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Effectiveness of Topical Minoxidil (5%) Plus Topical Finasteride (0.1%) Fixed-Dose Combination Versus Topical Minoxidil (5%) Plus Oral Finasteride (1 Mg/Day) in Grade II-IV Androgenetic Alopecia: A Randomized, Double Blind Clinical Trial

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Authors' contributions

This work was carried out in collaboration among all authors. Author DD designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author AS managed the analyses of the study. Authors RCG and DB managed the literature searches. Author NKD helped in drafting the final manuscript. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Male Androgenetic Alopecia is a common hair loss disorder that increases with age. The cornerstones of medical management are minoxidil and finasteride.No treatment is completely satisfactory.
Aims and Objectives: This study compared Topical Minoxidil 5%+Finasteride 0.1% combination (Group A) and Topical Minoxidil 5%+Oral Finasteride 1 mg/day (Group B) in treating Male Androgenetic Alopecia grade II-V by assessing efficacy and quality of life.

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Materials and Methods: In this double blind randomized, controlled trial, 72 patients were randomly allocated in 2 groups of 36 to receive either of the two treatments for six months. Patients received identically colored bottles of minoxidil 5% (Group B) or minoxidil 5%+finasteride 0.1% combination (Group A) and finasteride 1 mg tablets (Group B) or identical-looking placebo tablets (Group A).Changes in subject's self-assessment and investigator's assessment of hair growth, and patient's and physician's global assessment of disease activity improvement were recorded monthly. Symptoms and adverse effects were noted monthly. Clinical photographs were taken monthly. Hamilton-Norwood scale were recorded at baseline and end of treatment.
Results: 32 patients in Group B and 30 in Group A completed treatment. Modified intention-to-treat analysis showed significant improvement in both groups from baseline to end of treatment. No significant difference was noted between two groups in any visit in subject's self assessment, investigator's assessment of hair growth, and patient's and physician's global assessment of disease activity improvement in any visit. Mild adverse effects were noted in 6.67% of Group A and 9.37% of group B patients. Hamilton-Norwood Grade was improved in both groups and was comparable at the end of the treatment between both groups.
Conclusion: Both the treatments are equally effective without too many remarkable side effects.

Keywords: Hair; androgenetic alopecia; topical minoxidil; vascular endothelial growth factor.

1. INTRODUCTION

Androgenetic alopecia (AGA) refers to a special pattern of hair loss seen in genetically predisposed individuals of both sexes, affecting males more than females. Circulating androgens, particularly dihydrotestosterone (DHT) plays key role in the development of AGA [1]. DHT is derived from testosterone in presence of 5-alpha reductase (type 2 in scalp). Finasteride is an inhibitor of the 5 alpha reductase type 2 enzymes and thus beneficial in AGA [2]. Minoxidil, the first line topical therapy for AGA [1], possibly acts by local cutaneous vasodilation and increased levels of vascular endothelial growth factor.

Oral finasteride at 1 mg/day acts synergistically with topical minoxidil. Occasional side effects like erectile dysfunction and loss of libido are not of much concern as they disappear soon [2]. Topical use of finasteride is a recent practice, usually with fixed dose combination of minoxidil, but efficacy is yet to be established [3].

We have compared established treatment regimen of topical minoxidil and oral finasteride to new regimen of fixed-dose combination of topical minoxidil and finasteride to establish an alternative topical-only treatment of AGA, which will be easier to administer and have lesser side effects.

1.1 Aims and Objectives

1) To assess the clinical effectiveness of topical minoxidil 5%+finasteride 0.1% fixed dose combination versus topical minoxidil 5% and oral finasteride 1mg/day in cases of AGA grade II-IV (Hamilton-Norwood Scale)
2) To compare the safety and tolerability of two treatments

2. MATERIALS AND METHODS

2.1 Trial Design

It was an institution- based, double blind, randomized, non-inferiority, parallel group, clinical trial with an allocation ratio of 1:1.

2.2 Participants

The study was carried out at department of Dermatology, Venereology and Leprosy of a tertiary care center in Eastern India.

Consenting male patients of age 18-45 years with Hamilton-Norwood grade II-IV AGA who agreed; for follow up, maintaining same hair style, using same shampoo, and hair not to be shortened to less than 1 inch were included in the study.

Patients treated with minoxidil and/or finasteride within last 1 month, having co-morbidities like diabetes, hypertension, thyroid disorder, heart disease, hepatic/kidney dysfunction, immunosuppression in any form, dermatological scalp disorders, prior history of drug hypersensitivity, breast disorder or testicular disorder were excluded from the study.

