Efficacy of Isotretinoin and Antihistamine versus Isotretinoin Alone in the Treatment of Moderate to Severe Acne: A Randomised Control Trial

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ABSTRACT

Background

Acne vulgaris has considerable impact on physical and psychological health. Isotretinoin is considered most effective drug available for acne therapy but with limited acceptance because of its adverse effects. Antihistamine inhibits inflammatory mediators, *Propionibacterium acne* induced itching, reduction of squalene and sebum in sebocyte, reduces anxiety and further lessens hormonal derangement and inhibits mast cell induced fibrosis and scars. Clinical relevance is lacking in the use of antihistamine in the treatment of acne and its potential efficacy needs to be clarified.

Objective

To evaluate the efficacy and safety of combining isotretinoin and antihistamine compare to isotretinoin alone in patients with moderate to severe acne at week 12.

Method

One hundred patients with moderate to severe acne were included in this randomised, controlled comparative study. Fifty patients were treated with isotretinoin and 50 patients were treated with additional antihistamine, levocetirizine and assessment was done at baseline, 4, 8 and 12 weeks of treatment.

Result

At week 12, compared to isotretinoin only group, combination of isotretinoin and levocetirizine group showed more statistically significant decrease in score of global acne grading system (51.0 vs. 38.5%) and acne lesion counts (non-inflammatory lesion: 63.2 vs. 44.5%; inflammatory lesions: 75.9 vs. 62.7%; total lesions: 66.07 vs. 48.7%; all $p< 0.05$). Flaring up of acne occurred less frequently and adverse effects were more tolerable in levocetirizine group.

Conclusion

Use of antihistamine with isotretinoin provides synergic effect while minimizing the side effect of isotretinoin and greater clearance of the lesion and scars.

KEY WORDS

Acne, Antihistamine, Isotretinoin, Levocetirizine

INTRODUCTION

Acne vulgaris is one of the most common dermatologic disorders in the general population, highly affecting adolescents with approximately 80% prevalence rate.[1,2] Among the therapeutic agents, isotretinoin is considered to be the most effective drug available.[3,4] However, it needs careful use and monitoring because of unwanted muco-cutaneous side-effects and chance of acne flare leading to discontinuation at the beginning of therapy.[5,6]

To prevent unwanted side effects, not only various dose regimens are being introduced but also new alternatives in reducing sebum are being made. Antihistamine inhibits inflammatory mediators, *Propionibacterium acne* induced itching, reduction of squalene and sebum in sebocyte, reduces anxiety and further lessens hormonal derangement.[7-9]

Therefore, this is the study investigating the role of antihistamine (levocetirizine 5 mg/day) in combination with isotretinoin compared to isotretinoin only to evaluate efficacy and safety in patients with moderate to severe acne.

METHODS

It was an assessor blinded, randomised controlled trial. All patients with diagnosis of moderate to severe acne vulgaris attending Dermatology outpatient department (OPD) of BPKIHS were included in this study with the following exclusion criteria: Age < 18 years of age; female subjects who were pregnant, lactating or planning for pregnancy(teratogenicity of isotretinoin) or with other systemic diseases (e.g. liver disease, dyslipidemia, renal disease); concurrent use of other acne therapies; other dermatological condition requiring interfering treatment; acne global score less than 19 in Global Acne Grading System (GAGS); and any patient who did not give consent.[10]

A total of 92 acne patients (46 in each group) was required in this study to detect clinically significant difference of 26.9% in the reduction of total lesion count [45.6%(combination) versus 18.7% (isotretinoin only)] with an alpha error of 5% and power of 80% (two sided).[11] Considering a dropout rate of 10%, 50 patients in each group were enrolled. A block randomisation list was generated with the block sizes 4, 6 and 8 and seed of 423447893267 to produce two parallel groups (1:1 ratio) of patients with the help of www.sealedenvelope.com. A sequentially generated number with the treatment group was written in a sealed envelope, which was prepared by the independent dermatologist prior to the enrollment of patients.

A total, 100 consecutive patients (50 in each group) randomised to the treatment and assessed between July, 2015 and June, 2016, were included. A written consent was taken after explaining the treatment, possible outcomes and side effects. The patients were randomised into two groups: A) Treatment group: Subject took isotretinoin (10 mg and 20 mg capsule USP, PANAS PHARMACEUTICALS PVT LTD, Nepalgunj, Nepal) at the rate of 0.5-0.6 mg/kg/day in two divided dose with or after food and levocetirizine (5 mg tablet IP, UNICHEM LABORATORIES LTD, H.P, India) 5 mg/day just before sleep and B) Control group: Subject took only isotretinoin at the rate of 0.5-0.6 mg/kg/day in two divided dose with or after food.

