

Efficacy of Low Dose Flutamide in the Treatment of Hirsutism

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OBJECTIVES – To find out the efficacy of low dose (250 mg) flutamide in the treatment of hirsutism. **METHODS** – This is a non-randomized, prospective study. Twenty-eight women with hirsutism were recruited for the study. Hirsutism score was determined according to modified Ferriman and Gallwey¹ scoring system at the beginning and end of the study. The patients with abnormal liver or kidney function tests and testosterone level more than 2 ng/ml were excluded from the study. Each patient received 250 mg of flutamide once a day at bedtime for 6 months. **RESULTS** – Out of 28 patients, one had hepatic toxicity at the end of 3 months and was excluded from the study and the response in 27 patients was considered for analysis. All 27 patients responded positively to the treatment but the degree of response was different in each patient. Hence the responses were analysed under following headings. Hair reduction – The mean \pm SD Ferriman and Gallwey¹ hirsutism score before and after treatment was 19.52 ± 6.30 and 14.93 ± 5.90 respectively and the difference was statistically significant ($P=0.001$). Improvement in severity of hirsutism : The improvement in the severity of hirsutism was calculated by Semi objective Ferriman and Gallwey index² for hair reduction and it was 23.51%. Increase in time interval between use of cosmetic methods : We found a significant increase in the time interval with the use of flutamide. **CONCLUSION** – Flutamide could be a reasonable non-hormonal alternative pharmacological tool in the management of hirsutism especially in unmarried girls who would like to avoid hormonal therapy.

Key words : hirsutism, flutamide

Introduction

Although hirsutism may rarely be a manifestation of a serious underlying disorder, most often it results from a combination of increased androgen production and increased skin sensitivity to androgens. Until recently, hormonal suppression of androgens was the best therapy available to arrest the progression of hirsutism but it had minimal success. Lately, antiandrogens have been introduced into the treatment of hirsutism because of their ability to prevent androgens from expressing their activity at target sites. Among the drugs with antiandrogenic properties, mostly cyproterone acetate (CPA) and spironolactone have been used in clinical trials²⁻⁴. The efficacy of these two drugs has been limited by their relatively weak antiandrogenic activity and by undesirable pharmacological properties. The only available antiandrogen that is supposed to have no glucocorticoid, progestational, androgenic or estrogenic activity, is the nonsteroidal compound, flutamide⁵⁻⁶. Because there is a growing evidence that antiandrogen therapy represents the most rational approach for the treatment of hirsutism, we decided to investigate the efficacy and safety of flutamide in the treatment of hirsutism and its effect on various hormones.

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Material and Methods

This is a non-randomized, prospective study approved by the ethical committee of our institution. Informed consent was obtained from each patient.

Twentyeight patients with hirsutism were recruited for the study. None had used any medication for 3 months preceding the start of the study. All patients underwent general physical and gynecological examinations. Sonography of the whole abdomen was performed in all patients before flutamide treatment, presence or absence of polycystic ovary (PCO) was especially noted and any ovarian or adrenal mass was ruled out. Women with amenorrhea and oligomenorrhea were advised barrier contraception to prevent accidental pregnancy.

Hirsutism score was determined according to modified Ferriman and Gallwey² scoring system at the beginning and end of the study. Before hirsutism score assessment, all participants were advised to avoid cosmetic measures for at least 7 days. The interval at which cosmetic measures were used was noted.

Before starting the study, liver function tests (LFT) viz., total bilirubin, direct bilirubin, total protein, serum albumin, serum globulin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase, and renal function tests (RFT) viz., serum urea and serum creatinine, and hormonal analysis (FSH, LH, prolactin, TSH, testosterone) were performed. The patients with

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(28.57%) had onset of hirsutism with the onset of menarche and 20 (71.43%) had hirsutism within five years of menarche. Out of 28 patients, 12 were eumenorrhic, 12 were oligomenorrhic and 4 had secondary amenorrhoea. With the treatment, three patients who were eumenorrhic became oligomenorrhic (Table II).

Response to treatment : Out of 28 patients one had hepatic toxicity at the end of 3 months and was excluded from the study. Therefore, the response in 27 patients was considered for analysis. All 27 patients responded positively to the treatment but the degree of response was different in each patient. Hence the responses were analysed under following headings :-

Body mass index (n=28)

sq.mt.)	Before treatment	After treatment
D	20.52 ± 4.95	20.47 ± 4.47
	13.71 - 37.08	14.52 - 35.42

Menstrual cycle pattern (n=28)

	Before treatment	After treatment
rhic	12	9
orrhic	12	15
y amenorrhea	4	4

: Time interval between mechanical removal of hair (n=27)

No. of patients	Frequency (days)		p-value
	Before Treatment	After treatment	
1	3.0± 0	4.0 ± 0	Number too small
3	24.0 ± 2.65	30.0 ± 2.65	Number too small
5	17.0± 1.22	21.6 ± 1.22	<0.001
5	24.4 ± 1.52	32.2 ± 2.59	<0.001
7	30.9 ± 1.68	40.6 ± 3.26	<0.001
6	—	—	—

Pre – and post-treatment hormone levels (n=27)

