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Efficacy and Safety Profile of Spironolactone 50mg v/s Isotretinoin 10mg in the Treatment of Female Patients with Acne Vulgaris Grade 1-2 - A Double Blinded, Randomized Comparative Study

Authors
Natasha Vijayendran[1], Mohan Kale[2], Varsha Jamale[3], Balkrishna Nikam[4], Asma Hussain[5], Shraddha J. Patil[6]
[1,6]Junior resident (Dermatology) Krishna Institute of Medical Sciences, Karad, Maharashtra
[2]Professor and Head of the Department (Dermatology) Krishna Institute of Medical Sciences, Karad, Maharashtra
[3]Associate Professor (Dermatology) Krishna Institute of Medical Sciences, Karad, Maharashtra
[4,5]Assistant Professor (Dermatology) Krishna Institute of Medical Sciences, Karad, Maharashtra
Corresponding Author
Natasha Vijayendran
Department of Dermatology, Krishna Institute of Medical Sciences, Karad, Maharashtra, India – 415110
Email: *natashavijayendran@hotmail.com*, Phone No - +91 9820074189

Abstract
Background: *The recognition that post-adolescent women with AV respond to antiandrogenic hormonal therapies has prompted a sustained interest in oral spironolactone. We took this as an opportunity to determine the safety and efficacy of two treatment modalities for acne vulgaris grade 1-2 and provide standardized data regarding spironolactone as a treatment agent in acne vulgaris. This is the first double blinded study where low dose spironolactone and low dose isotretinoin has been studied.*
Aims: *To study the efficacy and safety profile of oral spironolactone v/s oral isotretinoin in the treatment of female patients with acne vulgaris grade 1-2.*
Materials and Method: *60 patients were enrolled in the study. Thirty patients were treated with oral spironolactone (50mg/day) with topical clindamycin 1% and the other thirty were given oral isotretinoin (10mg/day) with topical clindamycin 1%. Efficacy variables used were Global Acne Grading System (GAGS) score, Physicians Global Assessment (PGA) and Visual Analogue Scale (VAS). The response was evaluated fortnightly for a total period of 12 weeks.*
Results: *At the end of the study, there was a 32.8% reduction in GAGS scores in the spironolactone group and 68.4%, in the isotretinoin group. The response of female patients to acne vulgaris grade 1-2 with isotretinoin was superior to that of spironolactone and this difference was statistically significant ($p<0.05$). The side effects were minimal with no laboratory abnormalities.*
Conclusion: *Isotretinoin and spironolactone are both efficacious. However, isotretinoin is more efficacious than spironolactonein the treatment of acne vulgaris (grade 1-2).*
Keywords: *Acne vulgaris, Spironolactone, Isotretinoin, Clindamycin.*

Introduction

Acne vulgaris (AV) is usually perceived as a disorder that affects primarily teenagers; however, preteens and post-adolescents are commonly affected. Outpatient visits by patients 25 years of age or older has increased over the past 10 years.[1]

AV can have a significant impact on the emotional and psychological wellbeing of affected individuals and has been compared to other major diseases in terms of adverse impact on quality of life.[2] While many individuals experience AV that regresses soon after they complete their teenage years, there is a subset of patients that notes persistence throughout later adulthood, with some noting the onset of AV in their adult life, the latter especially in women. Adults may be more conscious of their acne because it is considered a "disease of teenagers".[1]

In recent years, due to better understanding of the pathogenesis of acne, new therapeutic modalities are designed.[3] Availability of new treatment options to complement the existing armamentarium should help to achieve the successful therapy of greater numbers of acne patients, ensure improved tolerability and fulfil patient expectations. Successful management of acne needs careful selection of anti-acne agents.

The recognition that post-adolescent women with AV respond to antiandrogenic hormonal therapies has prompted a sustained interest in oral spironolactone.[1]

We took this as an opportunity to determine the safety and efficacy of two treatment modalities for acne vulgaris grade 1-2 and provide standardized data regarding spironolactone as a treatment agent in acne vulgaris.

Application of this study for betterment of patient care and the community is of great significance as the treatment guidelines and various other parameters affecting treatment have been studied here. Thus, reducing the severity of the disease and providing comfort to the patient.

Materials and Method

This was a hospital based, randomised, prospective, double blinded, controlled comparative study carried out between June 2015 and December 2017 in patients attending Dermatology OPD.

60 patients who met the inclusion and exclusion criteria; after written and signed consent were randomised into 2 groups. All systemic and topical medication was stopped prior to the initiation of treatment as it could affect the outcome of the study.

Group A patients (n=30) received oral isotretinoin (10mg/day) and topical clindamycin 1%, while group B patients (n=30) received oral spironolactone (50mg/day) and topical clindamycin 1%. Efficacy variables used were Global Acne Grading System **(**GAGS) score, Physicians Global Assessment (PGA) and Visual Analogue Scale (VAS).

The response was evaluated fortnightly using the efficacy variables, clinical photographs and safety variables (clinical adverse effects and laboratory investigations) for a total period of 12 weeks. Laboratory tests consisting of complete blood count, urine routine microscopy, liver and renal function tests, lipid profile, chest x-ray, ECG and urine pregnancy test were performed at initiation of treatment and at 2^{nd} and 4^{th} visits. Patients were advised on each visit to have proper dual contraceptive methods to prevent pregnancy. (Table 1)

As this was a double blinded study, neither the patient nor the investigator knew which medication the patient was receiving. The role of the investigator was to evaluate the patient using the efficacy variables and assess the safety profile. The co-investigator would randomize the patients into the 2 groups and dispense the medication.

The study protocol was approved by the ethics committee before initiation.

Data collected was analysed using Student's t-test and ANNOVA test. Level of significance was set at $p < 0.05$.

Results

60 patients completed the study.

Mean age was high in group A (23.1years) compared to group B (22.2 years), but this difference was statistically not significant ($p>0.05$). Thus, demographic data of both the groups was comparable at baseline.

1. **Clinical Efficacy**

Baseline GAGS, PGA and VAS were comparable between the two groups.

