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Original Research Article

A randomised trial of 5% minoxidil versus combination of 5% minoxidil and oral spironolactone in treatment of female pattern hair loss

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ABSTRACT

Background: Female pattern hair loss (FPHL) is a common form of nonscarring hair loss. We compared the usefulness and safety of topical minoxidil alone with combination of oral spironolactone and topical minoxidil in the treatment of FPHL.
Methods: This prospective, single-centre, randomised open label study over 100 patients attending tertiary care hospital in Mumbai during period December 2011 to June 2012. The data were entered into SPSS version 21 for analysis. Data collected were coded and described as frequency and percentage for qualitative data and means and standard deviation for quantitative data. Statistical analysis was done using chi-square and student t test. Statistical significance was considered if p value was less than 0.05.
Results: There were 48 patients in Group I and 46 patients in Group II. At 6 months, significantly higher mean Sinclair grade was observed among Group I patients as compared to Group II patients (2.85±0.68 vs 2.56±0.50, p=0.02). We observed a significant improvement in women's androgenetic alopecia quality of life questionnaire in Group I patients at 12 months after treatment (26.93±2.25 vs 23.47±2.95, p<0.001). Minoxidil and spironolactone were tolerated well by the patients.
Conclusions: Combination therapy of topical minoxidil and oral spironolactone has an additive effect. However, plateau of effectiveness of the combination therapy in normoandrogenic patients at 6 months of therapy was observed. We recommend the combination for 6 months and continuation of therapy with minoxidil only.

Keywords: Alopecia, Minoxidil, Spironolactone, Clinical outcome

INTRODUCTION

Female pattern hair loss (FPHL) is a common form of nonscarring hair loss that primarily occurs in adult women. The condition is characterized by the progressive loss of terminal hairs over the frontal and vertex regions of the scalp, resulting in a visible reduction in hair density. FPHL is a common condition, with a reported prevalence of 19% among Caucasian women.[1] The prevalence of FPHL appears to be lower in the Asian population than among Caucasians.[2] The visible thinning of hair over the frontal scalp and vertex of the scalp in FPHL results from a progressive decrease in the ratio of terminal hairs to shorter, thinner vellus hairs in the affected areas, a process known as follicular miniaturization.[3] As part of this process, the duration of the anagen phase of hair follicles shortens from a normal duration of a few years to only weeks to months.[4] The mechanism through which follicular transformation occurs in FPHL is not completely understood. Although

the crucial roles of androgens and genetic susceptibility in male androgenetic alopecia are well-accepted, the degree to which these factors contribute to FPHL in most women is less clear. A number of agents have also been used in the treatment of female pattern hair loss including the androgen receptor antagonists as well as the 5-α reductase antagonist. These agents can be used either alone or in combination with topical minoxidil.[5]

In this study, we compared the usefulness and safety of topical minoxidil monotherapy with combination therapy of oral spironolactone and topical minoxidil in the treatment of FPHL.

