Comparative Study of Efficacy of Topical Minoxidil 5% and Combination of Topical Minoxidil 5%, Topical Azelaic Acid 1.5% and Topical Tretinoin 0.01% on the Basis of Dermoscopic Analysis in Androgenetic Alopecia

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Abstract

Background: Androgenetic alopecia (AGA) more commonly known as male pattern baldness affects up to 50% of men worldwide. Tretinoin prolongs anagen phase and increases percutaneous absorption of minoxidil three fold. Azelaic acid is an inhibitor of 5 alpha reductase and could be an effective agent in the treatment of androgen related pathology of human skin. Aims and Objective: 1) To study the efficacy of topical minoxidil 5% in treatment of androgenetic alopecia. 2) To study the efficacy of combination of topical minoxidil 5%, topical azelaic acid 1.5% and topical tretinoin 0.01% in treatment of androgenetic alopecia. 3) To compare the efficacy of foresaid topical preparation in treatment of androgenetic alopecia. Setting: Outpatient department of Dermatology, Venerology Leprology of a tertiary health care centre with an attached medical college. Material and methods: Topical minoxidil 5 % lotion was used in 23 (50%) patients of the present study. Combination of topical minoxidil 5%, azelaic acid 1.5 % and tretinoin 0.01 % lotion was used in 23 (50 %) patients of the present study. Statistical analysis used: Epi info version 7. Results: There was statistically significant increase in hair number and thickness after treatment in both the groups. The comparison of the increase of hair number and thickness was statistically insignificant. Conclusions: Topical Minoxidil 5% is equally effective to combination of topical Minoxidil 5%, azelaic acid 1.5% and tretinoin 0.01% in treatment of androgenetic alopecia.

Keywords: Androgenetic Alopecia, Azelaic Acid, Minoxidil, Tretinoin

1. Introduction

Androgenetic alopecia (AGA) more commonly known as male pattern baldness affects up to 50% of men worldwide. The disorder occurs in almost all patients before 40 years and in many patients below the age of 30 years. AGA is, for most men, an unwanted and stressful event that diminishes satisfaction with their body image.
It is a result of interplay of genetic, endocrine and aging factor. Pre-programmed follicles on the scalp undergo a transformation from long growth (anagen) and short rest (telogen) cycles to long rest and short growth cycles coupled with progressive miniaturization of the follicle. These changes are androgen dependent and require the inheritance of several genes. The gene that encodes the androgen receptor has been identified. The evolution of baldness progresses from thinning in the temporal areas producing a reshaping of the anterior part of the hairline (temporal recession) then on to the loss of hair from the vertex region.

There are many resources available for the assessment of patients who present with hair loss. Evaluations can be categorized as invasive (e.g., scalp biopsies), semi-invasive (e.g., trichogram), or noninvasive (e.g., hair counts, microscopic evaluation, trichoscopy). Each of these approaches, when interpreted with the comprehensive clinical picture, can provide valuable insights into patient diagnosis, treatment and monitoring. More recent studies have accumulated evidence that use of dermoscopy of hair and scalp (trichoscopy) in the clinical evaluation of hair disorders improves diagnostic capability beyond simple clinical inspection.

Without treatment, AGA takes a chronic progressive course with an average hair loss of 5–6% annually with great interindividual variability. Minoxidil increases the duration of anagen growth phase and gradually enlarges miniaturized hair follicles (vellus hairs) into mature terminal hairs. Minoxidil does not restores all the hairs, and the response varies among men. Even in those who respond, there may be disappointment at the limited extent of improvement. Treatment for 3–6 months is needed to reduce hair fall and 6–12 months to improve scalp coverage. Continued treatment is needed to maintain the benefit. Even though continuous use has been advocated for a sustained cosmetic benefit, in long-term use its efficacy has been found to decrease gradually. The extent of hair loss reverts to pre-treatment level six months after stopping minoxidil.

