human Research Ethics Committee Institute of Research and Community Engagement (Registration Number: PPZ20192057 and Letter Number: 1781-Int-DIR-KLPPM/Untar/X/2025). This study has been registered with ClinicalTrials.gov.

Study design

A Randomized Controlled Trial (RCT**)** was conducted at the Sukma Clinic, Mayapada Hospital, Indra Clinic, and Citra Semanan Clinic to evaluate the efficacy of an anti-acne cream formulation containing clindamycin 3%, tretinoin 0.05%, and dexamethasone 0.05% compared to a standard regimen containing 0.05% tretinoin and clindamycin 3%. Participants meeting the inclusion and exclusion criteria were recruited and randomly allocated to either the intervention group or the comparator group.

The trial was conducted over two weeks, with all patients in each group instructed to apply the assigned study medication to their facial acne lesions. Randomization was achieved using a computer-generated random sequence, ensuring allocation concealment to minimize bias. Blinding was implemented for both participants and assessors to further reduce bias.

Sampling Technique

Eligible participants were recruited consecutively and randomly assigned to one of the study groups. This method ensured that each participant had an equal chance of receiving the intervention or comparator treatment.

Intervention Protocol

- **Intervention group:** Anti-acne cream containing clindamycin 3%, tretinoin 0.05%, and dexamethasone 0.05%.
- **Comparator group:** Standard regimen/duotherapy (tretinoin 0.05% and clindamycin 3%)

Participants were instructed to:

1. Cleanse their faces with warm water and mild soap, then pat dry before application.
2. Apply a fingertip unit of the assigned medication to the acne lesions once daily.
3. Avoid application to mucous membranes, including the eyes, mouth, and nostrils.
4. Wash hands thoroughly before and after application.
5. Use sunscreen and avoid excessive sunlight, UV lamps, or photosensitizing agents to minimize the risk of photosensitivity.

Study endpoint

The mean percentage change and overall mean reduction in acne lesion counts from baseline to week 2 served as the primary efficacy endpoints (inflammatory, noninflammatory, and total lesion counts). The secondary objectives were Mean current change and Overall mean

reduction in the side parameter from baseline to week 2 (Spot, Pore, Wrinkle, UV Acne, UV Spot, Roughness, Acne, Sebum, Collagen, Pigmentation, and Hydration). In order to compare side parameters, digital observation is used, with assistance from artificial intelligence (Software from Bitmoji)

The tertiary objectives were percentage of patients with an ISGA score improvement of two grades from baseline to week 2 and who were evaluated as "clear" or "near clear" were the tertiary goals. In week 2 (or the early discontinuation visit), the investigator evaluates the the physician's global evaluation of efficacy score and classified it as "Excellent," "Good," "No change," "Bad," and "Worse." The Cardiff Acne Disability Index (CADI) were also examined from baseline to week 2 in this study.

Adverse events (AEs) and laboratory tests are monitored to gauge safety. Both the patient and the doctor conducted local tolerability assessments, which were recorded in the patient's diary. In addition, systemic tolerance was also assessed, such as constipation, diarrhea, gastroesophageal reflux disorder, increased blood glucose, pyrexia, urinary tract infection, jaundice (increase bilirubine), allergies, and moon face. The patient was assessed by the doctor for local tolerability at each visit/week based on the degree of scaling and erythema (none (grade 0) to severe (grade 3)). Every day during the research period, patients were requested to take note about their skin if there are any itching, burning, and stinging (none to severe (rate 0 to 3)).

Statistical analysis

According to prior studies, the minimal sample size for each group was 150 respondents, with 80% power level, 5% of superiority margin, and 5% of significance level to identify a statistically significant difference between the two groups. analysis of descriptive data based on the data's nature. Quantitative data will be displayed with a central distribution of data (mean, standard deviation, median, minimum, and maximum), whereas qualitative data will be presented with proportions (%).

Data analysis regarding the relationship between variables is adjusted to the type of data for each variable. If the two variables are qualitative data, the statistical test used is Pearson Chi Square with Fisher Exact as an alternative test. For the type of categorical-numeric data that is paired, use the Paired T-test statistic and the Wilcoxon alternative test. For non-paired categorical-numeric data types, statistical tests using the Independent T-test and alternative Mann-Whitney tests are used. Kolmogorov Smirnov test were used to determine the distribution of data (p-value> 0.05). The relationship between variables is expressed by a p-value with a significance limit of 0.05.

Research Time

No	Activity	Month												
		8	9	10	11	12	1	2	3	4	5	6	7	8
1	Research proposal session	v												
1	Research ethics submission	v	v											
2	Coordination with Hospitals, Indra Clinic, Precious Me Clinic, and Citra Semanan Clinic			v	v									
3	Implementation of research and data collection					v	v	v	v					
4	Data analysis								v	v	v			
5	Writing research results											v	v	

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