After 15 days, in group A mean GAGS score was significantly reduced to 11.97, that is 15.5% reduction from baseline while in group B mean GAGS score was reduced to 10.1 that is 15.1% reduction from baseline. Statistically this was not significant. In group A mean PGA score was reduced to 3.73 (8.4% improvement) and mean VAS was reduced to 78.0 that is 22% reduction from baseline. While in group B, mean PGA score was reduced to 3.47 (10.3% improvement) and mean VAS was reduced to 86.67 that is 13.33% reduction from baseline. Group B showed better improvement in reducing the PGA score as compared to group A. However, there was no statistically significant difference between both the groups. Group A showed better improvement in reducing the VAS score as compared to group B. There was a statistically significant difference between both the groups.

After 30 days, in group A mean GAGS score was significantly reduced to 10.07, that is 28.9% reduction from baseline while in group B mean GAGS score was reduced to 9.77 that is 17.9% reduction from baseline. in group A mean PGA score was reduced to 3.03 (25.6% improvement) and mean VAS was reduced to 61.33 that is 38.67% reduction from baseline. While in group B, mean PGA score was reduced to 3.27 (15.5% improvement) and mean VAS was reduced to 79.33 that is 20.67% reduction from baseline. Group A showed better improvement in reducing the PGA score as compared to group B. However, there was no statistically significant difference between both the groups. Group A showed better improvement in reducing the VAS score as compared to group B. There was a statistically significant difference between both the groups.

After 45 days, in group A mean GAGS score was significantly reduced to 8.90, that is 37.2% reduction from baseline while in group B mean GAGS score was reduced to 9.03 that is 24.1% reduction from baseline. In group A, mean PGA score was reduced to 2.6 (36.1% improvement) and mean VAS was reduced to 47.67 that is 52.33% reduction from baseline. While in group B, mean PGA score was reduced to 2.97 (23.2% improvement) and mean VAS was reduced to 73.0 that is 27.0% reduction from baseline. Group A showed better improvement in reducing the PGA and VAS score as compared to group B. There was statistically significant difference between both the groups.

After 60 days, in group A mean GAGS score was significantly reduced to 6.83, that is 51.8% reduction from baseline while in group B mean GAGS score was reduced to 8.53 that is 28.3% reduction from baseline. Group A showed better improvement in reducing the GAGS score as compared to group B. In group A, mean PGA score was reduced to 2.0 (50.9% improvement) and mean VAS was reduced to 29.0 that is 71% reduction from baseline. While in group B, mean PGA score was reduced to 2.77 (28.4% improvement) and mean VAS was reduced to 68.33 that is 31.67% reduction from baseline. Group A showed better improvement in reducing the PGA and VAS score as compared to group B. There was statistically significant difference between both the groups.

At the end of the study (90 days), in group A mean GAGS score was significantly further reduced to 4.47, that is 68.4% reduction from baseline while in group B mean GAGS score was reduced to 8.0 that is 32.8% reduction from baseline. There was a statistically significant difference in the results between both the groups.

Thus, group A and group B are efficacious in reducing the GAGS score in acne vulgaris grade 1-2. However, group A is much more statistically significant compared to group B. (Table 2) In group A, mean PGA score was reduced to 1.37 (66.3% improvement) and mean VAS was reduced to 12.0 that is 88% reduction from baseline. While in group B, mean PGA score was reduced to 2.63 (32.1% improvement) and mean VAS was reduced to 64.0 that is 36% reduction from baseline. Group A showed better improvement in reducing the PGA and VAS score as compared to group B. There was statistically significant difference between both the groups. Group A and group B are efficacious in reducing the PGA and VAS score in acne vulgaris grade 1-2. However, group A is much more statistically significant compared to group B. (Figure 1, 2, 3, 4, 5, 6, 7)

2. Side effects

56.6% patients of group A and 66.7% patients of group B showed one or more side effects during their visits.

In group A, cheilitis was the most common complaint seen in 53.3% patients, followed by cheilitis with headache which was observed in 3.3% patients.

In group B, menstrual irregularity was the most common complaint seen in 63.4% patients, followed by menstrual irregularity with headache which was observed in 3.3% patients. (Table 2)

Table 1: Visit schedule

PARAMETER	Baseline visit	1st visit	2nd visit	3rd visit	4th visit	5th visit
INFORMED CONSENT	Yes					
MEDICAL HISTORY	Yes					
Physical examination &vitals	Yes	Yes	Yes	Yes	Yes	Yes
Blood Pressure	Yes	Yes	Yes	Yes	Yes	Yes
GAGS	Yes	Yes	Yes	Yes	Yes	Yes
VAS	Yes	Yes	Yes	Yes	Yes	Yes
PGA	Yes	Yes	Yes	Yes	Yes	Yes
Cutaneous examination	Yes	Yes	Yes	Yes	Yes	Yes
Photographs	Yes	Yes	Yes	Yes	Yes	Yes
Chest X-ray	Yes	-	-	-	-	-
Adverse clinical event monitoring	-	Yes	Yes	Yes	Yes	Yes
Investigation	Yes	No	Yes	No	Yes	Yes

Table 2: Results summary

Parameters (% reduction)	Group A	Group B
Mean GAGS	68.4%	32.8%
Mean PGA	66.3%	32.1%
Mean VAS	88%	36%
Side effects seen in	56.6%	66.7%

