

# Treatment of Post Adolescent Female Acne with Spironolactone and Low Dose Isotretinoin

Treatment of Acne with Spironolactone and Isotretinoin

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## ABSTRACT

**Objective:** To assess the synergistic efficacy and side-effects of spironolactone added to 20 mg isotretinoin/day.

**Study Design:** Observational study

**Place and Duration of Study:** This study was conducted at the Dermatology Department, Shalamar Hospital Lahore from March 2015 to December 2017.

**Materials and Methods:** 96 adult females between the ages of 25 and 45 years (mean age 31.6 years) were selected. All 96 women included in the study had regular menstrual history without any signs or symptoms of hyperandrogenism. They were treated with 50-100 mg spironolactone daily, in addition to 20 mg isotretinoin irrespective of age and weight of the patient for six months. Patients were clinically examined in the beginning, then every month during the treatment and on the follow up visits. Serum testosterone, DHEA-S, Serum Potassium levels were measured in the beginning and at the end of the treatment.

**Results:** Out of 96 patients 80 completed the study. 75 (93.75%) of patients were declared completely cured in six months. 5(6.25%) patients were not declared cured but showed satisfactory improvement. Recurrence was seen in 16(20%) patients. 17(21.25%) patients showed menstrual cycle irregularities, breast tenderness, cheilitis and xerosis. Potassium levels remained within normal limits. Serum testosterone, DHEA-S levels either decreased or remained at the same level at the end of the treatment.

**Conclusion:** Spironolactone given with isotretinoin was found to be more effective in adult female patients with acne than either drug alone. The drugs were well tolerated and showed good results with minimum side effects.

**Key Words:** Female adult onset acne, Spironolactone, Isotretinoin

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## INTRODUCTION

Acne is considered as the eighth most prevalent disease around the world<sup>1</sup>. Adult acne is defined as acne that presents after 25 years of age. Adult acne mainly affects women and is resilient to conventional treatment in 79-82% of cases<sup>2</sup>. Post adolescent acne may continue past the teenage years (Persistent Acne) or develop at or after 25 years till 45 years of age even beyond (Adult Onset Acne)<sup>3</sup>. Acne in adult women presents with nodules, pustules, inflammatory papules or comedons. The most common part is the face but the lesion may appear on the trunk as well<sup>4</sup>. The most common problem faced by females because of acne vulgaris is the cosmetic issue and it may have a negative impact on a patient's quality of life.

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Adult acne in females is frequently related with nervousness, depression, and it effects the quality of life badly<sup>5</sup>. Acne is a disease of sebogenesis despite of the age factor<sup>6</sup>. Most women with acne have normal serum androgen levels. Local production of androgens or an increased sensitivity of sebaceous glands to androgens may contribute to acne in these women<sup>7</sup>. Assessment should include a menstrual history, premenstrual flare and examination for clinical signs of hyperandrogenism<sup>8</sup>. Other important history points include Age of onset, Family history, Obstetric/Gynecological history, Oral contraceptive pills<sup>9</sup>, Obesity, Diabetes, Recent systemic illness<sup>10</sup>. History of drug intake, smoking and sun exposure is also important<sup>11</sup>. Females should be asked about the pregnancy and future plans for childbirth as it is desirable to avoid acne treatments during pregnancy<sup>12</sup>.

**Treatment:** There remains a requirement for treatment options with enhanced efficacy and tolerable side effects. The general principles of the treatment are to reduce sebum secretion, comedon formation, reducing propionibacterium acne and inflammation<sup>13</sup>. There are high rates of treatment failure and side effects with traditional therapies<sup>14</sup>. Multiple courses of antibiotics failed approximately in 80% of women and around 30% of patients reverted after numerous therapeutic courses

of isotretinoin<sup>15</sup>. It is found that females even with normal levels of androgen have shown significant improvement when treated with antiandrogen drugs. Moreover addition of antiandrogens to isotretinoin can have a synergistic effect<sup>16</sup>. The American Academy of Dermatology has suggested the use of multiple agents with dissimilar mode of action in the management and treatment of acne<sup>17</sup>. Patients must be encouraged to complete the full course of treatment as response to treatment is slow<sup>18</sup>.

**Isotretinoin** is the only therapy that impacts on all the major etiological factors implicated in acne<sup>19</sup>. Low-dose systemic isotretinoin (20 mg/kg/day) for the duration of about 6 months helps in resolution and reduction of acne. Low doses of isotretinoin are tolerated well with minimum side effects<sup>20</sup>.

**Spirolactone.** For the last 3 decades it has been used for the management of hirsutism and acne<sup>21</sup>. It is not FDA approved for acne treatment but has been used off label for the treatment of adult onset acne. To get the anti-androgenic effects there are several mechanisms:

1. Competition with testosterone and DHT for androgen receptors.
2. Inhibition of local androgen synthesis.
3. Inhibition of 5 $\alpha$ -reductase, reducing the conversion of testosterone to DHT.
4. Increasing the level of SHBG thus reducing free testosterone level<sup>22</sup>.