METHODS

This prospective, single-centre, randomised open label study comparing 5% minoxidil lotion as a monotherapy with combination therapy of 5% minoxidil and oral spironolactone in management of female pattern hair loss was conducted in the outpatient department of a tertiary care hospital at Mumbai. Patients were recruited for the study from December 2011 to June 2012. The study including follow up period was carried out from December 2011 to June 2013. All adult female patients presenting with hair loss were screened to have female pattern hair loss. One hundred such patients were enrolled for the study from December 2011 to June 2012 fulfilling the inclusion criteria. We included patients, aged between 18 and 50 years, clinically diagnosed with female pattern hair loss based on Sinclair scale (grade 2 and above), who were willing to avoid pregnancy for one year and were not taking any other hair treatment for past 3 months. We excluded patients who were pregnant and were planning pregnancy within a year, had associated co-morbidities like diabetes mellitus, hypertension, hypothyroidism, anaemia, menstrual irregularities, kidney disease, liver disease, patients on chemo or radio therapy, renal insufficiency, anuria, hyperkalemia, abnormal uterine bleeding. Patients with a family or personal history of estrogen dependent malignancy or taking hair treatment for past 3 months were excluded as well. Patients satisfying the inclusion criteria were explained the purpose of the study and those agreeing to participate were requested to sign an informed consent document before enrolment in to the study. Patients satisfying the inclusion criteria were sequentially randomised into two equal groups of fifty patients each ensuring equal age distribution in both groups. At baseline, age, biophysical profile and medical history of the patients was noted. Clinical photographs of patients were taken at the commencement of study and patients were graded on the basis of Sinclair's pictographic 5 point scale.[6] A through clinical examination was carried out to assess duration, severity of hair loss, associated comorbidity, signs of hyperandrogenism, menstrual irregularities, evidence of estrogen related malignancy, and psychological morbidity for all patients. Furthermore, all patients were assessed for the presence of stress based on a semi structured perceived stress questionnaire. All patients underwent a set of investigations in order to rule out chronic telogen effluvium and associated co-morbidities. Hemoglobin, cell counts, liver and kidney function tests, lipid profile, blood sugar, thyroid profile, luteinizing hormone and follicle-stimulating hormone levels, testosterone, serum electrolytes, ultrasonography of pelvis (to rule out polycystic ovaries), and urine pregnancy test in selected patients were ordered for the patients. Group I patients in this group were treated with topical application of 5% minoxidil lotion 1 ml twice a day for a period of twelve months. Patients in both groups were explained and demonstrated the method of minoxidil application, ensuring they avoided trickling of lotion on forehead. It was applied at least two hours before retiring to bed in order to prevent contact with pillow and subsequent transfer to face causing hypertrichosis. Group II patients were treated with combination of topical application of 5% minoxidil lotion twice a day and with oral spironolactone. Starting with a dose of 100 mg of oral spironolactone per day in two divided doses, gradually increasing by 25 mg every 2 to 4 weeks to a maximum of 200 mg per day in two divided doses. This increment was closely monitored and only done if allowed by side effects like breast tenderness, and menstrual irregularity. Patients in this group were counselled adequately to avoid pregnancy and were requested to use contraception other than oral contraceptive pills. All patients were followed up in the outpatient clinic once every two months, or early if required. At each visit clinical evaluation was done to assess improvement as well as side effects of the therapy for all patients. One objective and one subjective method were used at each visit to assess the clinical response. Objective assessment was done by comparing clinical photographs and grading on Sinclair scale.[6] For subjective improvement a modified Women's androgenetic alopecia quality of life questionnaire (WAGAQOL) was devised. The WAGAQOL contained eight questions regarding perception, behaviour, and social dysfunction due to hair loss. Each question's response was graded maximum 5 and minimum 1. Thus maximum WAGAQOL was 40 indicating most severe negative impact on patient's quality of life, and minimum score 8 with minimal impact. Side effects of topical minoxidil and spironolactone were noted as well. The data were entered into SPSS version 21 for analysis. Data collected were coded and described as frequency and percentage for qualitative data and means and standard deviation for quantitative data. Statistical analysis was done using chi-square and student t test. Statistical significance was considered if p value was less than 0.05.

RESULTS

A total of 100 patients were enrolled for the study. During the course of the study 6 patients were lost to follow up. At the end of the study there were 48 patients in Group I and 46 patients in Group II, which were included in the final analysis. Table 1 describes the baseline characteristics of the patients. Mean age,