The findings that tretinoin prolongs anagen phase and increases percutaneous absorption of minoxidil three fold has been impetus for the use of combination of tretinoin and minoxidil in AGA. There is evidence that tretinoin, when combined with minoxidil, may enhance its efficacy. Azelaic acid is an inhibitor of 5 alpha reductase and has been tried in AGA and it could be an effective agent in the treatment of androgen related pathology of human skin. There are no sufficient reports regarding the efficacy of topical tretinoin and azelaic acid in treatment of androgenetic alopecia and there added advantage in treatment of androgenetic alopecia along with minoxidil.

In this study we intend to compare efficacy of topical 5% minoxidil versus efficacy of combination of topical minoxidil 5%, topical azelaic acid 1.5% and topical tretinoin 0.01% in treatment of androgenetic alopecia on the basis of dermoscopic analysis in the patients of androgenetic alopecia.

2. Aims and Objectives

- To study the efficacy of topical minoxidil 5% in treatment of androgenetic alopecia.
- To study the efficacy of combination of topical minoxidil 5%, topical azelaic acid 1.5% and topical tretinoin 0.01% in treatment of androgenetic alopecia.
- To compare the efficacy of foresaid topical preparation in treatment of androgenetic alopecia.

3. Setting

The study was undertaken in the outpatient department of Dermatology Venerology and Leprology of a tertiary health care centre with an attached medical college after approval from the institutional ethics committee.

4. Material and Methods

The present prospective comparative interventional study was carried out in department of dermatology of a tertiary health care institute. A total of 46 male patients were included in the study during the period of August 2012 to December 2014. Approval of institutional ethical committee was taken. A written informed consent of each patient was taken.

4.1 Patient Selection

4.1.1 Inclusion Criteria

1. Male patients in the age group of 18–50 years.
2. Clinically diagnosed cases of androgenetic alopecia.
3. Patients willing to participate in the study and ready to sign the informed consent form and patients willing to follow up.

4.1.2 Exclusion Criteria

1. Use of following drugs during 1 year prior to the screening.
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4.2 Treatment Modalities

1. Topical minoxidil 5% lotion was used in 23 (50%) patients of the present study.
2. Combination of topical minoxidil 5%, azelaic acid 1.5% and tretinoin 0.01% lotion was used in 23 (50%) patients of the present study.

4.3 Method

4.3.1 During Visit 1

The eligible patients according to inclusion criteria were enrolled in the study and written informed consent was obtained after counseling. Baseline assessment in terms of medical history, physical examination, general scalp examination including evaluation of scalp for signs of alopecia other than scalp and blood investigations (complete blood count, random blood sugar, antinuclear antibody titre, thyroid stimulating hormone and anti thyroid antibodies) were done. Hamilton’s classification was used for grading the alopecia.

In patients with normal blood investigations global photographs were taken from frontal and temporal view using digital camera (SONY CYBER SHOT DSC TX1) followed by selection of two patches from the scalp, one from the affected area (vertex region at the cross between nose line and ear implantation line) and one from the unaffected area (occipital region – occipital protuberance), in 1 cm by 1 cm area; marked with a permanent marker, shaved with a disposable razor, and photographed with digital camera and dermoscope (ARAMO SMART NAVI ASN-202). The digital images were transferred to the computer.

Calculations of total number of hair per cm² and average hair thickness in mm/cm² was made both for unaffected and affected area after magnifying the images further in the computer. The patients were given the drug on sequential basis by dermatologist like first patient who came on day one was given 5% topical minoxidil, day two combination of 5% minoxidil, azelaic acid 1.5% and tretinoin 0.01% around 1ml to be applied twice daily on the affected area (at night, 2-3 hours before sleeping and next morning after washing the hair).

4.3.2 Follow up Guidelines

Patients were asked to follow up after 1 month, 3 months and 6 months from the baseline visit. At each visit global photographs, photographs of the marked area were taken by digital camera and dermoscope, calculations of total number of hair and average hair thickness was made both for unaffected and affected area after magnifying the images further in the computer of the same marked area. Final result was compiled after 4th visit.

4.3.3 Evaluation

Total no of hair- each hair emerging from the follicular ostia was counted per cm². Hair thickness – Average hair thickness in mm per cm².