2.3 Interventions

One group of patients received topical minoxidil 5%+finasteride 0.1% combination to apply twice daily with placebo tablets to be taken once daily. The other group received topical minoxidil 5% lotion to apply twice daily and finasteride 1 mg tablets to be taken once daily. This was continued for six months.

2.4 Outcomes

Efficacy was measured by Hamilton-Norwood grade at the beginning and at the end of treatment. Investigator's assessment of hair growth (IAHG): A 5-point visual analogue scale was used: Patient's and Physician's global assessment of disease activity improvement (PaGA and PhGA) based on 5 point Likert scale, and a subject's self assessment (SA) of hair growth questionnaire relating to efficacy and satisfaction with treatment was noted monthly. For assessing safety and tolerability, any side effect detected by physician and symptoms experienced by patient was also recorded monthly.

2.5 Sample Size

In each group 36 patients were recruited; thus, a total of 72 patients were included in the study with an allocation ratio of 1:1.

2.6 Randomization

Eligible patients were randomized into either group A (receiving topical minoxidil 5%+finasteride 0.1% fixed dose combination) or group B (receiving topical minoxidil 5%+systemic finasteride 1 mg/day) with allocation ratio 1:1 as per a computer-generated randomization schedule.

2.7 Allocation Concealment

was done by sequentially numbered opaque sealed envelopes.

2.8 Blinding

Dispensing physician and assessing physician were two different persons and the assessing physician was unaware of dispensed medication. Thus, investigator blinding was achieved. For patient blinding, identical looking dummy tablets (containing inert substance) matching the appearance of tablet containing finasteride, were used in sequentially numbered opaque envelopes. The topical agents were dispensed in identical-looking bottles (Figs. 1,2 and 3).

2.9 Study Procedure

Patients were diagnosed clinically, screened, and general and physical examination conducted. Classification according to Hamilton Norwood scale was done and baseline photographs were taken. The procedure was explained and patients were asked to report after 1 month. Both groups were advised to apply lotion 1 ml twice daily on dry scalp, and take 1 tablet orally every day.

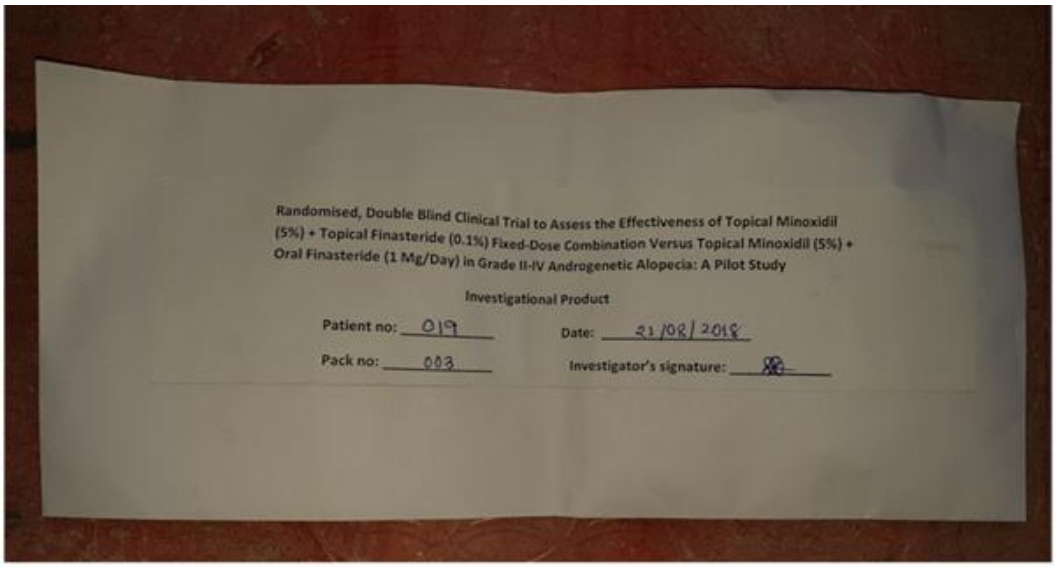

Fig. 1. Sealed envelope containing randomization number overleaf and tablets inside it

