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ORIGINAL ARTICLE

COMPARATIVE STUDY OF CLINICAL EFFICACY AND SIDE EFFECTS OF ADAPALENE 0.1% GEL AND BENZOYL PEROXIDE 2.5% GEL AS MONOTHERAPIES AND COMBINATION THERAPY IN FACIAL ACNE: INDIAN PERSPECTIVE

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Adarsh Gowda, Sanmitha S. K, Satish K. S. "Comparative Study of Clinical Efficacy and Side Effects of Adapalene 0.1% Gel and Benzoyl Peroxide 2.5% Gel as Monotherapies and Combination Therapy in Facial ACNE: Indian Perspective". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 14, April 07;
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ABSTRACT: A fixed dose combination gel with adapalene 0.1% and benzoyl peroxide 2.5% has been developed for the once daily treatment of acne vulgaris .This fixed combination was approved by U.S FDA in December 2008. This study was done in the Department of Dermatology, KIMS, Bangalore to assess the efficacy and adverse effects of topical adapalene 0.1%–benzoyl peroxide 2.5% combination gel as compared to topical adapalene 0.1% gel and 2.5% benzoyl peroxide gel (monotherapies) in the treatment of facial acne vulgaris. To the best of our knowledge, this is one of the few studies conducted in India. It was an open label study. Participants received either adapalene 0.1% gel, benzoyl peroxide 2.5% gel or adapalene 0.1% – benzoyl peroxide 2.5% combination gel for 12 weeks. Follow up was done at the end of 1,2,4,8 and 12 weeks. Evaluation included lesion count and adverse events. Participants included males and females aged between 18-38 years with grade 2 or 3 facial acne vulgaris as per investigators global assessment of acne scale. A total of 62 participants were recruited out of which 23 were males and 39 were females.88.71% participants completed the study. The study revealed that combination of adapalene 0.1% and benzoyl peroxide 2.5% gel was more effective in the treatment of facial acne as compared to adapalene 0.1% gel and benzoyl peroxide 2.5% gel (topical) monotherapies. The safety of combination of adapalene 0.1% and benzoyl peroxide 2.5% gel was comparable with adapalene 0.1% gel and benzoyl peroxide 2.5% gel monotherapies.
KEYWORDS: ACNE, Topical therapy, Benjoyl peroxide, Adapalene.

INTRODUCTION: The term acne is derived from ἀκνή, a scribal error for the Greek ἀκμή (akmē), literally meaning "point, edge", but in the sense of a "skin eruption."[1] The appearance of acne varies with skin color. Acne could result in many psychological and social problems.[2] The center for disease control defines a particular disease as 'chronic' that in general terms, has a prolonged course, that does not resolve spontaneously, and for which a complete cure is rarely achieved. In accordance with that definition, acne vulgaris can be termed a chronic disease[3], because of its long duration and recurring nature.

Types of Acne: Non inflammatory lesions: whiteheads, blackheads Inflammatory lesions: papules, pustules, nodules

Clinical Features[4]: Acne vulgaris is characterized by comedones, papules, pustules, and nodules in a sebaceous distribution (e.g., face, upper chest, back). The face may be the only involved skin surface, but the chest, back, and upper arms are often involved.

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A comedone is a whitehead (closed comedone) or a blackhead (open comedone) without any clinical signs of inflammation. Papules and pustules are raised bumps with obvious inflammation. Non inflamed lesions are the earliest to develop in younger patients.[5]

Subtypes of comedones: sandpaper. macrocomedones, submarine, secondary (following exposure to dioxins, pomades, topical steroids).

Nodules are most frequently seen in males and when exudative or hemorrhagic, they are particularly disfiguring. Nodules may extend deeply and over large areas showing little surface involvement.

Sinus formation between nodules and/or deep pustules leads to devastating cosmetic effects and severe scarring.[6, 7] Itching is a rare symptom of acne. Scarring follows deep seated inflammatory lesions but may also occur as a result of more superficial inflamed lesions in scar prone patients. Scars may show increased collagen [hypertrophic scars and keloids] or be associated with loss of collagen [ice-pick scars, depressed fibrotic scars, atrophic macules and perifollicular elastolysis.