	Before Treatment		After Treatment		P-value
	Mean ± SD	Range	Mean ± SD	Range	
(ml)	5.80 ± 1.61	2.7 – 8.5	5.99 ± 2.12	1.5 – 9.3	0.82
nl)	10.08 ± 6.81	1.8 – 34	10.58 ± 5.47	0.5 – 24.8	0.77
	1.78 ± 0.98	0.3 – 4.3	1.99 ± 1.53	0.33 – 8.4	0.48
ml)	1.98 ± 0.95	0.7 – 5.3	1.80 ± 0.81	0.5 – 3.3	0.22
ng / ml)	15.86± 8.0	3.5 – 31.1	14.20 ± 5.52	5.2 – 27.4	0.20

Table V : Comparison of Side effects

	Current study (250 mg / day x 6 months)	Cusan et al ⁸ (500mg / day x 13 months)
Dizziness	7 (25.0%)	5%
Tiredness	7 (25.0%)	15%
Increased appetite	4 (14.3%)	25%
Dry skin	3 (10.7%)	70%
Hot flushes	3 (10.7%)	27%
Alteration of menses	3 (10.7%)	16%
Headache	3 (10.7%)	16%
Nausea	2 (7.1%)	10%
Liver toxicity	1 (3.5%)	-
Breast discomfort	-	5%

Discussion

In cases of hirsutism, patients' distress is the prime indication for therapy. Most women respond to medical therapy. It is easier to prevent hair growth than to treat established hirsutism. Adolescent girls who are beginning to develop hirsutism and who have a family history of excessive hair growth are excellent candidates for medical therapy.

Various therapeutic agents have been used in the treatment of hirsutism. Until recently, hormonal suppression of androgens was the best therapy available to arrest the progression of hirsutism but it had minimal success. However, antiandrogens have lately been introduced into the treatment of hirsutism because of their ability to prevent androgens from expressing their activity at target sites.

Pure non-steroidal antiandrogens may not be the treatment of choice in cases of hirsutism due to excessive production of androgens. In such cases, the aim is to suppress the cause of hyperandrogenemia and not to act only at the end organ. But, in cases with normal plasma testosterone levels (<2 ng/ml), pure antiandrogens form good alternative for treatment⁶.

Flutamide is a potent non-steroidal antiandrogen devoid of any other hormonal or antithromonal activity and hence is a pure antiandrogen⁵. The maximum effect of the drug is observed at 6 months of therapy with any dose. No further significant improvement in hirsutism score is observed after 6 months^{7,8}. We selected the low dose (250mg/day)

regimen to avoid liver toxicity and to evaluate whether improvement can be seen with this low dosage. This regimen was also economical for our patients.

In our study, majority of the patients were below 25 years of age (82.14%) and unmarried (75%). Those who were married also had infertility which was their prime concern. Since study protocol required avoidance of pregnancy during treatment we could not recruit many married patients for our study. Polycystic ovarian syndrome (PCOS) was present in 68% of the patients and remaining 32% had idiopathic hirsutism.

Despite the low dose, one patient had liver toxicity as shown by the LFT done at 3 months and she was excluded from the analysis of response to treatment. She was hospitalized and treated conservatively. She responded well to conservative treatment and was discharged after 10 days.

Remaining 27 patients responded positively to the treatment but the degree of response was different in each patient. Hence the responses were analysed under following headings :

1. Hair reduction according to Ferriman and Gallwey Score¹.
2. Improvement of hirsutism by Ferriman and Gallwey Index²
3. Interval between cosmetic measures

The mean Ferriman and Gallwey¹ score was reduced from 19.52 ± 6.30 to 14.93 ± 5.90 and this reduction

tistically highly significant ($p=0.001$).
 vement in hirsutism in terms of Ferriman and
 y Index was 23.51%. This was not comparable
 her reported studies^{9,10}. In the study of Muderris
 flutamide. treatment resulted is a particularly
 and marked decrease in the hirsutism score
 7.48 ± 5.35 to 5.07 ± 2.89 after 6 months whereas
 study the decrease was from 19.52 ± 6.30 to
 ± 5.90 . The lower index in the present study
 e because majority of our patients had well
 shed hirsutism. The mean age of onset of
 sm was 17.03 ± 4.48 years whereas the mean
 initiation of the treatment was 22.96 ± 5.18 years.
 nd ethnic background may also influence the
 rement. The previous studies have been done
 European countries and the patients belonged
 e population. There are no published Indian
 with similar treatment protocol for us to put
 d this as a reason for lower index. The response
 S and idiopathic groups were comparable in
 dy i.e., 22.64% and 25.25% respectively.

t study demonstrates that there was a
 ant increase in time interval between use of
 ic methods of hair removal. Medical therapy
 er flutamide or other drugs does not remove
 r that is already present nor prevent hair
 . Many of our patients felt that their hair
 fine, it was easy to remove them and there
 ay in reappearance of the hair.

dy further established the pure antiandrogenic
 of flutamide. In concurrence with other
¹¹, the present study also showed no effect of
 amide administration on FSH, LH, TSH,
 n and testosterone levels. Hence, flutamide
 a better alternative for those who would like
 hormonal treatment for hirsutism, especially
 iving PCOS.

idence of the various side effects was higher
 mpared with other studies^{9,10} which used the
 se for the same duration. This could be due to
 erance of our patients. But when compared
 dy with 500 mg dose^{8,12} the incidence of side
 as much less suggesting that 250 mg may be
 hold dosage for our population (Table V).

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