The dose 50 to 200mg daily is usually given for the treatment of acne. In order to minimize the side effects associated with the higher dose, the lower doses with almost same effectiveness can be given in the management of acne<sup>23</sup>. Menstrual irregularities, hyperkalemia and tenderness of the breast are the most common side effects<sup>24</sup>. Feminization of the male fetus is the side effect of Spirolactone and it is contraindicated in pregnancy<sup>25</sup>.

## MATERIALS AND METHODS

This was an uncontrolled, open label, non-comparative, observational study, number of study participants were 96 living in Lahore and neighboring areas. The patients had mild to severe acne, ages between 25 years to 45 years were selected randomly from the outpatient of the Dermatology Department, Shalamar hospital Lahore, after obtaining ethical permission from hospital ethical committee and informed consent from participants. The study period was from March 2015 to December 2017. Global Acne Grading System(GAGS)<sup>26</sup> was used for assessing severity of the acne. Following criteria was used in selecting the patients:

### Inclusion Criteria:

1. Patients between 25 to 45 years of age.
2. Patients with mild to severe acne.
3. Patients having normal menstrual cycle.

4. Patients giving written consent not to get pregnant during treatment or after 1 month of stopping treatment.

### Exclusion Criteria:

1. Patients suffering from Diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia.
2. Patients with signs/symptoms of hyperandrogenism.
3. Patients with signs/symptoms of hyperprolactinemia.
4. Patients planning to conceive.
5. Females on contraceptives or on any other medicines which may have side effects of acne.

The patients received 25 to 100 mg spironolactone as morning dose depending on the severity and weight of the patient. 20mg Isotretinoin was given after lunch to all patients irrespective of their weight. Written consent "not to get pregnant" was signed from all the study participants. Before the start of the drug treatment the lesions were counted and patient's acne was graded before, during and at the end of the therapy. After taking consent pictures of the participant were taken. Before and after the treatment DHEAS, serum potassium and testosterone levels and blood pressure was analyzed. The duration of treatment was planned for 6 months and follow up visits were conducted every month for 6 months after completion of treatment. During the follow-up visit Blood pressures was also recorded. Regarding face cleansing same advice were given to all the research participants.

**Statistical Analysis:** For Data entry and Statistical analysis SPSS version 17 was used. Chi-square were used where appropriate. P value less than or equal to 0.05 was considered as significant.

## RESULTS

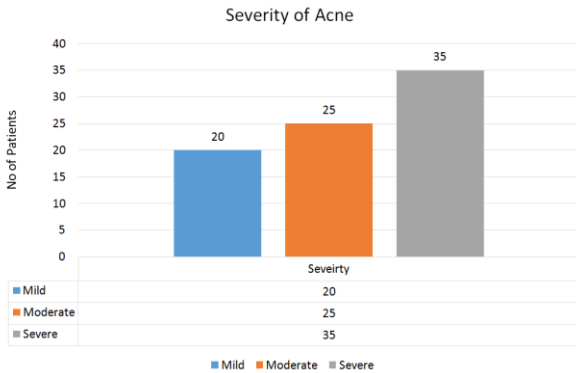
In this study we incorporated 96 patients who followed the inclusion criteria; out of ninety-six patients 80 completed the study. Due to severe menstrual irregularities 4 of the study participants stopped the drug. Other 12 patients were excluded because they did not come for the treatment regularly and they all were those who experience of ineffective treatments previously. The ages of the patients were between 25 to 45 years (mean age was 31.6 years). Duration of the disease was variable between 2 to 10 years mean 6.5 years (Table 1). The number of participant who had undergone some kind of treatment before were 66 patients. As per severity 20(25%) patients had mild, 25(31.25%) patients had moderate and 35(43.75%) patients had severe acne (Figure 1).

After 6 months of treatment clinically full improvement was observed in 75 study participants (93.75%) and were declared cured, these result are significant (p<0.05). The remaining 5(6.25%) patients were not cured completely but showed satisfactory response. All

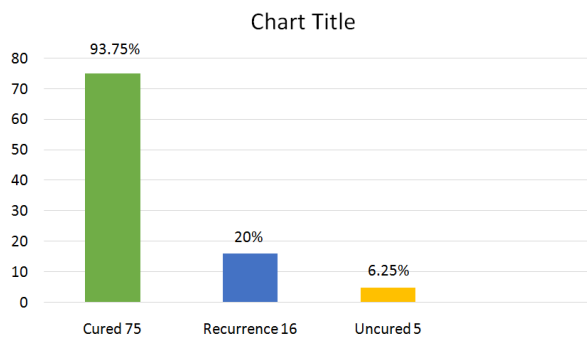
not cured patients had severe acne before the start of the treatment.