Keloids extend beyond the extent of original inflammation. Hypertrophic scars do not extend beyond the extent of original inflammation. Atrophic scars are usually multiple and they represent soft distensible lesions. Ice pick scarring can result from comedones alone. Persistent post inflammatory hyper pigmentation is seen most commonly in pigmented skin. The pigmentary change may take many months to resolve and may also be permanent in some cases.

Investigator's Global Assessment of Acne Scale:

0 - Clear skin with no inflammatory or non-inflammatory lesions.
1 - Almost clear; rare non-inflammatory lesions with no more than 1 small inflammatory lesion.
2 - Mild severity; greater than grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions).
3 - Moderate severity; greater than grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions; but no more than 1 small nodular lesion.
4 - Severe; greater than grade 3; up to many non-inflammatory and inflammatory lesions but no more than a few nodular lesions.

CAUSES: Acne develops as a result of: seborrhea, comedo formation, colonization of the intrafollicular duct with P. acnes, inflammation.

Hormonal: [8-10] Menstrual cycles, Puberty, Anabolic steroids, Androgens (testosterone, DHT, DHEAS, IGF-1).

Genetic: Polymorphisms in CYP17-34T/C[11-13],TNF-alpha[14], IL-1 alpha [14]

Physiological: Stress [15]

Infectious: Propionibacterium acnes [16,17], Staphylococcus aureus [18]

Diet: Milk consumption [19-21], High glycemic index foods [19,22]

Poor Prognostic Factors in Acne:

- Family history
- Early onset: mild facial comedones, early and more facial sebum production, early onset relative to menarche.
- Hyperseborrhoea

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- Site of acne: truncal
- Scarring
- Persistent

TREATMENT OF ACNE:

Non pharmacotherapy: Diet therapy like low glycemic index diet[22] and avoidance of junk food.

Pharmacotherapy:

- Topical acne therapies:
  retinoid like agents[23] (adapalene, tretinoin, tazarotene), benzoyl peroxide, azelaic acid, nicotinamide, salicylic acid, dapsone, sulphur, resorcin, steroids
- Oral therapy includes:
  1. Antibiotics[24] –tetracycline, doxycycline, lymecycline, minocycline, trimethoprim/sulfamethoxazole, erythromycin, azithromycin
  2. Oral isotretinoin
  3. Selective aldosterone antagonists: spironolactone[24]
  4. Combined oral contraceptive pills[21,22]: ethinyl estradiol and noretindrone /norgestimate /drosperinone

Topical acne therapies[28]:

Agent	Sebum production	Comedogenesis	Antimicrobial activity	Inflammation
Adapalene	_	+++	_	++
Tretinoin	_	+++	_	+
Azelaic acid	_	+	+	+
Benzoyl peroxide	_	+	+++	++
Clindamycin	_	+	+++	+++
Erythromycin	_	+	+++	+++
Tetracycline	_	+	+++	++
Nicotinamide	_	+	+	+

- Topical retinoids: vitamin A acid and other topical retinoids reduce abnormal growth and development of keratinocytes within pilosebaceous duct. The reversal of hypercornification within the canal as well as the induction of follicular epithelium helps to unplug the follicle.[29] This also inhibits the development of microcomedo and non- inflamed lesions resulting in less anaerobic conditions with fewer P. acnes, making the microenvironment less favorable for development of inflammation. Some novel retinoids reduce rupture of comedones into surrounding skin which results in less inflammation.[29, 30]

  Adapalene binds to specific retinoic-acid nuclear receptors and modulates cellular differentiation, keratinization, and inflammatory processes; [31] exact mechanism of action for

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treatment of acne is unknown. Adverse effects include dryness, scaling, burning/stinging, erythema, skin discomfort, pruritus, desquamation, sunburn.