Patient's history was recorded in a preset proforma and complete blood count, liver function test and fasting lipid profile was measured at baseline and alanine transaminase (ALT), aspartate aminotransferase (AST) and triglyceride (TG) was measured at the end of 8 weeks as per the standard methods. All patients were assessed at baseline and followed up for 12 weeks at an interval of 4 weeks to evaluate the efficacy and tolerability of these two regimens. Both the study groups were well matched and were similar for the various variables. No any topical medication was allowed except for washing procedure and moisturizer. Ethical approval was taken from the Institutional Review Committee of BPKIHS prior to the conduction of the study (IRC No: 535/015).

Global Acne Grading System (GAGS) was used to grade the patient's acne.[10] Six acne prone areas was delineated and final global score defined the patients from none to very severe acne.

Data regarding the GAGS scores, inflammatory and total lesion counts were collected at baseline and at weeks 4, 8 and 12 and was recorded in the follow-up sheet of proforma by the blinded assessor. Macules were not included in the lesion counts. The efficacy analysis was conducted as intent to treat analysis. The primary efficacy end points were calculated on the basis of the percent reduction from baseline to week 12 in the GAGS scores and lesion counts (inflammatory, non-inflammatory and total lesion count). For all patients who discontinued treatment before 12 weeks, the last observation was carried forward for all efficacy end points for Intention to treat analysis. Digital photographs at baseline and at each follow up visits were taken for objective assessments by an independent dermatologist.

Frequency and severity of acne was assessed at each visit. Severity of acne flare was ranked by using 4-point scales (no new nodules: 1; nodule up to 5:2; nodule 6-10: 3 and nodules > 10:4).

The incidence and severity of cheilitis, dryness of skin and mucosa, facial erythema, scaling, stinging/burning and pruritus, epistaxis, hair loss, photosensitivity, nail changes, and systemic side effects like fatigue, bone/joint pains, muscular cramps etc. were recorded. Safety and tolerability was assessed through evaluations of local signs and symptoms (erythema, scaling, dryness, stinging/burning and pruritus) on a scale of 0 (absent), 1 (mild), 2 (moderate) or severe (3) in each patient at each visit. Any

tolerance parameter (signs or symptoms) classified as "severe" was also recorded as an adverse event. These data were recorded on each visit in follow up sheet of proforma.

The data obtained from the proforma were collected, checked and entered in SPSS data sheet version 10. Statistical analysis was conducted by intention-to treat population basis using two sided tests. An alpha of 0.05 was considered significant. All data were evaluated on the software SPSS version 10 for the comparison of the two groups at the base line and between group differences in the percentage reduction of lesion counts or GAGS by using the Wilcoxon rank sum test. The incidence rate of cutaneous and systemic side effects were compared between the groups by Chi square test. The mean score of dryness, erythema, scaling, stinging/burning and pruritus was also evaluated using Wilcoxon rank sum test.

RESULTS

A total of 80 patients, 41(82%) from the combination group and 39(78%) from the isotretinoin alone group completed the study. Nineteen patients failed to follow up for personal reasons and one from the combination group had to stop the treatment due to transaminitis and hypertriglyceridemia (fig. 1). Both the groups were almost comparable and there was not much difference in baseline characteristics (Table 1).

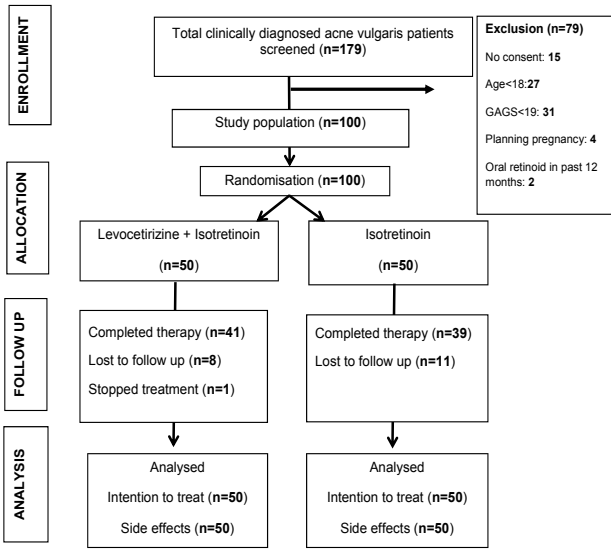


Figure 1. **Flow diagram of the patient through different stages**

Both the non-inflammatory lesions and inflammatory lesions decreased significantly during follow-up visits in both groups. There was significant reduction of 63.2% vs. 44.5% (p=0.005) in the combination group compared to control group at the end of 12 weeks in non-inflammatory lesion count (fig. 2).