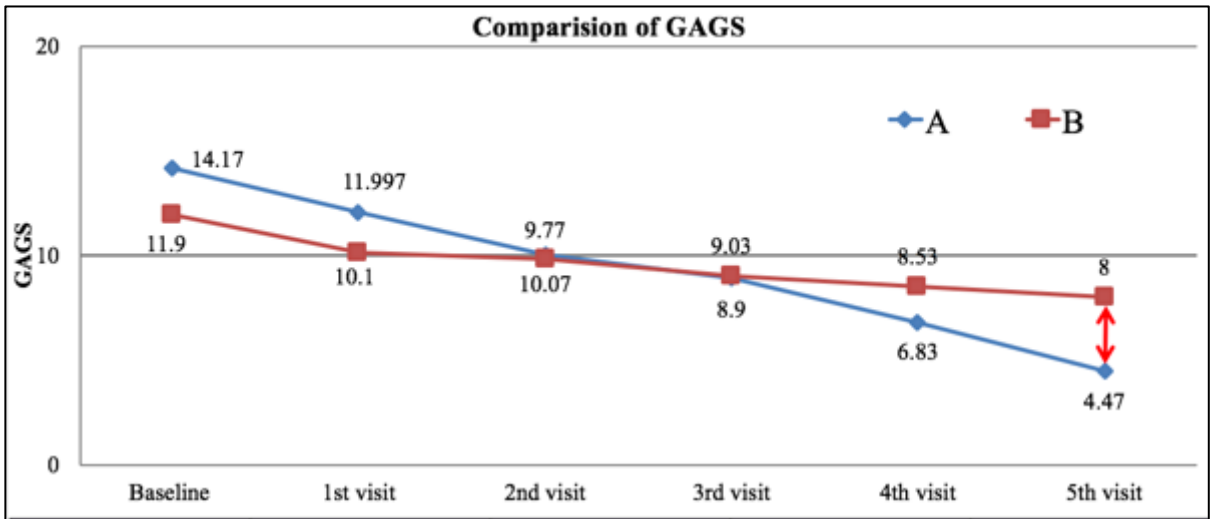
Table 3: Isotretinoin studies

ISOTRETINOIN	Hermes et al. (1998)	Agarwal et al. (2011)	Amichai et al. (2006)	Sardana et al. (2009)	Current study (2017)
Sample size	94	120	638	320	**30**
Mean age (years)	23.5	19.08	16.9	-	**23.1**
Treatment dose	10-50mg/day	Variable regimens	20mg	20mg alternate day	**10mg/day**
Adjuvant dose	-	Topical clindamycin Oral Azithromycin weekly pulse	-	Topical clindamycin	**Topical clindamycin**
Treatment duration (months)	8.3	6	6	6	**3**
Degree of improvement (%)	94.7	88.75	93.7	87.54	**68.4**
Side effects	Low	Significant	Significant (91%)	Mild	**Moderate (56.6%)**

Table 4: Spironolactone studies

SPIRONOLACTONE	Charny et al. (1998)	Vaswani et al. (2011)	Goodfellow et al. (2006)	Muhlemann et al. (2009)	Current study (2017)
Sample size	110	15	36	21	**30**
Mean age (years)	-	-	24	-	**22.2**
Treatment dose	100-150mg/day	100mg/day	50-150mg/day	200mg/day	**50mg/day**
Adjuvant dose	Topical + Oral antibiotics Contraceptive Pills	-	-	Oral contraceptive pills	**Topical clindamycin**
Treatment duration (months)	17	3	3	3	**3**
Degree of improvement (%)	73.1	73.3	75	75	**39**
Side effects (%)	46	20	52	52	**66.7**

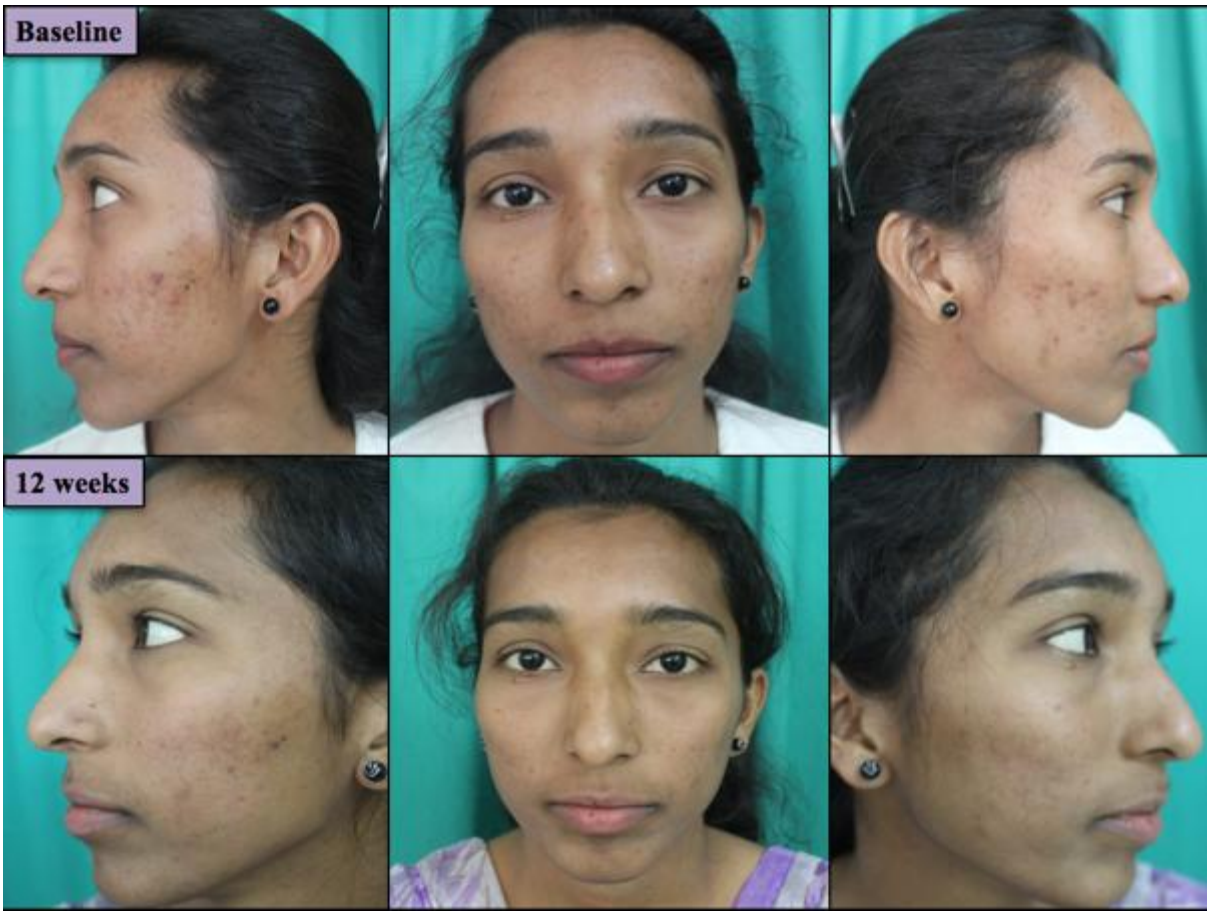
Figure 1: Analysis& comparison of mean GAGS at various time intervals in group A and B