- Benzoyl peroxide: Benzoyl peroxide is a powerful antimicrobial agent [32] destroying both surface and ductal bacterial organisms and yeasts. Its lipophilic properties permit penetration of the pilosebaceous duct and its efficacy is largely against superficial inflammatory lesions. Once applied to the skin, benzoyl peroxide decomposes to release free oxygen radicals, which have potent bactericidal activity in the sebaceous follicles and anti-inflammatory action. It also has effects on noninflammatory lesions by reducing follicular hyperkeratosis to some degree. Adverse effects include dryness or peeling of skin, feeling of warmth, tingling, slight stinging, burning, blistering, itching, redness, rash, swelling.
- Azelaic acid: It reduces comedones by normalizing the disturbed terminal differentiation of keratinocytes in the follicle infundibulum. It also has direct anti-inflammatory effect. It is not sebosuppressive.
- Topical nicotinamide: it has anti-inflammatory actions and does not induce P.acnes resistance.
- Salicylic acid: effective in reducing acne lesions both non inflammatory and inflammatory
- Topical dapsone
- Others:
  Sulphur: it is both comedogenic and comedolytic. Rarely used because of its smell.
  Resorcin
  Steroids: potent steroids like clobetasol propionate applied twice daily for 5 days can reduce inflammation in active inflammatory nodule.

Oral Therapy: Systemic therapy for the treatment of acne include: antibiotics, hormones, isotretinoin and steroids

Antibiotics[33, 34]**:** indicated in cases of severe acne, moderate facial acne not responding to topical therapies and/or extensive truncal acne

Antibiotic	Dosage	Adverse effects
Azithromycin[35]	250-500 mg three times weekly	GI upset, diarrhea (most commonly)
Oxytetracycline	500 mg twice daily	GI upset, onycholysis, photosensitivity, benign intracranial hypertension
Lymecycline	300-600 mg daily	As oxytetracycline but better tolerated
Doxycycline	100-200 mg daily	As oxytetracycline; photosensitivity dose dependent
Minocycline	100-200 mg daily	Headaches and dizziness associated with benign intracranial hypertension, pigmentary changes, autoimmune hepatitis, LE like syndrome
Erythromycin	500 mg twice daily	GI upset, nausea, diarrhea
Trimethoprim	200-300 mg twice daily	Maculopapular rash, hepatic/renal toxicity, agranulocytosis

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Mechanism of action: there are several mechanisms of action; they have anti- inflammatory effects[36] as well as antibacterial activity. Tetracycline and erythromycin are bacteriostatic especially in large doses. In smaller doses oral antibiotics do not reduce the number of organisms, but they do affect their function. Support for the important role of antibacterial therapy in the management of acne includes the fact that P.acnes is integral to the mediation of inflammation in acne; successful treatment with antibiotics is associated with significant reduction in P.acnes. Antibiotics also inhibit various enzyme activities and modulate chemotaxis, lymphocyte function and proinflammatory cytokines.

Hormonal: Hormonal therapies can be used in females with acne, especially those with premenstrual acne flares in whom other therapies have failed. Patients may also have signs of hyperandrogenism (e.g., hirsutism, irregular menses, menstrual dysfunction). Serum androgen levels may or may not be elevated.

Available options include combination estrogen-progestin oral contraceptive pills, which suppress ovarian androgen production as well as androgen receptor blockers that block the effect of androgens peripherally at the sebaceous gland.

Ethinyl estradiol, drospirenone, and levomefolate: Combination of estrogen and progestin. Suppresses ovarian production of androgens.
Ethinyl estradiol and norethindrone: Combination of estrogen and progestin. Suppresses ovarian production of androgens.
Ethinyl estradiol and norgestimate: Combination of estrogen and progestin. Suppresses ovarian production of androgens.
Ethinyl estradiol and drospirenone: Combination of estrogen and progestin. Suppresses ovarian production of androgens.
Aldosterone antagonists: Aldosterone antagonists may reduce free testosterone levels and compete with androgens binding at the sebaceous gland.
Spironolactone: Aldosterone antagonist that competes with testosterone and dihydrotestosterone binding at the receptor in the sebaceous gland. It also reduces free testosterone levels as more blood is bound by increased quantity of SHBG.

Oral Isotretinoin: it is a synthetic vitamin A analogue (13-cis-retinoic acid). Oral isotretinoin is the only treatment that has an effect on all the major etiological factors involved in acne, by influencing cell cycle progression, cellular differentiation, cell survival and apoptosis.[37] It lowers sebum production, reduces comedogenesis and surface and ductal P. acnes. It also has anti-inflammatory effects.