Safety evaluation- safety monitoring was designed to detect any potential local intolerance of topical minoxidil, tretinoin and azelaic acid and systemic cardiovascular effects of topical minoxidil. Clinical history & physical examination including evaluation of scalp for signs of dermatitis, measurement of blood pressure, pulse rate, auscultation of the chest, evaluation of extremities for signs of peripheral edema. At each follow up visit, physical condition was checked by medical examination and any adverse effect was noted.

4.3.4 Statistical Analysis

Statistical analysis was done using Epi info version 7.

5. Results

<table>
<thead>
<tr>
<th>Table 1. Age distribution of cases in study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
</tr>
<tr>
<td>20-25</td>
</tr>
<tr>
<td>26-30</td>
</tr>
<tr>
<td>31-35</td>
</tr>
<tr>
<td>36-40</td>
</tr>
<tr>
<td>&gt;40</td>
</tr>
</tbody>
</table>
Figure 1. Age distribution of cases in study groups.

In this study youngest patient was 23 years old and oldest patient was 56 years old.

There were 17 (36.9%) patients in age group of 31-35 years, which formed majority of the study population.

Least number of patients i.e. 6 (13%) were seen in age group of 20-25 years and greater than 40 years (Table 1 & Figure 1).

Table 2. Distribution of cases according to duration of alopecia in study groups

<table>
<thead>
<tr>
<th>Duration</th>
<th>5% Minoxidil</th>
<th>Combination</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>17.3</td>
</tr>
<tr>
<td>13-24 months</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>25-36 months</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>17.3</td>
</tr>
<tr>
<td>37-48 months</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>19.5</td>
</tr>
<tr>
<td>49-60 months</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>10.8</td>
</tr>
<tr>
<td>&gt;60 months</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>8.6</td>
</tr>
</tbody>
</table>

There were 12 patients in age group 13-24 months which formed majority (26%). Least number of patients i.e. 4 (8.6%) were seen in age group greater than 60 (Table 2 & Figure 1).

Figure 2. Distribution of cases according to duration of alopecia in study groups

There were 12 patients in age group 13-24 months which
formed majority (26%). Least number of patients i.e. 4 (8.6%) were seen in age group greater than 60 (Table 2 & Figure 2).

Table 3. Comparison of mean age in study groups

<table>
<thead>
<tr>
<th>Duration</th>
<th>Minoxidil</th>
<th>Combination</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>37.04</td>
<td>38.60</td>
<td>0.82</td>
<td>NS</td>
</tr>
<tr>
<td>SD</td>
<td>24.58</td>
<td>20.77</td>
<td>0.817</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 3. Comparison of mean age in study groups.

In this study mean duration of alopecia in minoxidil group were 37.04 months and 38.6 months in combination. After applying chi square test, mean duration in two groups was comparable and the difference was not significant (chi square 2.14, t 0.232, degree of freedom 44, p value 0.82) (Table 3 & Figure 3).

Table 4. Distribution of cases according to grades of alopecia in study groups

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment</th>
<th>5% Minoxidil</th>
<th>Combination</th>
<th>Total</th>
<th>%</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6.5</td>
<td>0.56</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td></td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td></td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>9</td>
<td>15</td>
<td>32.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>10.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were 15 patients in grade IV which formed majority; there were 11 patients of grade III and II, 5 patients of grade V, 3 patients of grade I and 1 patient in grade VI. After applying Chi square test, distribution of grades of alopecia were comparable in both groups and the difference was not significant (df 5, chi square 3.94, p value 0.56) (Table 4 & Figure 4).
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Figure 4. Distribution of cases according to grades of alopecia in study groups.

Table 5. Comparison of mean values of number of hair at each sitting

<table>
<thead>
<tr>
<th></th>
<th>Minoxidil Mean ± SD</th>
<th>Combination Mean ± SD</th>
<th>Unpaired t test</th>
<th>P value &amp; significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>31.65 ± 4.15</td>
<td>31.65 ± 6.32</td>
<td>O</td>
<td>1 NS</td>
</tr>
<tr>
<td>Visit 2</td>
<td>30.30 ± 4.17</td>
<td>30.52 ± 6.25</td>
<td>-0.140</td>
<td>0.88 NS</td>
</tr>
<tr>
<td>Visit 3</td>
<td>37.52 ± 5.05</td>
<td>37.43 ± 6.14</td>
<td>0.054</td>
<td>0.95 NS</td>
</tr>
<tr>
<td>Visit 4</td>
<td>40.43 ± 5.56</td>
<td>40.21 ± 6.61</td>
<td>0.122</td>
<td>0.90 NS</td>
</tr>
</tbody>
</table>

Figure 5. Comparison of mean values of number of hair at each sitting.