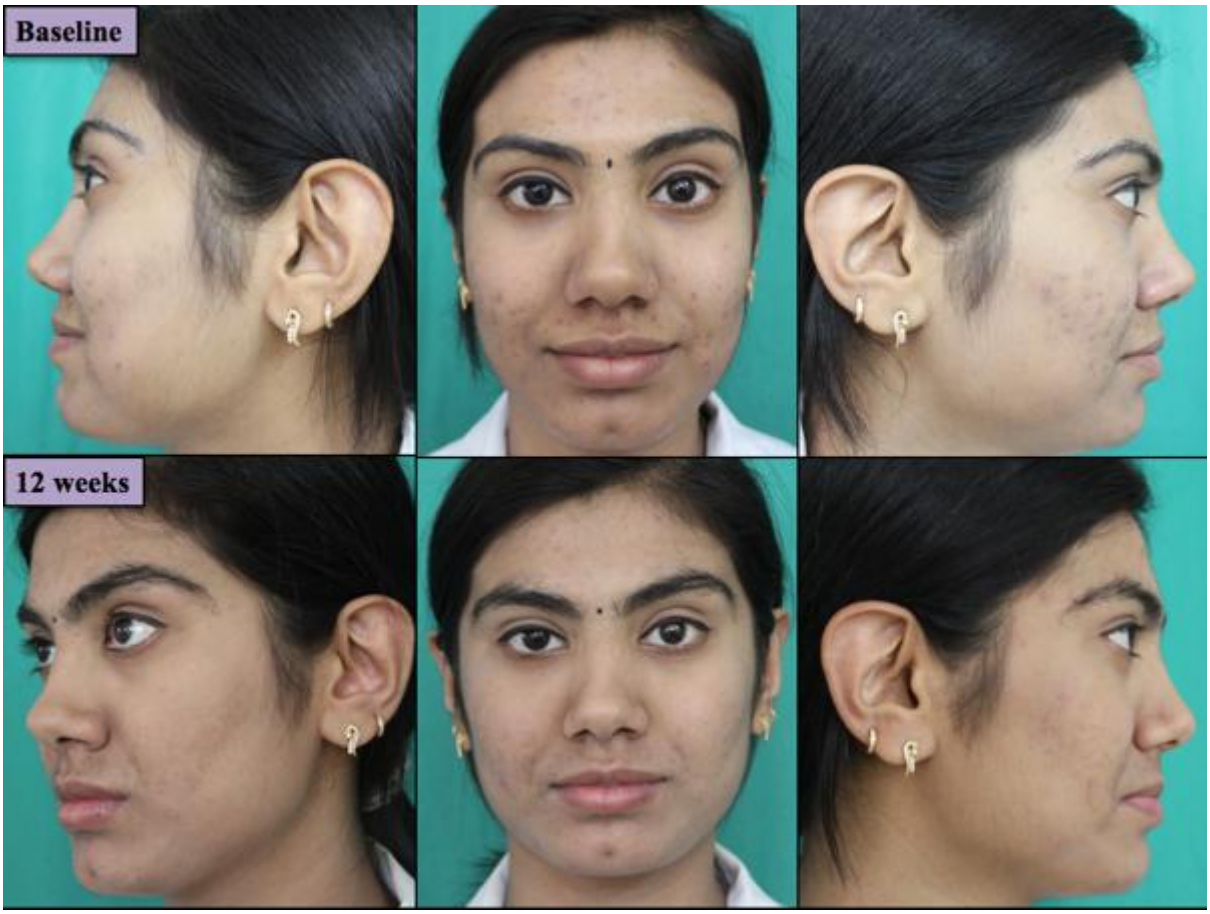


GAGS	Group A Mean	Group B Mean	p value	Difference is
Baseline visit	14.17	11.9	>0.05	Not significant
1st Visit	11.97	10.1	>0.05	Not significant
2nd Visit	10.07	9.77	>0.05	Not significant
3rd visit	8.90	9.03	>0.05	Not significant
4th Visit	6.83	8.53	>0.05	Not significant
5th Visit	4.47	8.0	<0.05	Significant