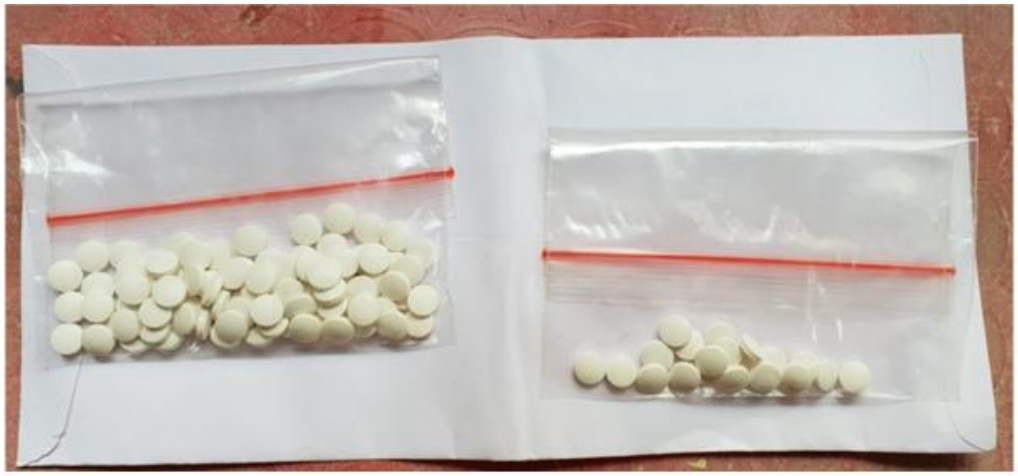

Fig. 2. Identical finasteride and placebo tablet packets

Fig. 3. Identical looking bottles of topical medication containing 5% minoxidil in one and topicalminoxidil5%+finasteride 0.1% combination in the other

On the second visit (1 month), hair growth was assessed using Hamilton-Norwood scale and photograph taken. IAHG and SA of hair growth, PaGA and PhGA disease activity were all evaluated. Patients were supplied with medicine and asked to come for next follow up after one month. The same procedure was repeated for third (2month), fourth (3month), fifth (4month), sixth (5month) and seventh (6month) visits.

To assess the hair growth in the bald area and scalp, following 5-point visual analogue scale was used: 1 – marked improvement 2 – moderate improvement 3 – minimum improvement 4 – unchanged, no visual hair growth, 5-decreased hair growth. At each follow

up any side effect detected by physician and any symptoms complained by patient was recorded.

SA of hair growth was done by five questions, relating to efficacy of treatment and satisfaction with appearance of scalp hair. Both PaGA and PhGA were recorded by a 5 point Likert scale: • 0 – no improvement • 1 – mild improvement • 2 – moderate improvement • 3 – marked improvement • 4 – excellent improvement.

2.10 Statistical Analysis

Descriptive statistics were expressed as ratio, percentage and proportion for categorical data and mean ±SD, median, interquartile range for numerical data. Parametric data was analyzed using Students' T-test and ANOVA test (as applicable). For non-parametric data, Mann-Whitney test, Wilcox on rank sum test, Friedman's ANOVA with post hoc Dunn's test were done. The homogeneity of the population was tested by variance ratio test (F test). Categorical data was analyzed using Chi Square test and Fisher's exact test (as applicable). The statistical software Medcalc® v 17 was used for analysis .Modified intention to treat analysis was done.

3. RESULTS

3.1 Participant Flow

After screening 103 patients with AGA it was found that13 patients had scalp dermatoses, 8 patients were on antihypertensives, 4 were having hypothyroidism, and another 6 were having various systemic diseases; hence total 31 patients were excluded from the study.

3.2 Recruitment

In 12 months, 72 patients were enrolled and randomized into 2 groups of 36. Group A received topical minoxidil (5%)+finasteride (0.1%) fixed-dose combination and Group B received topical minoxidil (5%) + systemic finasteride (1 mg/day). Fourteen patients in Group A and 21 Patients in Group B completed 6 months' treatment.