Similarly, the reduction in inflammatory lesion count was more i.e. 75.9% and significant (p= 0.010) in combination group compared to isotretinoin alone group i.e. 62.7% at the end of 12 week (fig. 3).

Table 1. **Baseline demographic and clinical characteristics of acne patients**

Characteristics	Group		P value
	Levocetirizine + Isotretinoin	Isotretinoin	
Age (years), Mean ± SD (Median)	21.76±3.88 (21.00)	21.58±4.22 (20.00)	0.825
Sex, N(%)			
Male	11(22)	23(46)	1.00
Female	39(78)	27(54)	
Duration (years)			
Mean±SD	2.76±1.66	3.04±1.22	0.483
(Median)	(2.00)	(3.00)	
Length of treatment (years)			
Mean±SD	2.23±2.31	2.14±1.43	0.870
(Median)	(1.00)	(1.5)	
Family history, N(%)			
Father	11(22)	4(8)	0.050
Mother	7(14)	2(4)	0.081
Siblings	12(24)	17(34)	0.271
Site of lesion, N(%)			
Face, chest and back	45(90)	47(94)	0.461
Face	50(100)	50(100)	1.00
Chest	47(94)	47(94)	1.00
Upper back	45(90)	47(94)	0.461
GAGS			
Mean±SD	29.52±3.861	29.98±4.302	0.51
(Median)	(29.00)	(28.50)	
Non inflammatory lesions			
Mean±SD	149.06±107.6	130.02±67.22	0.29
(Median)	(120.50)	(118.50)	
Inflammatory lesions			
Mean±SD	43.06±33.31	39.00±29.60	0.52
(Median)	(33.50)	(30.50)	
Total lesions			
Mean±SD	192.04±123.27	169.02±77.38	0.26
(Median)	(166.00)	(149.50)	

Along with these findings, there was also significant reduction (p=0.002) in total lesion count (both inflammatory and non-inflammatory) in the treated group compared to control group (66% vs. 48.7%) at 12 week (fig. 4).

The mean GAGS score was 29.52 ± 3.861 and 28.98 ± 4.302 which significantly (p=0.005) reduced to 14.46 ± 5.467 (51.0%) and 17.82 ± 6.07 (38.5%) in the treated and control group respectively at the end of 12 weeks (fig. 5).

Using 4 point scale, 76.2% of patients were 'satisfied' and 23.8% were 'very satisfied' in the isotretinoin alone group. In combination group, 5.3% were 'slight satisfied', 52.6% were 'satisfied' and 42.1% were 'very satisfied'.

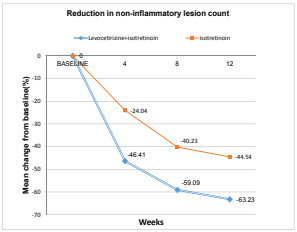


Figure 2. Comparison of reduction in mean non-inflammatory lesion count between two groups.

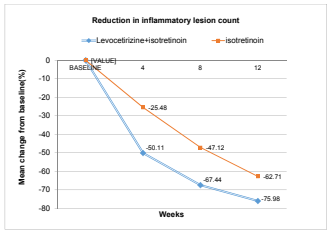


Figure 3. Comparison of reduction in mean inflammatory lesion count between two groups.

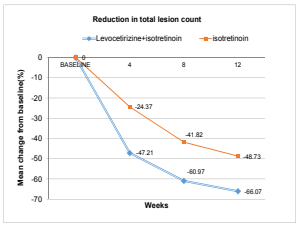


Figure 4. Comparison of reduction in total lesion count between two groups.