**Table No.1: Age and Duration of the Disease**

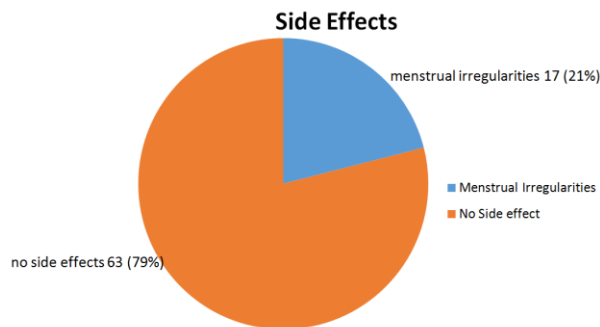
	Minimum	Maximum	Mean
Age of the participant	25 years	45 years	31.68 ±5.27
Duration of The Disease	2 years	10 years	6.46 ± 2.24



**Figure No.1: No of participants with different mild, moderate and severe cases of Acne**



**Figure No.2: Distribution of cases at the end of the treatment**



**Figure No.3. Side Effects observed during treatment.**

The lesions completely disappeared in those who were declared cured. Acne reoccurred in 16(20%)patients during 6-month follow-up period (Figure 2).17 patients (21.25%) experienced menstrual irregularities. Out of 17 patients, 13 (16.25%) had intermenstrual bleeding, 4 (5%) had hypermenorrhea. 63 (79%) showed no side effects (Figure 3). Additional side effects were

observed in those patients already reported for menstrual irregularities, 2(2.5%) developed breast tenderness, 2(2.5%) nausea and vomiting, and 2(2.5%) developed xerosis and cheilitis. Menstrual complaints vanished within 2–3 months of treatment; all further symptoms disappeared within 15 to 45 days of the treatment. The Potassium levels were found within normal limits before and after treatment. No significant change in blood pressure was found. Serum testosterone and DHEA-S levels decreased or remained same at the end of the treatment.

## DISCUSSION

In this study we analyzed the role of spironolactone along with low dose of isotretinoin for the treatment of Post Adolescent Female Acne. We found that 82.6% (n=66) of the study participants had taken the treatment before. Despite advances in the acne treatment, treatment failures are common in a significant number of adult women. Majority of the patients fail to respond to standard therapies and have a strong cyclical acne pattern, suggesting hormonal mediation<sup>27</sup>. In our study we found significant improvement in the patients.

Multiple researches have been conducted to find out the effect of spironolactone in the treatment of adolescent acne alone or in addition to antibiotics or isotretinoin. Yemisci et al<sup>28</sup> conducted a similar research and established that 85% of the participants with major improvements in acne. In a study on 139 female patients conducted in Japan with a 5 months tapering regime of oral spironolactone. Out of 139 patients, 64 completed the study and this study reported 100% response with around half of the patients showed excellent response<sup>29</sup>. The result of this study also favors our findings. In agreement to our results a trial was conducted, in which 27 female patients were treated with 50 to 200 mg/day spironolactone with acne for the duration of One month to one and half year and exhibited around 90% mean clinical improvement in varying degrees<sup>30</sup>. Our study results are in accordance with the study in which 85 female patients of acne were treated with spironolactone, 50–100 mg/day, Out of 73 patients who completed the treatment 48(66%) were completely cured or demonstrated marked improvement<sup>31</sup>. In a 4 year comparative retrospective study on 400 patients reported significant results with spironolactone along with topical and oral agents , moreover spironolactone with topical and oral drugs have better cure ratio than previously treated patients<sup>32</sup>. We have observed complete clinical improvement in 75(93.75%) of our patients. Only 5(6.25%) patients were not completely cured however we found significant decreased in the mean number of lesions after the completion of the treatment. We also found that the DHEA-S and total serum testosterone levels reduced or remained unchanged. Hughes and Cunliffe<sup>33</sup>

performed a study to find out the Spironolactone tolerance in females; 72% of the females with 200 mg/day of Spironolactone reported menstrual irregularities and 30% reported breast tenderness. Whereas in the present study, menstrual irregularities were present in only 17 patients (21.25%) and breast tenderness was reported only in 2 patients (2.5%). It is previously reported that 50-100 mg/day of spironolactone is linked with a considerable lower occurrence of side effects than as observed with higher doses<sup>31</sup>. The incidence of side-effects of low dose Spironolactone is usually mild and most females tolerate the treatment easily<sup>34</sup>.

## CONCLUSION

Our study indicates that for women with hormonal flare of acne, spironolactone can be a helpful addition. Spironolactone in low doses added to Isotretinoin is a safe and effective medication for adult females with acne. For a better and evidence-based results it is recommended that double-blind, randomized comparative studies with higher number of female patients should be conducted.

### Author's Contribution:

Concept & Design of Study:	Habib ur Rehman
Drafting:	Uzma Sarwar
Data Analysis:	Muhammad Mansoor Majeed, Muhammad Azam Bokhari
Revisiting Critically:	Uzma Sarwar, Habib ur Rehman
Final Approval of version:	Habib ur Rehman

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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