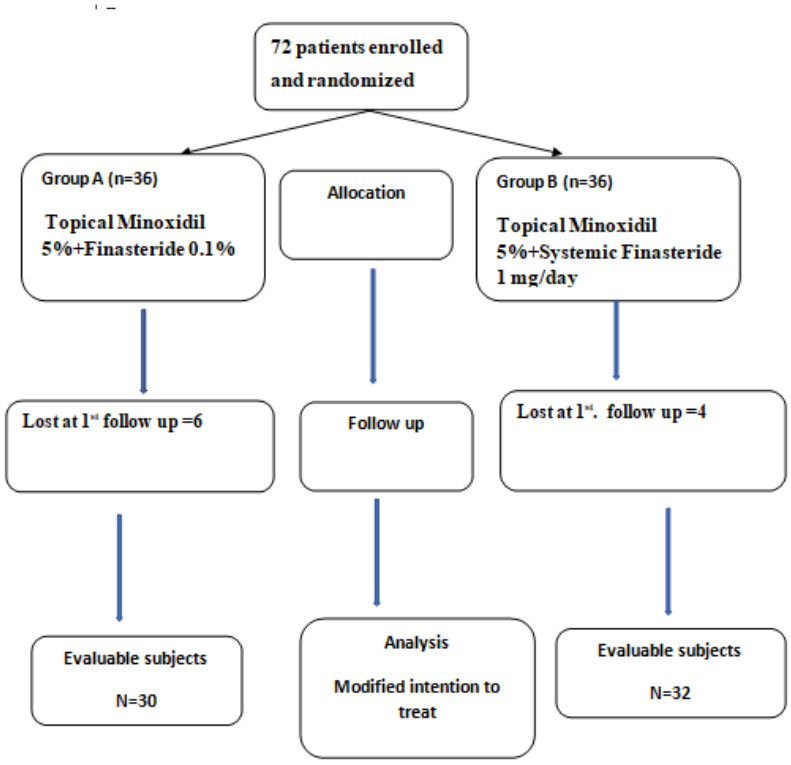

Fig. 4. Flow chart showing recruitment, randomization and follow up of study patients

3.3 Baseline Data

Demographic data in both the groups were similar (Table 1).

3.4 Numbers Analyzed

Modified intention-to-treat analysis were done. Modified intention-to-treat analysis done for patients who completed at least one follow up.

3.5 Outcomes and Estimation

Difference in improvement between two groups was negligible (P>0.05, Mann-Whitney test). In each visit, significant improvement was noted (P<0.001, Friedman's ANOVA) in both groups. The end results showed significant improvement in both groups as per investigator's assessment of hair growth (Fig. 4, Table 2), physician's global assessment of disease activity improvement, (Table 3) patient's global assessment of disease activity improvement (Table 4) and subjects' self-assessment of hair growth (Table 5).

3.6 Investigator's Assessment of Hair Growth

It was a 5 point scale for assessing the hair growth in the bald area and scalp by the investigator. The assessment scale is rated as follows:1=markedly improved (bald area almost entirely covered with hair identical to non bald area) 2=moderately improved(bald area partly covered with low density hair than non bald area) 3=slightly improved ; 4= no change, 5=worsened

Table 1. Baseline demography in both the study groups

Parameters	Group A N=36	Group B N=36	P value
Age (years) Mean ± SD	25.08±5.89	25.22±5.33	0.9704
Residence			0.912
Rural	5 (13.9%)	11(30.56%)	
Urban	31(86.1%)	25(69.44%)	
Literacy			0.9698
Primary	2 (5.56%)	2 (5.56%)	
Secondary	13 (36.11%)	14 (36.89%)	
Graduate and above	21 (58.33%)	20 (55.56%)	
Occupation			0.8296
Student	16 (44.44%)	14 (36.89%)	
Businessman	3 (8.33%)	6 (16.66%)	
Manual laborer	6 (16.66%)	5 (13.9%)	
Teacher	2 (5.56%)	3 (8.33%)	
Other	9 (25%)	8 (22.24%)	
Income			0.1759
Below poverty line	7 (19.44%)	3(8.33%)	
above poverty line	29 (80.56%)	33 (91.67%)	

Table 2. Investigator's assessment of hair growth

Follow up	Group A N= 30	Group B N=32	P value between group Mann Whitney test
2nd	2.66±0.79	2.82±0.68	0.3662
3rd	2.34±0.70	2.24±0.56	0.6744
4th	2.25±0.76	2.15±0.51	0.6576
5th	2.25±0.76	2.15±0.51	0.6576
6th	2.19±0.74	2.09±0.52	0.6819
7th	2.19±0.74	2.06±0.55	0.5489
P-value within group Friedman test	<0.001	<0.001	