The primary indication for Isotretinoin is the treatment of severe cystic acne vulgaris.[38,39] Many dermatologists also support its use for treatment of lesser degrees of acne that prove resistant to other treatments. A dose of 0.5-1.0 mg/kg body wt is usually prescribed.

Common adverse effects include chelitis, dermatitis, dry skin, localized exfoliation, pruritus, rash, erythematous, skin fragility, anemia, increased red blood cell sedimentation rate, thrombocytopenia, thrombocytosis, blepharitis, conjunctivitis, dry eyes, eye irritation, arthralgia, myalgia, back pain.

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Steroids: Oral prednisolone (0.5-1.0 mg/kg body wt/day) could be prescribed in patients with severe inflammatory acne vulgaris and in acne fulminans and pyoderma faciale.[40] It is also indicated in patients whose acne flares badly while taking oral isotretinoin.[40]

Procedures:

- Manual extraction of comedones[41]
- Intraleisional steroid injection[42]
- Superficial peels using glycolic and salicylic acid

COMBINATION OF ADAPALENE AND BENZOYL PEROXIDE

Mechanism of Action: Adapalene: Binds to specific retinoic acid nuclear receptors and modulates cellular differentiation, keratinization and inflammatory processes; exact mechanism of action for treatment of acne is unknown.

Benzoyl peroxide: Elicits action by releasing active oxygen; effective in vitro against Propionibacterium acnes, an anaerobe found in sebaceous follicles and comedones; also elicits a keratolytic and desquamative effect which may also contribute to its efficacy.

Pharmacokinetics: Absorption: Benzoyl peroxide absorbed by the skin where it is converted to benzoic acid.

Excretion: adapalene (bile), benzoyl peroxide (urine)

Adverse Effects: >10%:stinging/ burning, dryness, scaling, erythema

1-10%: contact dermatitis, application site burning, application site irritation, skin irritation

METHODS:

Study Design: This is an open label study conducted in the Department of Dermatology, KIMS hospital, Bangalore. Participants were randomized in 1:1:1 ratio to topical adapalene 0.1% gel monotherapy, topical benzoyl peroxide 2.5% gel monotherapy and topical adapalene 0.1% – benzoyl peroxide 2.5% gel combination therapy. Participants were instructed to apply their respective treatment to the face once daily at night for 12 weeks. A total of 62 participants were randomized and 20 participants received adapaene 0.1% gel, 20 participants received benzoyl peroxide 2.5% gel and 22 received combination of 0.1% adapalene & 2.5% benzoyl peroxide combination gel. Efficacy and adverse effects were noted at the end of 1, 2,4, 8 and 12 weeks.

Participants: Male and female participants in the age group of 18 to 38 years with grade 2 or 3 facial acne vulgaris as per investigators global assessment of acne scale were recruited.

Exclusion Criteria: Participants with

- Diabetes mellitus
- Hypertension
- Pregnant or lactating women
- Allergy to adapalene or benzoyl peroxide
- Those who failed to follow up/ unwilling to give their consent
- Participants on oral/ injectable steroids, anti-epileptic, anti-tuberculosis and anti-psychotic drugs.
- Those unwilling to participate in the study.

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Outcome Assessment: Efficacy of treatment based on total lesion count reduction and adverse effects (dryness/erythema/stinging or burning/scaling) were noted.

Statistical Analysis: Percentage lesion count reduction and adverse effects (dryness/erythema/stinging or burning/scaling) were analyzed by chi square test and anova. A p value of <.05 was considered significant.

RESULTS: in this study 50% participants had grade 2 acne and 50% had grade 3 acne as per investigators global assessment of acne scale. Out of 62 participants in the study, 55 participants completed the study. The rate for discontinuation was 4.54% for combination of adapalene 0.1% and benzoyl peroxide 2.5% group(group BPA) whereas 15% each for adapalene 0.1%(group A) and benzoyl peroxide 2.5% (group BP) monotherapy group.