duration of hair loss, body mass index and proportion of patients with a positive family history were similar in both the groups. Clinical presentation of patients from Group I and Group II was statistically not significantly different as well (Table 2). Mean levels of haemoglobin, thyroid stimulating hormone and testosterone were similar in patients in both the groups as described in (Table 3). Means value on Sinclair scale was calculated and compared between the patients in the two treatment groups. No significant difference was noted till the 2nd month after treatment. At 6 months, significantly higher mean Sinclair grade was observed among Group I patients as compared to Group II patients (2.85±0.68 vs 2.56±0.50, p=0.02). Even at 12 months after treatment, mean Sinclair scale was higher among Group I patients as compared to Group II patients, though the difference was not statistically significant. Furthermore, at the end of 6 months 6.25% and 13.04% of patients in Group I and II respectively showed improvement based on the Sinclair scale. At the end of 12 months 64.58% and 69.56% of the patients in Group I and Group II respectively showed improvement. We observed a significant improvement in WAAQOL in Group I patients at 12 months after treatment (26.93±2.25 vs 23.47±2.95, p<0.001). Dryness, headache, hypertrichosis and skin irritation were some of the commonly reported adverse effects reported by patients in both the groups (Table 4). Group II patients reported adverse effects like breast tenderness and irregular menses.

Table 1: Baseline characteristics of the patients included in the study.

	Group I (n=48)	Group II (n=46)
	N (%)	N (%)
Age distribution (in years)		
20 to 29	18 (38)	14 (30)
30 to 39	23 (48)	21 (45)
40 to 49	6 (12)	11 (25)
More than 50	1 (2)	0 (0)
Mean age (Mean±SD)	32.54±7.25	34.07±7.73
Duration of hair loss (months)		
1 to 12	31 (65)	20 (44)
13 to 24	12 (25)	11 (24)
25 to 36	3 (6)	6 (13)
37 to 48	0 (0)	4 (8)
49 to 60	0 (0)	5 (11)
61 to 72	0 (0)	0 (0)
73 to 84	0 (0)	0 (0)
85 to 96	2 (4)	0 (0)
Mean time duration (Mean±SD)	19±17.85	24.5±17.27
Positive family history		
Maternal	7 (35)	5 (25)
Paternal	10 (50)	10 (25)
Both	3 (15)	5 (25)
Body mass index (kg/m^2)		
Less than 18.50	0 (0)	0 (0)
18.50 to 22.99	14 (29)	15 (32)
23.00 to 27.49	26 (54)	16 (35)
More than 27.50	8 (17)	15 (33)

Table 2: Clinical history reported by patients in both the groups.

	Group I (n=48)	Group II (n=46)
	N (%)	N (%)
Clinical symptoms		
Itching	24 (49)	20 (44)
Dandruff	29 (60)	27 (59)
Acne	10 (21)	6 (13)
Hirsutism	6 (13)	7 (15)
Menopause	2 (4)	6 (13)
Stress	8 (17)	12 (26)
Acanthosis nigricans	13 (27)	10 (22)

Continued.

	Group I (n=48)	Group II (n=46)
	N (%)	N (%)
Contraception used		
Barrier	29 (60)	22 (48)
Intrauterine contraceptive device	2 (4)	0
Tubectomy	6 (13)	9 (19)
Vasectomy	0 (0)	1 (2)
Laboratory investigations		
Hemoglobin (gm%) (Mean±SD)	13.02±0.64	13.05±0.62
Thyroid stimulating hormone (mIU/l) (Mean±SD)	2.89±1.29	2.92±1.06
Testosterone (ng/dl) (Mean±SD)	26.31±13.18	29.87±13.15

Table 3: Assessment of patients using the Sinclair staging and WAGAQOL at regular intervals.

	Group I (n=48)	Group II (n=46)	P value
	Mean±SD	Mean±SD	
Sinclair			
Pre-treatment	2.93±0.63	3.02±0.64	0.52
At 2 months	2.50±0.58	2.30±0.93	0.22
At 6 months	2.85±0.68	2.56±0.50	0.02
At 12 months	2.06±0.52	1.80±0.83	0.07
WAGAQOL			
Pre-treatment	30.92±3.42	31.06±3.77	0.84
At 2 months	28.56±2.52	29.26±2.74	0.20
At 6 months	26.71±1.81	26.93±2.25	0.59
At 12 months	26.93±2.25	23.47±2.95	<0.001

Table 4: Adverse drug reaction reported by the patients.