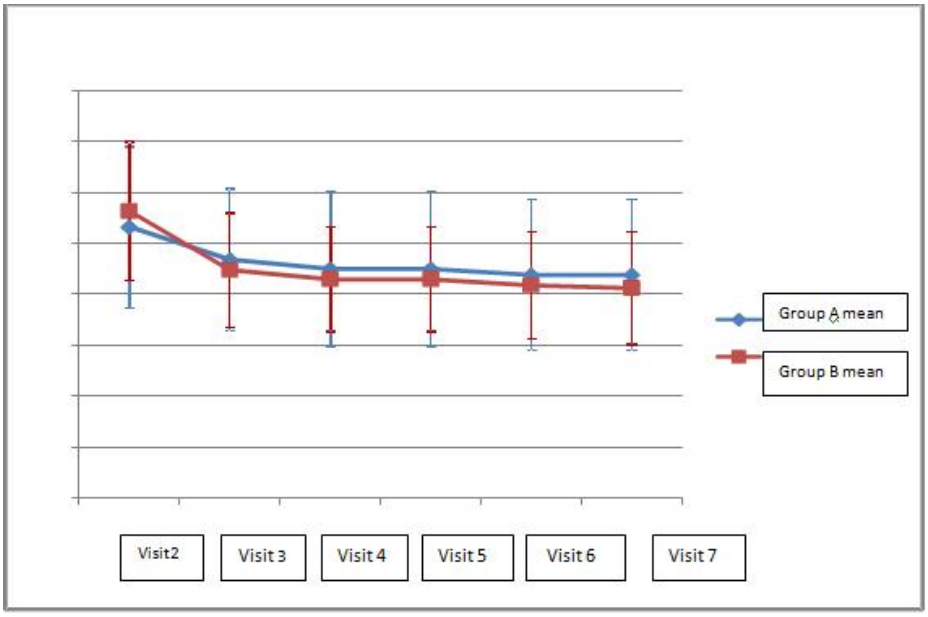

Fig. 5. Investigator's assessment of hair growth

Table 3. Physician's global assessment of disease activity improvement

Follow up	Group A N= 30	Group B N=32	P value between group Mann whitney test
2nd	2.30±2.79	2.09±0.78	0.2818
3rd	2.6±0.77	2.78±0.66	0.485
4th	2.77±0.82	2.84±0.57	0.8759
5th	2..77±0.82	2.84±0.51	0.8643
6th	2..77±0.82	2.93±0.50	0.6329
7th	2..77±0.82	2.93±0.56	0.652
P value within group Friedman test	0.0005	<0.0001	

Table 4. Patient's global assessment of disease activity improvement

Follow up	Group A N= 30	Group B N=32	P value between group Mann whitney test
2nd	2.10±1.16	2.31±1.26	0.4891
3rd	2.57±1.14	2.84±1.02	0.2768
4th	2.73±1.11	3.06±0.80	0.2458
5th	2.67±1.09	2.97±0.78	0.2794
6th	2.70±1.09	3.13±0.71	0.0878
7th	2.77±1.14	3.19±0.74	0.1241
P value within group Friedman test	<0.0001	<0.0001	

Baseline Grade and DLQI were comparable in both groups.

EOT Grade and EOT DLQI showed no significant difference between the two groups (P value >0.05, Wilcoxon matched pairs signed rank test) either.

Change from baseline to EOT grade was non-significant in either group (P value >0.05, MannWhitney test).

Change in DLQI from baseline to end of treatment was significant (P value<0.05, Mann Whitney test) in both the group

Table 5. Subject's Self Assessment of hair growth

Follow up	Group A N= 30	Group B N=32	P value between group Mann whitney test
2nd	17.50±5.08	18.47±4.88	0.4006
3rd	15.37±5.56	13.62±3.25	0.3586
4th	14.27±5.28	12.59±3.05	0.2290
5th	14.43±5.15	12.63±2.89	0.2028
6th	13.93±5.36	12.34±3.08	0.6191
7th	13.73±5.48	11.72±3.24	0.2784
P value within group Friedman test	<0.0001	<0.0001	

Table 6. Hamilton Norwood scale at the beginning and at the end of the treatment

Hamilton Norwood Grade*	Group A [Median (IQR)]	Group B [Median (IQR)]	P value (Mann Whitney test)
Baseline Grade	3(2-4)	3(3-5)	0.082
End of treatment Grade	3(2-4)	3(3-4)	0.418
Pvalue (Wilcoxon matched pairs signed rank test)	0.5	0.0625	

**Grade II=1, IIA=2, III=3, IIIA=4, Iv=5, IV=6, IVA=7, V=8, VA=9*

Table 7. DLQI at the beginning and at the end of the treatment

Group A [Median (IQR)]	Group B [Median (IQR)]	P value (Mann Whitney test)	
DLQI Baseline	8(5-10)	7.5(5-10.5)	0.807
DLQI EOT	4(2-7.75)	2.5(1-5.5)	0.767
P value (Wilcoxon matched pairs signed rank test)	0.0002	<0.0001	

IQR=Interquartile Range; EOT=End of treatment; DLQI=Dermatology Life Quality Index

3.7 Adverse Effects

Minor symptoms in the form of itching in 1 patient in each group, and flaking in 2 patients (6.67%) of Group A and 3 (9.37%) patients of Group B were seen. No significant adverse effect was detected by attending physician.

4. DISCUSSION

4.1 Limitations of the Study

The study was of a short duration; hence long-term maintenance of hair regrowth and long-term safety profile with the drugs could not be monitored. Secondly, due to lack of resources and sophisticated instruments, Patient and investigator assessments were not determined using validated instruments and only subjective outcomes were included. Efficacy and safety profile of the treatment in females were not done. Many patients were lost to follow up,; hence 'intention to treat analysis' for efficacy assessment was done. A study with larger sample size and longer duration may better address these issues.