REDUCTION IN GROUP A IS FAR STEEPER THAN THAT IN THE GROUP B

Figure 2, 3, 4 : Group A (Isotretinoin) patients at baseline and 12 weeks





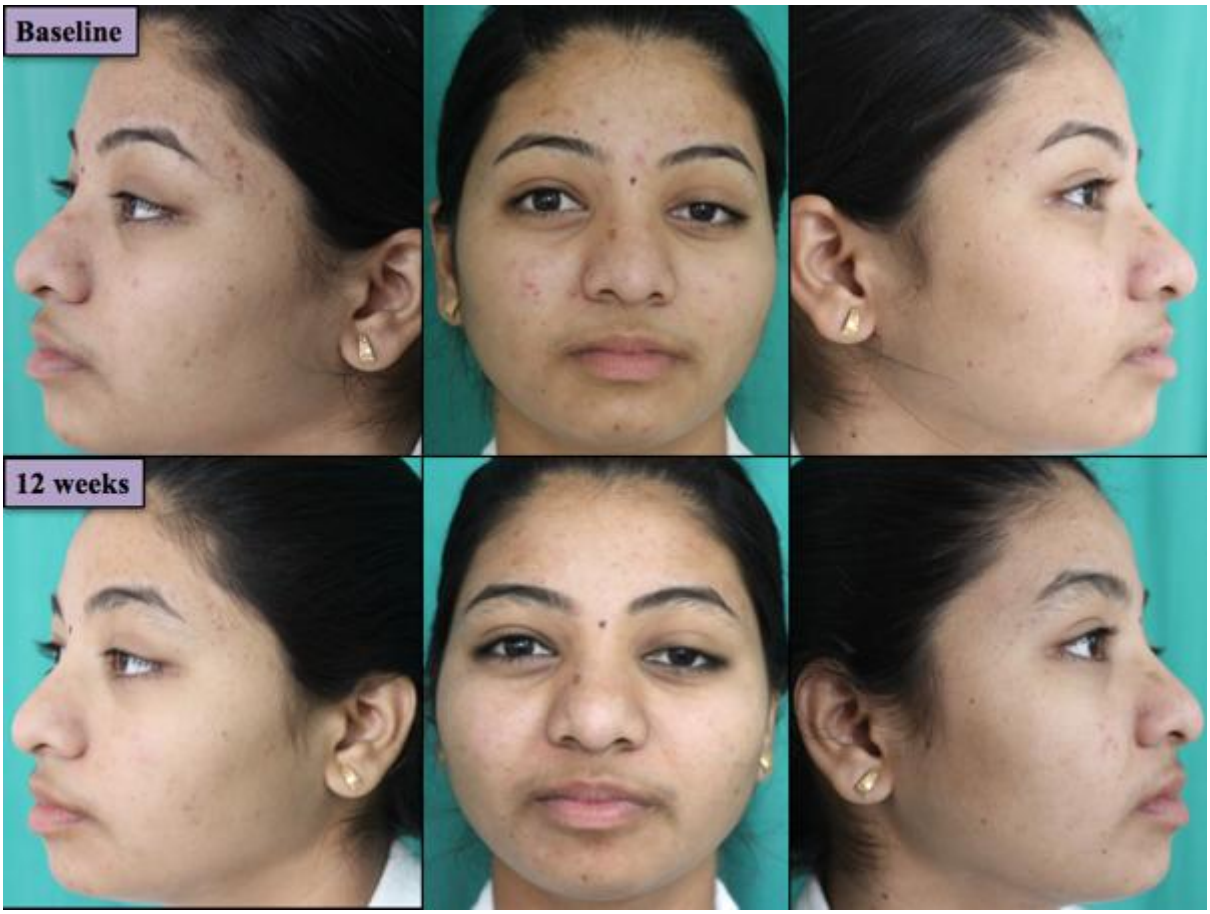
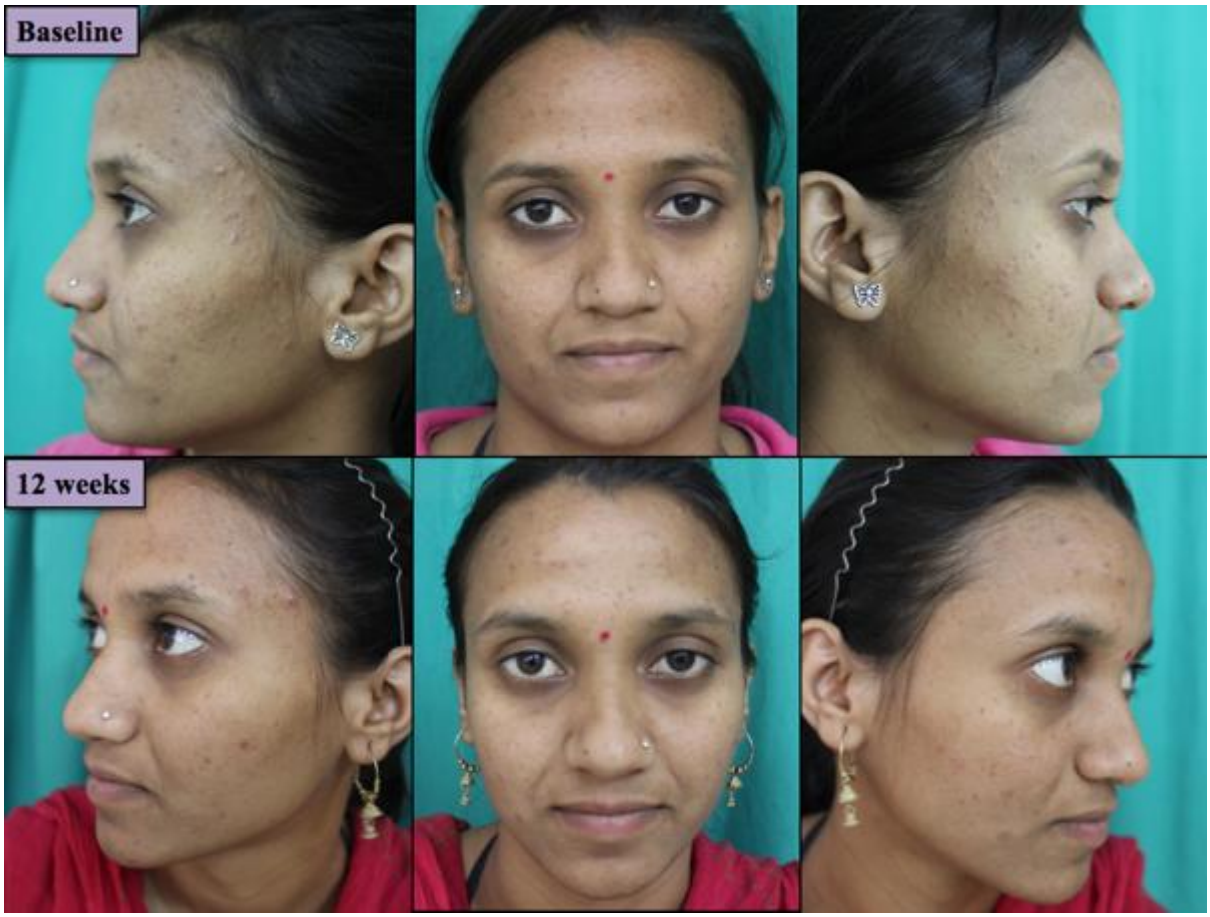
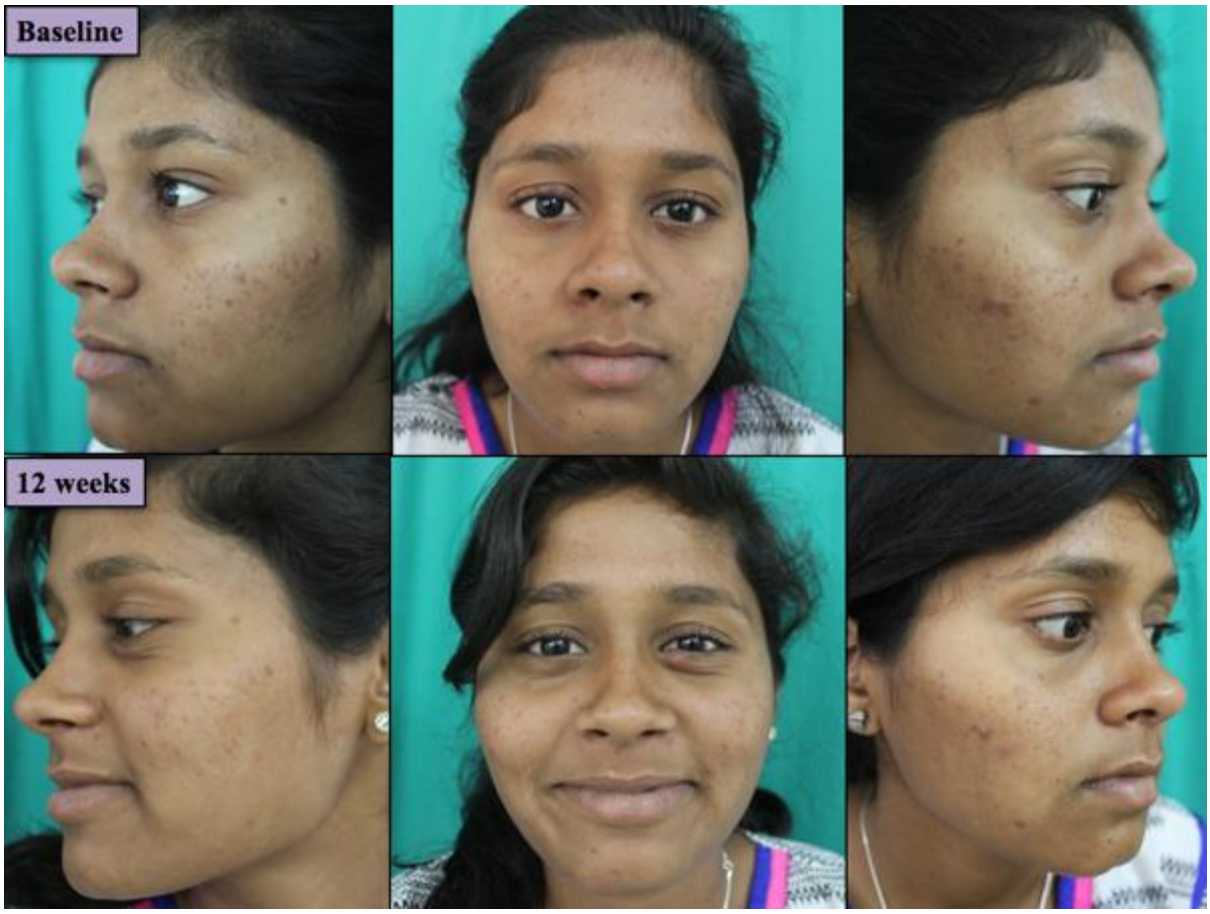
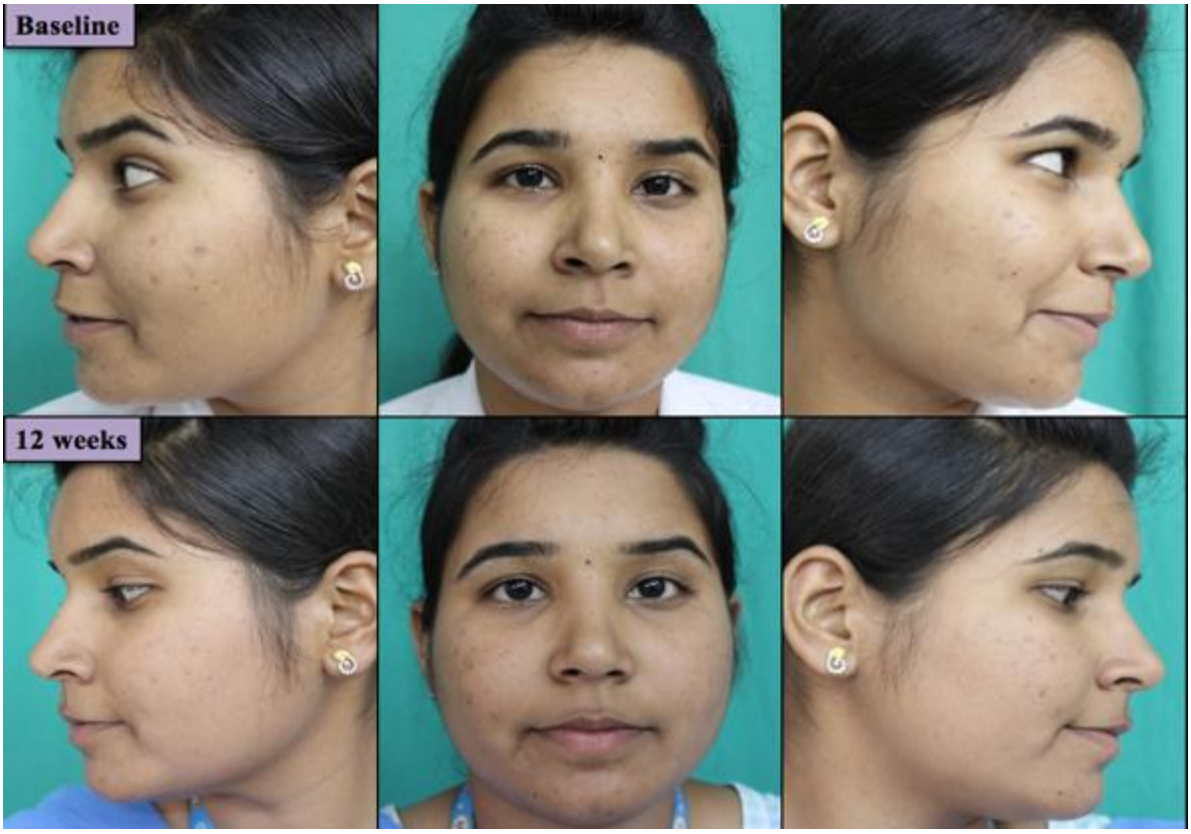