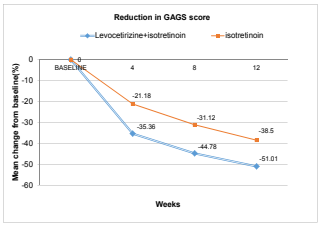
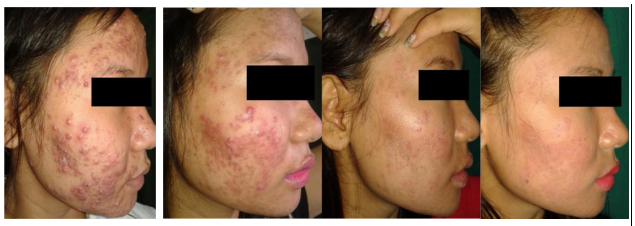
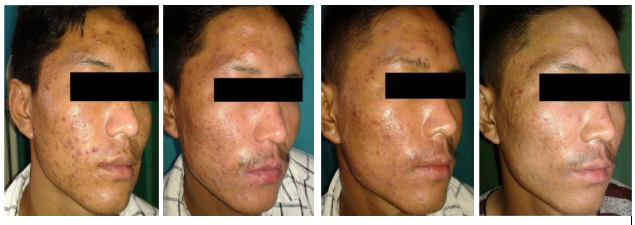


Figure 5. Percentage change in mean GAGS score compared in between two groups.



Baseline GAGS: **36** | At 4 weeks: **26** % reduction: **27.7** | At8 weeks: **21** % reduction: **41.66** | At 12 weeks: **12** % reduction: **66.66**

Illustration 1. Serial photographs showing response of the treatment in Combination group.



Baseline GAGS: **32** | At 4 weeks: **33** % Reduction: **-3.12** | At 8 weeks: **30** % Reduction: **6.25** | At 12 weeks: **30** % Reduction: **6.25**

Illustration 2. Serial photographs showing response of the treatment in Isotretinoin alone group.

Out of 100 patients, 14% got acne flare up. Among the flare ups, only one patient was from the combination group while rest 13 (26%) were from isotretinoin alone group ranging from mild to moderate and it was significantly more in isotretinoin group than combination group. None of the patients got severe flare up in both the groups.

DISCUSSION

Acne is one of the most common dermatological disorders which have a considerable impact on physical and psychological health. Among the therapeutic agents, isotretinoin is considered to be the most effective drug available for inducing a dramatic reduction in size and output of sebaceous glands. However, it has its limitation in acceptance because of its adverse effects (teratogenic and mucocutaneous) and discontinuation of the drug because of flare up of acne at the beginning of treatment. To prevent unwanted side effects and flare up, new alternatives and adjuvants are being considered. Among the adjuvants considered, there is a possible role of antihistamine.

Histamine plays an important role as an inflammatory mediator in the process of immune reaction of inflammatory acne.[12] Likewise *Propionibacterium acnes* produces an optimal environment for the production of histamine or histamine-like products by changing the microenvironment of the acne follicle leading to itching in patients with acne.[7] In addition, itching is a common concomitant symptom of acne lesions.[13] Moreover, itching may also be a complication of acne therapy. Adding up, an in vitro study identifying histamine-1 receptors in sebaceous glands, and histamine-1 receptors antagonists significantly decreases squalene levels leading to a new paradigm for anti-acne therapy as an inhibitor of sebum production.[9] Other considered strength of antihistamines includes anti-anxiety effects of sedative antihistamine lessening further hormonal derangement in patients with acne and inhibition of mast cell induced fibrosis and scars.[8,14]

Bringing together, antihistamine not only acts as an effective anti-inflammatory drug but also has shown to decrease the lipogenesis in sebocytes. Additionally, since isotretinoin has been shown to reduce sebum, antihistamine activity in sebocytes and antipruritic activity may represent an alternative or perhaps an adjunctive treatment to isotretinoin therapy for acne.

However, evidence is lacking regarding the clinically relevant action of antihistamine in the treatment of acne, and its potential efficacy also needs to be clarified. There is only one pilot study done by Lee et al.[11] who compared desloratadine and isotretinoin versus isotretinoin alone and showed more statistically significant decrease in acne lesion counts (non-inflammatory lesions: 44.8% vs. 17.8%; inflammatory lesion: 55.8% vs. 22.9%; total lesions: 45.6% vs. 18.7%, all $p<0.05$).