4.2 Generalizability

Topical minoxidil and oral finasteride have established efficacy in treating AGA in males, among many other treatment modalities with variable response. Topical finasteride is emerging as a treatment option for the same [3,4]. As per our study, we can substitute topical finasteride for oral finasteride in the combination treatment with minoxidil without much changes in outcome or adverse effects in the short term in male patients. Fig. 5 and 6 (a,b,c).

4.3 Interpretation and Comparison to other Similar Studies

In 2014 [5], a topical formulation of finasteride 0.25% was compared against oral finasteride 1 mg tablet which showed similar levels of finasteride in blood and similar levels of

dihydrotestosterone inhibition in either routes. Finasteride slows AGA-associated hair loss by modulating DHT levels, while reducing systemic exposure to the medication.

A Chinese trial in 2015 compared oral finasteride with minoxidil and a combination of both and found oral finasteride to be superior to minoxidil, and the combination to be superior to both [6].

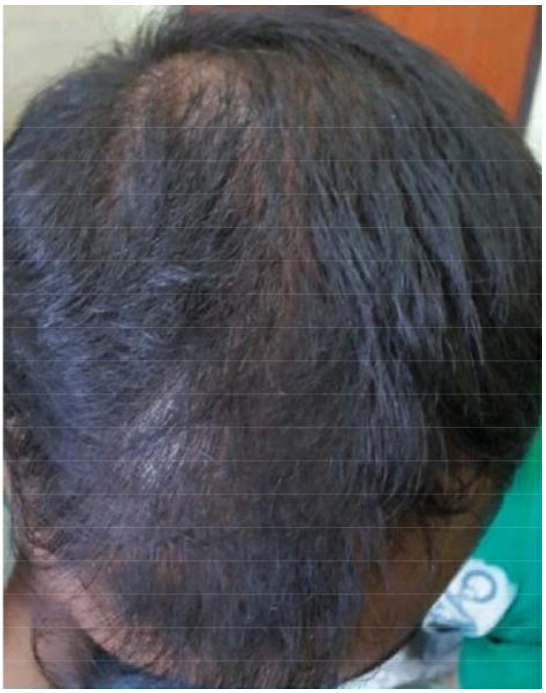

Fig. 6a. Topical finasteride baseline

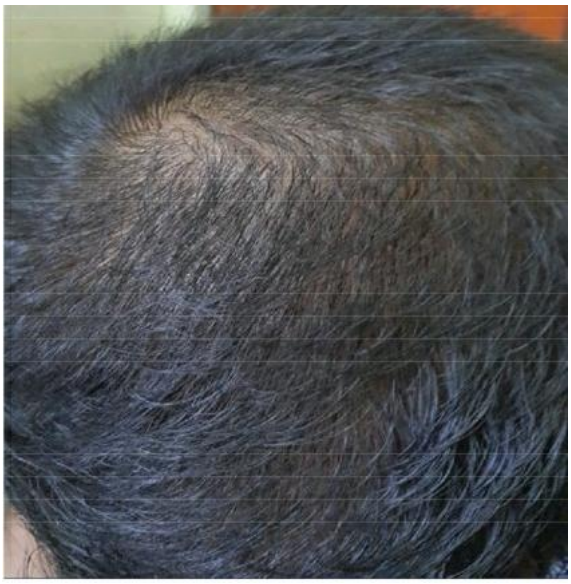

Fig. 6b. Topical finasteride at 2 months

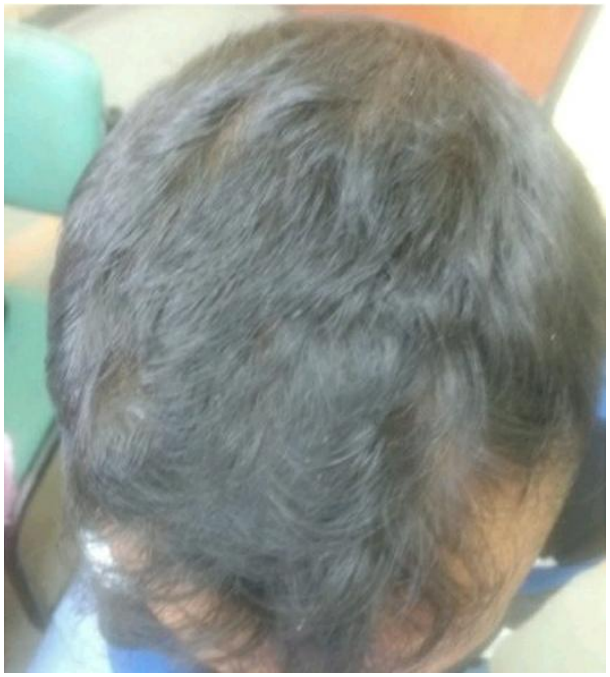

Fig. 6c. Topical finasteride after 6months

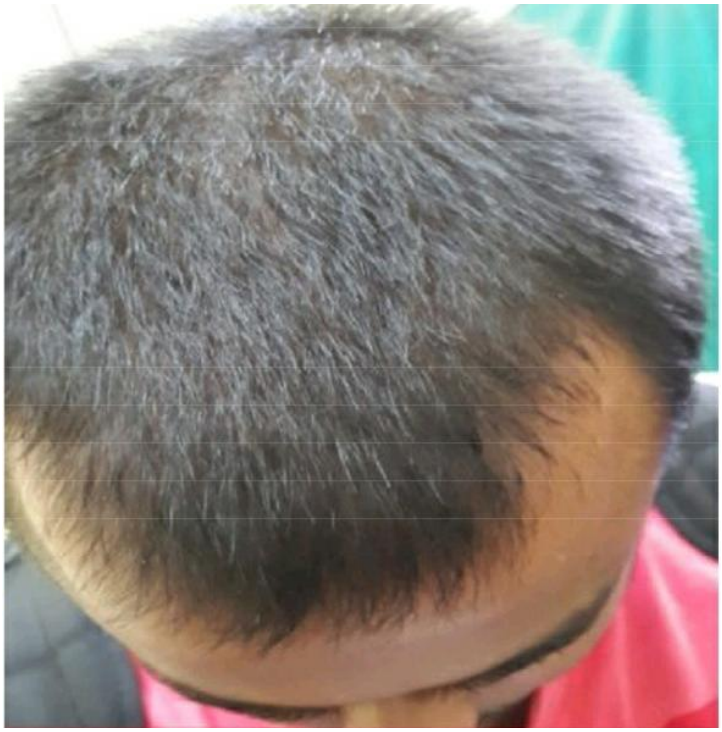

Fig. 7a. Oral finastride baseline

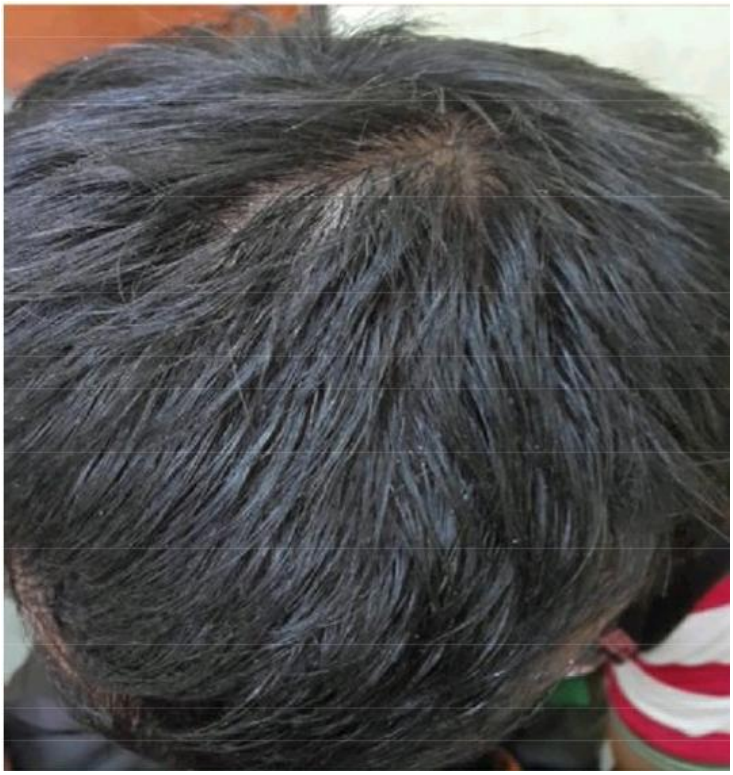

Fig. 7b. Oral finasteride at 2m

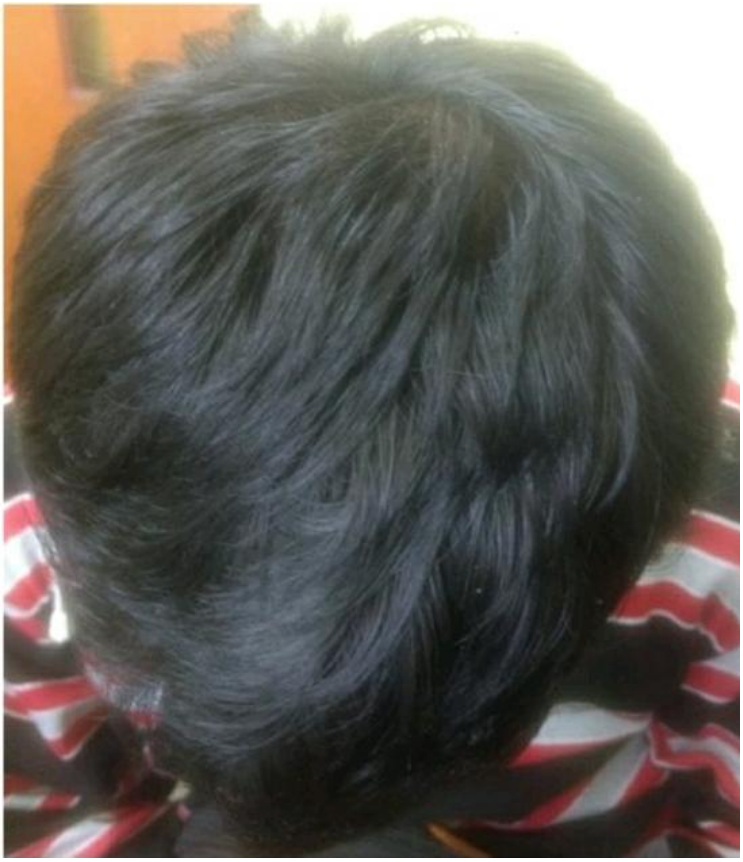

Fig. 7c. Oral finasteride after 6m