Figure 5, 6, 7: Group B (Spironolactone) patients at baseline and 12 weeks




Baseline
12 weeks


Baseline
12 weeks

Discussion

This is a hospital based double blinded randomised prospective controlled trial, to study the safety and efficacy profile of oral spironolactone versus oral isotretinoin in the treatment of female patients with acne vulgaris (Grade 1-2).

A total of 66 patients were enrolled in the study after fulfilling the inclusion and exclusion criteria. 33 patients (Group A) received oral isotretinoin (10mg/day) with topical clindamycin (1%) and the other 33 patients (Group B) received oral spironolactone (50 mg/day) with topical clindamycin (1%)for 12 weeks duration. 60 patients completed the study.1 patient dropped out due to menstrual irregularities, 1 due to extreme concern about her skin, which had not improved and 4 patients dropped out of the study after baseline evaluation due to unknown reasons which were not confirmed on repeated telephonic attempts.

Isotretinoin and spironolactone are useful therapeutic advances in the management of acne. While using a high dose treatment protocol the incidence of side-effects is quite high and requires regular monitoring of all blood counts. To decrease the incidence and severity of side effects and to make the therapy protocol simpler, the lower dose regimen has been tried by various authors for the treatment of mild to moderate acne. Although studies have been published on the above drugs individually, this is the first clinical study comparing the above 2 drugs and demonstrating a significant improvement and difference.

Demographic data comparison

In the present study, mean age of the patients was 22.6. Hermes B et al[4] in a study on medium dose isotretinoin for the treatment of acne treated a group of 94 patients where the mean age was 23.5 years. Goodfellow A et al[5] in a study oral spironolactone improves acne vulgaris and reduces sebum excretion found 36 patients and the mean age was 24 years. Erdemir U et al[6] in a clinical prospective case–control study of the oral side effects of isotretinoin treatment in acne vulgaris enrolled 90 patients with a mean age of 21.7 years. Amichai B et al[7] conducted an open, prospective, non-comparative study on efficacy of low-dose isotretinoin in the treatment of acne and found 495 patients, with a female/male ratio of 2:1, mean age 16.9 years, and a mean body weight of 51.3 kg. The findings in our study was similar to those previously undertaken.

Efficacy and safety of medications

This is the first double blind trial where low dose spironolactone (50mg/day) is studied in the treatment of acne vulgaris.

In this study, the decline in GAGS scores along with a marked improvement in PGA and VAS scores supports the conclusion that isotretinoin and spironolactone are both efficacious in the treatment of patients with acne vulgaris.

I. Isotretinoin

In the current study 68.4% improvement in the GAGS scores was observed at the end of 12 weeks. The effect begins after 2 weeks with 15.5% improvement and accelerates rapidly upto 8 weeks with 51.8% improvement. Isotretinoin showed an improvement of acne lesions with clinically inflammatory papules and comedones present all over the face with no site predilection.

Hermes B et al[4] in a study of medium dose isotretinoin for the treatment of acne enrolled 94 patients with moderate to severe acne and administered isotretinoin in an initial dosage of 10 mg/day with a variable increase to 50mg/day, with a mean dosage of 31.4mg/day for a mean duration of 8.3 months. He reported very good results in 62.8% and good results in 31.9% (T-94.7%) of the patients. Side effects of cheilitis was observed in 95.7% of patients followed by dry mucosal membranes, hair loss, facial erythema and impaired fitness and myalgia. This favourable variance in results could be due to the variably increasing dosage used, longer duration of therapy and a larger study group. Also, the efficacy parameters used was not an established parameter and was based only on subjective and objective

evaluation. This could probably be why the total percentage of improvement is much higher in the above study. Cheilitis was seen in 53.3% of the patients in our study with no evidence of other cutaneous and systemic side effects which is attributed to the lower dose used.

Amichai B et al[7] conducted an open, prospective, non-comparative study on efficacy of low-dose isotretinoin in the treatment of acne. He enrolled 495 patients and administered 20mg/day for 6 months. There was a mean improvement of 93.7% which was evaluated by the revised Leeds grading system. The most common side effects were mild cheilitis and mild xerosis in 91% and 43%, respectively followed by epistaxis (2.5%), transient mild elevation of liver enzymes (4.8%) and slight derangement in lipid profile (4.2%). This contrast in results is due to the longer duration of therapy which in turn increases the total dose given (70.2mg/kg) and hence the better results. Also, the scoring system used was different leading to a different method of evaluation of improvement. We learn that isotreinoin should be given at a higher dose and for a longer duration to attain better results. Side effects at this dose was comparable with our study however we did not have any laboratory abnormalities.

Sardana K et al[8] in a prospective, non-comparative study, enrolled 320 adult patients with moderately severe acne. He treated them with fixed-dose isotretinoin at 20 mg every alternate day (approximately 0.15 mg/kg/day to 0.28 mg/kg/day) for 6 months along with topical clindamycin gel and reported a clinically significant result in 87.54% of patients. Side effects noted were found mild cheilitis (91%) and xerosis (43%), laboratory abnormalities in the form of elevated hepatic enzymes (5%) and elevated serum lipids (6%). The higher improvement in the above study may be due to the longer duration of treatment thus leading to a higher mean total dose (38.4mg/kg). The side effect profile is lesser with a lower dose which was comparable with our study.

A longer duration of treatment with cumulative dose of more than 120mg/kg helps in reducing acne without any relapse. It is well known that the severity of isotretinoin induced side effects are dose related and higher the dose, more serious side effects are seen. The higher dose regimen does produce better improvement, which we continue to recommend to be used in more severe cases of acne. However, a low dose regimen seems to be a good therapeutic option in moderate grade acne patients which shows both a clinical and pathophysiological improvement of acne. (Table 3)

II. Spironolactone

In the current study, the effect of spironolactone begins after 2 weeks where in patients showed a 15.1% betterment in GAGS scores. There was a slow gradual decline in the GAGS score with a 17.9% improvement at the end of 4 weeks and 28.3% at the end of 8 weeks. The end improvement was 32.8% reduction in the GAGS scores at 12 weeks. Spironolactone showed an improvement of women with clinically inflammatory papules which were located predominantly on the lower half of the face and anterior-lateral neck region as compared to lesions which were comedogenic and present over the forehead and nose.