	Group I	Group II
	N (%)	N (%)
Minoxidil related		
Dryness	11 (23)	8 (17)
Headache	6 (12)	6 (12)
Hypertrichosis	2 (4)	1 (2)
Irritation	2 (4)	3 (6)
Spironolactone related		
Breast tenderness	NA	11 (24)
Irregular menses	NA	10 (22)
Both	NA	2 (4)

DISCUSSION

In the absence of treatment, FPHL leads to progressive hair loss in affected areas, though not to complete baldness. Women may find the loss of hair distressing, and many women who present for the evaluation of FPHL desire treatment. As in the treatment of many other forms of hair loss, it is essential to thoroughly inform the patient of the therapeutic options (including the side effects of treatments), the importance of long-term, consistent adherence to treatment, the prolonged time usually required to achieve a clinically evident response (often several months) and a realistic expectations for the results of treatment. The primary therapeutic goals in women with FPHL are to minimize further hair loss and to induce regrowth of terminal hairs. Patients in Group I were treated topically with 5% minoxidil alone. The exact mechanism through which minoxidil improves FPHL is not completely understood. It is theorized that the drug may prolong the anagen phase of hair follicles, shorten the telogen phase, and induce enlargement of miniaturized follicles, thereby contributing to the conversion of miniaturized hairs to terminal hairs.[7] The efficacy of topical minoxidil for FPHL is supported by a systematic review and meta-analysis of randomized trials that found that women treated with topical minoxidil (1, 2, or 5% formulations) were significantly more likely to report clinically significant hair regrowth than women in

the placebo groups (relative risk 1.86, 95% CI 1.42-2.43).[8] In addition, the mean increase in hair counts within treated areas was higher in women treated with minoxidil than in women in the placebo groups. In the present study, topical minoxidil was well tolerated by the patients in both the groups.

Spironolactone is an aldosterone antagonist that competitively blocks androgen receptors and weakly inhibits androgen synthesis.[9] Spironolactone decreases testosterone production in the adrenal gland by depleting microsomal cytochrome p450 and by affecting the cytochrome p450-dependant enzyme 17a-hydroxylase and desmolase. The action of spironolactone is limited to tissues with a high microsomal 17a-hydroxylase activity and thereby decreasing steroid 17-hydroxylation.[10] Sinclair et al supported the use of spironolactone for FPHL in an open-label study of 80 women with normal androgen levels.[11] Moreover, in a case report, the addition of minoxidil 5% solution (applied twice daily) appeared to augment clinical improvement in FPHL in a woman who was taking spironolactone (200 mg per day).[5] Other systemic agents that inhibit androgen action or production such as cyproterone acetate, finasteride and flutamide, may be useful in some patients and further studies are necessary to define which patients would benefit from these agents.[11,12] In the present study breast tenderness and menstrual irregularities were observed in 24%% and 22% patients respectively. Menstrual complaints have previously been reported by Hughes et al as well.[13]

In the present study, WAGAQOL was found to be highly subjective, varying greatly with socioeconomic status, education level, perception of the disease by patient, her expectation from treatment, and her mood on the day of evaluation. Moreover, evaluation based on WAGAQOL varied greatly and was not in correlation with investigator's evaluation based on Sinclair grading.

CONCLUSION

Combination therapy of topical minoxidil and oral spironolactone has an additive effect. We observed plateau of effectiveness of the combination therapy in normoandrogenic patients at 6 months of therapy. Therefore we recommend the combination for 6 months and continuation of therapy with minoxidil only. Double blinded multi-centric placebo controlled trials are required in future to support our findings and establish the role and optimal dose of spironolactone in treating FPHL.

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