Levocetirizine dihydrochloride, the R-enantiomer of Cetirizine has potent ability to inhibit cutaneous histamine-induced itching and the wheal and flare reaction; exhibits rapid absorption giving a fast onset and longer duration of receptor occupancy.[15] Levocetirizine acts more effectively than desloratadine on skin weal reactivity.[16,17]

Therefore this study had been undertaken to evaluate the efficacy and safety of combining isotretinoin (0.5 mg/kg/day) and antihistamine (levocetirizine 5 mg/day) compared to isotretinoin alone in patients with moderate to severe acne.

Baseline demographic and clinical characteristics in both the group was almost comparable. However, the mean duration of illness in both the group was slightly lower than Lee et al. findings.[11] This delay in treatment can be

attributed to general belief in adolescents that it subsides with time and another could be inadequate past treatment.

There was significant reduction in non-inflammatory lesion count in all the three follow ups in combination group compared to isotretinoin alone group. The reduction in former and latter group was 63.2% vs. 44.5% at the end of 12 weeks ($p<0.05$). In a similar study in the past, Lee et al. observed significant reduction in non-inflammatory lesion 44.8% vs. 17.8% in the treated and control group respectively at the end of 12 weeks.[11]

Likewise in the present study the reduction in inflammatory lesion count was more and statistically significant in levocetirizine and isotretinoin group compared to isotretinoin alone group, 75.9% vs. 62.7% at the end of 12 week (p value= 0.010). Similarly, Lee et al. also found similar reduction in desloratadine and isotretinoin group compared to isotretinoin alone group (55.8% vs. 22.9% respectively) and was significant.[11]

There was 51% reduction of mean GAGS score in levocetirizine and isotretinoin regimen compared to 38.5% reduction in mean GAGS score in isotretinoin alone regimen at the end of 12 week, which was statistically significant ($p=0.005$).

Along with these findings, there was also significant reduction in total lesion count (both inflammatory and non-inflammatory) in the treated group compared to control group. At each follow up there was significant reduction and the final reduction was by 66.0% in the former and 48.7% in the latter group at the end of 12 weeks. In the study done by Lee et al. they found similar finding of 45.6% and 18.7% reduction from the baseline total lesion count in treated group compared to control group and was statistically significant.[11] This may be due to additional antihistamine induced anti-inflammatory effects and decrease squalene synthesis and decrease lipogenesis in the sebocytes.

The most common side effect observed in both groups was cheilitis, skin dryness, facial erythema, nose dryness, pruritus, eyes dryness and scaling (Table 2). Other side effects observed were burning sensation, skin rash, photosensitivity and, epistaxis, oiliness and hair loss. Among these side effects, skin dryness and pruritus was found to be significantly reduced from baseline in the treated group compared to control group. This may be attributed to additional blockage of histamine receptors and inflammatory cytokines in the sebocyte. In the similar type of study done by Lee et al. the most common side effects observed were cheilitis (75% and 90%) followed by skin dryness (40% and 45%) followed by pruritus (15% and 45%) respectively in the treated and control group.[11]

Table 2. Overall tolerability recorded during follow-up in each group

Adverse effects	Levocetirizine + isotretinoin (N=50)	Isotretinoin (N=50)
Skin dryness	76	92
Nose dryness	46	27
Mouth dryness	100	100
Eye dryness	22	10
Epistaxis	8	2
Face erythema	72	66
Scaling	16	14
Pruritus	18	50
Burning	4	12
Oiliness	2	6
Skin rash	10	8
Hair loss	10	0
Photosensitivity	6	12

Levocetirizine as an adjuvant with isotretinoin has shown significant clinical benefit in terms of clearance of non-inflammatory, inflammatory and total lesion count along with significant reduction in GAGS score compared to isotretinoin alone in the treatment of moderate to severe acne in our study. The local side effects were minimal and tolerable in both the groups, but skin dryness and pruritus were significantly less in combination group than in isotretinoin alone group.

Thus, our study supports the result of previous pilot study done by Lee et al. which showed greater efficacy of combination of desloratadine and isotretinoin as compared to isotretinoin alone when given for a 12 weeks period.[11]

The main limitations of our study were: Single centered study; single blinded (assessor blinded); if any flare up of lesion after 12 weeks, could not be assessed and long term follow up was not done because of limited time period.

CONCLUSION

Combination of levocetirizine and isotretinoin is more efficacious in terms of clearance of both non-inflammatory and inflammatory lesion and significant reduction in GAGS score with less adverse effect and less flare up and further; multicenter, double blinded studies are required to support the current study and evaluate future relapse at long term follow up.

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