A recent randomized trial [3] comparing topical minoxidil+ finasteride combination with topical minoxidil + oral finasteride, has demonstrated good efficacy with both regimens over 12 months. The topical minoxidil with oral finasteride group was efficacious in 65% for hair growth maintenance and the topical combination group worked well in 83% patients f or maintenance (excluding dropouts in both groups).

In our study we have found combination of topical minoxidil and topical finasteride (group A) had similar efficacy to topical minoxidil and oral finasteride (group B) An earlier similar study,[6] few adverse effects (finasteride 1.8%, minoxidil 6.1%) were noted, which disappeared after stopping the drugs .We have noted only minor adverse effects like itching and flaking (8.33% in Group A, vs 11.11% in Group B).

Suchonwanit et al (2018) [7] compared 0.25% finasteride +3% minoxidillotion with 3% minoxidil lotion and reported greater improvement in hair density and diameter with combination treatment. Itching and flakiness of scalp was almost same in both groups.

Hajheydari et al (2009) in their study comparing finasteride gel 0.1% and finasteride tablet 1 mgin AGA, noted improvement in both groups, without any significant difference in hair thickness, hair count and size of bald area between the two groups [8].

Tanglertsampan (2012) performed a randomized comparative trial between 3% minoxidil and 3%minoxidil + 0.1% finasteride lotion and noted that while the two showed no significant difference of hair counts at 24 weeks, global photography showed the combination to have a higher efficacy than minoxidil. Adverse events were unremarkable [9].

A study in 2015 assessed the maintenance of hair density with topical minoxidil and finasteride combination in AGA after the patients were treated initially with minoxidil 5% and oral finasteride for 2 years. 84.44% patients

using the topical minoxidil-finasteride combination for maintenance retained good hair density. Hence this combination demonstrated an excellent scope as maintenance treatment for AGA [10].

A review in 2017 [11] concluded that topical minoxidil for AGA can be used indefinitely for maintenance of hair regrowth; oral finasteride has similar efficacy and safe even after 10 years of continuous use. Occasionally mild erectile dysfunction and loss of libido can occur. Data is still lacking regarding long term use of topical finasteride, a newer modality.

5. CONCLUSION

In conclusion, we didn't get any significant difference between the two study groups as far as investigator's assessment of hair growth, physician's global assessment of disease activity improvement, patient's global assessment of disease activity improvement and subjects' self-assessment of hair growth are concerned; hence we recommend combination of topical minoxidil and finasteride asa safe and equally efficacious alternative to topical minoxidil plus oral finasteride.

CTRI registration no. -**CTRI/2017/03/008250**

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The study conformed to the ethical guidelines laid down by the Declaration of Helsinki for Biomedical Research involving human subjects. Subject recruitment commenced once written approval was obtained from the Institutional Ethics Committee. Informed Study-related activity started after obtaining patients' consent in the written Informed Consent Form for voluntary participation. Confidentiality of the study participants was ensured.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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