	Group BPA	Group BP	Group A	P value
White Heads	11.76±4.98	16.54±7.74	13.57±6.91	0.150
Black heads	15.00±8.27	14.27±6.08	9.53±5.88	0.065+
Papules	2.85±1.35	3.56±1.46	2.93±1.59	0.310

White heads, Black heads and Papules in three groups studied (at beginning of study)

Grade ACNE	Group BPA	Group BP	Group A	Total
Grade 2	9(40.9%)	8(40%)	14(70%)	31(50%)
Grade 3	13(59.1%)	12(60%)	6(30%)	31(50%)
Total	**22(100%)**	**20(100%)**	**20(100%)**	**62(100%)**

Grade ACNE (at beginning of study)

In this study a significant reduction in whiteheads i.e. by 16.49%, 52.46%, 76.11%, 85.78% and 93.96% at the end of weeks 1,2, 4, 8 and 12 respectively with p<0.05 was noted in participants using combination therapy. In case of participants using adapalene 0.1% gel monotherapy the reduction was 74.2% and 69.77% in those using benzoyl peroxide 2.5% gel monotherapy at the end of week 12 of the study.

Assessment of lesion count-whiteheads	Group BPA	Group BP	Group A	P value
1st week	9.82±5.53	16.54±7.74	12.50±5.46	0.021*
2nd week	5.59±5.83	12.45±6.65	12.08±6.20	0.007**
4th week	2.81±4.46	9.50±8.64	5.50±6.43	0.046*
8th week	1.67±3.09	7.22±7.12	5.50±6.43	0.049*
12th week	0.71±1.82	5.00±7.07	3.50±6.69	0.162

Assessment of lesion count-whiteheads at follow up

In case of blackheads, reduction noted was 6.66%, 9%, 44.53%, 61.27% and 74.2% at the end of weeks 1, 2, 4, 8 and 12 respectively in participants using combination therapy. In case of

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participants using adapalene 0.1% gel monotherapy the reduction was28.33% and 45.83% in those using benzoyl peroxide 2.5% gel monotherapy at the end of week 12 of the study.

Black heads	Group BPA	Group BP	Group A	P value
1st week	14.00±7.54	13.40±6.08	9.53±5.88	0.129
2nd week	13.65±7.89	13.85±6.18	9.21±6.18	0.139
4th week	8.32±4.83	11.67±4.44	9.25±7.05	0.255
8th week	5.81±5.28	9.55±5.68	6.83±5.17	0.213
12th week	3.87±4.70	7.73±6.07	6.83±5.17	0.155
Assessment of lesion count: Black heads at follow up				

In case of papules, reduction noted was 3.51%, 7.01%, 25.96%, 48.42% and 64.91%(p=0.027) at the end of weeks 1,2, 4, 8 and 12 respectively in participants using combination therapy. In case of participants using benzoyl peroxide 2.5% gel monotherapy the reduction was 26.4% at the end of week 12 of the study. In participants using adapalene 0.1% gel monotherapy an increase in papules by 10.92% at the end of week 12 of study though a reduction was noted in the initial study period.

Papules	Group BPA	Group BP	Group A	P value
1st week	2.75±1.45	3.56±1.46	2.79±1.76	0.244
2nd week	2.65±1.42	3.47±1.55	2.92±1.80	0.320
4th week	2.11±1.41	2.86±1.56	2.58±1.68	0.369
8th week	1.47±1.33	2.85±2.30	2.58±1.68	0.089+
12th week	1.00±1.26	2.62±2.36	3.25±2.90	0.027*
Assessment of lesion count: Papules at follow up				

Dryness was noted in 54.5% participants using combination therapy, 45% participants using adapalene 0.1% gel and 45% participants using benzoyl peroxide 2.5% gel at the end of week 1 of the study. Dryness was noted in 4.5% participants using combination at the end of week 12 of study whereas it was absent in participants using monotherapies at the end of week 12 of study.

Dryness	Group BPA (n=22)	Group BP (n=20)	Group A (n=20)	Total (n=62)
1st week	12(54.5%)	9(45%)	9(45%)	30(48.4%)
2nd week	10(45.5%)	4(20%)	4(20%)	18(29%)
4th week	3(13.6%)	1(5%)	1(5%)	5(8.1%)
8th week	2(9.1%)	0(0%)	1(5%)	3(4.8%)
12th week	1(4.5%)	0(0%)	0(0%)	1(1.6%)

Erythema was noted in 13.4% participants using combination therapy at the end of week 1 of study whereas no such adverse effect was noted in participants using monotherapies.