Goodfellow A et al[5] in a study of oral spironolactone improves acne vulgaris and reduces sebum excretion in 36 patients on 50 to 200mg of spironolactone daily, over a mean treatment duration of 3 months, reported at least a 50-percent improvement of facial acne vulgaris and truncal acne vulgaris in 37.5 percent of the cases. Suppression of sebum excretion is seen at a dose of more than 100mg/day. Side-effects were observed in 60% of the patients with the most common being menstrual abnormalities (spot bleeding and amenorrhea) and least common was transient diuresis.In comparison, the current study showed remission or moderate improvement in 32.8% of the patients despite a similar duration of treatment. This disparity in results could be due to the degree of concurrence between the efficacy

variables used to assess the improvement in the above study (subjective, objective and photographic) as compared to our study where an established severity index (GAGS) was used. Also, the higher and variable dose regimen used in the above study has a higher benefit however this is associated with an increased side effect profile. Even though our dose regimen was lower, we observed the same 66% of side effects with majority of it being menstrual irregularities in the form of spot bleeding. Amenorrhea and transient diuresis was not noticed in any patient, which is again due to the lower dose of spironolactone used. Thus, the clinical response is dose dependent with a maximum benefit in a dose of 150mg-200mg/day. This dose should be titrated according to the grade of acne and side effects experienced by the patient during the course of treatment.

Muhlemann MF et al[9] in a double-blind, placebo-controlled crossover study of oral spironolactone: an effective treatment for acne vulgaris in 21 women reported a significant (50-70%) improvement in acne lesions over a duration of 3 months on a dose of 200mg/day along with unspecified oral contraceptive. Improvement was assessed by objective, subjective and photographic data. Side effect of menstrual irregularity was noticed in 75% of patients who were not on oral contraceptive pills, followed by nausea, dizziness and breast enlargement. Contrary to our study, the efficacy variables used to assess the improvement in the above study (subjective, objective and photographic) are not as precise and unambiguous as GAGS which was used in our study. This could attribute to the higher improvement rate in the study by Muhlemann MF et al. though the duration was similar. The dose was 4 times higher leading to a higher window for side effects. In our study, we did not notice any dizziness, nausea or breast enlargement. This suggests that these side effects are observed at larger doses.

Vaswani N et al[10] in a study of treatment of acne vulgaris with anti-androgens enrolled 32 patients with moderate to severe acne; where 15 were given spironolactone and 15 cimitidine. He reported 73.3% improvement in lesions at a dose of 100mg/day for 12 weeks in the spironolactone group and 42.8% improvement in the cimetidine group. Efficacy was measured by lesion count. Side effect of menstrual irregularities was seen in 20% patients on spironolactone. The dissimilitude in results is due to the higher dose and the higher grade of acne in the above study as compared to the duration which is the same. Also, Vaswani N et al. has used total lesion count as an efficacy variable which is not as accurate as GAGS which was used in our study. This could probably be the reason why the percentage of improvement is much higher in the above study. The side effects are comparatively less at a 100mg/day dose and Vaswani N et al. noticed that they generally became milder as the treatment continued.

Charny JW et al[11] in a retrospective study of 110 patients of spironolactone for the treatment of acne in women reported 73.1% improvement in GAGS scores over a duration of 17 months, on a dose of 100-150mg/day along with adjuvant therapy of topical and oral antibiotics or oral contraceptive pills. 46% of patients showed side effects which included breakthrough bleeding or spotting followed by amenorrhea, light headedness and non-specific gastrointestinal disturbances. As compared to our study, this was not a double blind controlled trial. The higher percentage of improvement may be due to the variable dose regimen used and longer duration of treatment. We learn from the above study that a higher dose which is effective in maintaining a disease-free state and it should be maintained for at least 2 months. Adjuvant treatment modalities and a longer duration of therapy may help in better improvement of acne lesions. The side effects were comparable to our study despite a lower dose regimen and this could probably be due to the adjuvant use of oral contraceptive pills. Amenorrhea, light headedness and gastrointestinal disturbances were not noticed in our study with low dose spironolactone.

Spironolactone retains its utility over the course of long-term therapy. The dose of spironolactone should be titrated according to the severity of acne and the side effects experienced by the patient. With a lesser side effect profile, which outweighed the benefits of the acne improvement; regardless of the duration of treatment, it may be a safer treatment option than oral antibiotic medications and retinoids for chronic acne treatment. Hence, spironolactone should be used in late onset, severe and persistent acne and acne with hirsutism. Its conjunction with oral contraceptive pills may enhance the therapeutic benefits and may reduce the menstrual related side effects. (Table 4)

Limitations of the study

- Our study duration was comparatively shorter.
- Follow up of patients to assess the duration of clinical remission and relapse rate was not studied.
- The dose of spironolactone used was fixed and studies with titrated doses are suggested.

Conclusion

Isotretinoin and spironolactone are both efficacious in the treatment of acne vulgaris (Grade 1-2) however, isotretinoin is more efficacious than spironolactone. In this study, the onset of response is the same with both the drugs however, the effects with isotretinoin accelerates rapidly after 1 month as compared to spironolactone with a significant difference in results at the end of the study. Doses of isotretinoin and spironolactone should be titrated according to the severity of acne vulgaris. The use of the above drugs in rational combination with other topical and systemic agents helps in accentuating improvement with complete or near-complete control on their acne flares. Spironolactone shows an improvement in clinically inflammatory lesions which are located predominantly on the lower half of the face and anterior-lateral neck region and works better in hyperandrogenic women. Spironolactone, with a lesser side effect profile regardless of the duration of treatment, should be considered as a major agent in the armamentarium for treatment of adult women with chronic persistent acne. Larger studies are needed to assess which individuals are likely to respond to spironolactone; the relative effectiveness of spironolactone; and the clinical and metabolic differences that separate responders from non-responders to spironolactone treatment.

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Conflict of interest - None

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