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Erythema	Group BPA (n=22)	Group BP (n=20)	Group A (n=20)	Total (n=62)
1st week	3(13.6%)	0(0%)	0(0%)	3(4.8%)
2nd week	3(13.6%)	0(0%)	0(0%)	3(4.8%)
4th week	0(0%)	0(0%)	0(0%)	0(0%)
8th week	0(0%)	0(0%)	0(0%)	0(0%)
12th week	0(0%)	0(0%)	0(0%)	0(0%)

Stinging/burning was noted in 45.5% participants using combination therapy, 20% participants using benzoyl peroxide 2.5% gel and 30% of participants using adapalene 0.1% gel at the end of week 1 of study. No such adverse effects were noted in any of the groups at the end of week 12 of study.

Stinging/burning	Group BPA (n=22)	Group BP (n=20)	Group A (n=20)	Total (n=62)
1st week	10(45.5%)	4(20%)	6(30%)	20(32.3%)
2nd week	9(40.9%)	1(5%)	2(10%)	12(19.4%)
4th week	1(4.5%)	1(5%)	1(5%)	3(4.8%)
8th week	1(4.5%)	0(0%)	0(0%)	1(1.6%)
12th week	0(0%)	0(0%)	0(0%)	0(0%)

Scaling was noted in 9.1% participants using combination therapy, 5% participants using benzoyl peroxide 2.5% gel and 10% participants using adapalene 0.1% gel. No such adverse effects were noted in any of the groups at the end of week 12 of study.

Scaling	Group BPA (n=22)	Group BP (n=20)	Group A (n=20)	Total (n=62)
1st week	2(9.1%)	1(5%)	2(10%)	5(8.1%)
2nd week	2(9.1%)	0(0%)	0(0%)	2(3.2%)
4th week	0(0%)	1(5%)	0(0%)	1(1.6%)
8th week	0(0%)	0(0%)	0(0%)	0(0%)
12th week	0(0%)	0(0%)	0(0%)	0(0%)

Week 1 Week 2

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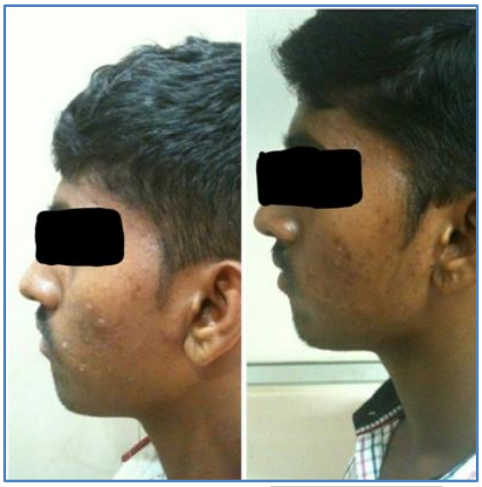

Week 1 Week 4

DISCUSSION: To the best of our knowledge there are only a few studies comparing the combination of adapalene and benzoyl peroxide against adapalene monotherapy and benzoyl peroxide monotherapy in acne treatment on Indian skin.

In one of the studies, do Nascimento et al [43] the efficacy and safety of 0.1% adapalene and 4% benzoyl peroxide on 178 patients after 11 weeks of treatment. They found benzoyl peroxide more effective than adapalene on non-inflammatory and inflammatory lesions at weeks 2 and 5, and they found both drugs safe.

Handojo [44] used topical 5% benzoyl peroxide gel and retinoic acid cream in combination and alone and reported that combination therapy was more superior.

In a North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne[45], it was reported that: in a large clinical trial, the fixed dose combination gel had shown superiority in efficacy compared with adapalene and benzoyl peroxide monotherapies vehicle, with an early onset of efficacy and a good safety profile.

In our study, a combination of topical adapalene 0.1% and benzoyl peroxide 2.5% gel was found to be more efficacious in comparison to topical adapalene 0.1% gel or topical benzoyl peroxide 2.5% gel monotherapy in facial acne treatment.

The most common side effects noted for participants using combination therapy were dryness followed by stinging/burning. Other side effects noted were erythema and scaling. These side effects were more pronounced during beginning of treatment and reduced as treatment continued.

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