To compare mean values of number of hair at each visit in both the groups unpaired t test was used.

At visit 1 distribution of number of hair in cases between 2 groups was comparable with no significant difference (p value 1) (Table 5 & Figure 5).

At visit 2 there was decrease in number of hair (by 4.26% in minoxidil group, 3.57% in combination group) from the baseline, decrease was comparable with no significant difference (p value 0.88).

At visit 3 there was increase in number of hair among 2 groups (18.54% in Minoxidil group and 18.3% in combination group) from the baseline, increase was comparable in both the groups with no significant difference (p value 0.95).

In visit 4 there was increase in number of hair among 2 groups (27.74% in Minoxidil group & 27.04% in combination group) from the baseline, increase was comparable in both the groups with no significant difference (p value 0.90).

Table 6. Comparison of mean values of number of hair after treatment in both groups

<table>
<thead>
<tr>
<th>Number of hair</th>
<th>Minoxidil Mean ± SD</th>
<th>Combination Mean ± SD</th>
<th>Unpaired t test</th>
<th>P value &amp; significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.43</td>
<td>40.21</td>
<td>0.122</td>
<td>0.90</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Figure 6. Comparison of mean values of number of hair after treatment in both groups.

Statistically insignificant difference was found between mean values of number of hair after two therapeutic regimen, after applying unpaired t test (t value 0.122, p value 0.90 not significant) (Table 6 & Figure 6).

Table 7. Comparison of mean values of average hair thickness at each visit

<table>
<thead>
<tr>
<th></th>
<th>Minoxidil Mean ± SD</th>
<th>Combination Mean ± SD</th>
<th>Unpaired t test</th>
<th>P value &amp; significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>0.036 ± 0.004337</td>
<td>0.036 ± 0.004499</td>
<td>0.01</td>
<td>1 Not significant</td>
</tr>
<tr>
<td>Visit 2</td>
<td>0.040 ± 0.004679</td>
<td>0.041 ± 0.004288</td>
<td>-0.765</td>
<td>0.44 Not significant</td>
</tr>
<tr>
<td>Visit 3</td>
<td>0.045 ± 0.004315</td>
<td>0.046 ± 0.004181</td>
<td>-7.99</td>
<td>0.42 Not significant</td>
</tr>
<tr>
<td>Visit 4</td>
<td>0.050 ± 0.005128</td>
<td>0.051 ± 0.003801</td>
<td>-7.54</td>
<td>0.45 Not significant</td>
</tr>
</tbody>
</table>
To compare mean values of average thickness of number of hair at each visit in both the groups unpaired t test was used.

At visit 1 distribution of average thickness of hair in cases between 2 groups was comparable with no statistically significant difference (p value 1) (Table 7 & Figure 7).

At visit 2 there was increase in average thickness of hair among 2 groups (11.11% in minoxidil and 13.8% in combination) from the baseline, increase was comparable with no significant difference ((p value 0.44).

At visit 3 there was increase in average thickness of hair among 2 groups (25 % in minoxidil and 27.7 % in combination group) from the base line, increase was comparable with no significant difference (p value 0.42).

At visit 4 there was increase in average thickness of hair among 2 groups (38.8 % in Minoxidil group and 41.6 % in combination) from the baseline, increase was comparable with no significant difference (p value 0.45).

Table 8. Efficacy of Minoxidil

<table>
<thead>
<tr>
<th>Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>31.65</td>
<td>30.30</td>
<td>37.52</td>
<td>40.43</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number of Hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Significant</td>
</tr>
<tr>
<td>Mean</td>
<td>0.036</td>
<td>0.040</td>
<td>0.045</td>
<td>0.050</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

There was increase in mean value of number of hair at visit 4 compared to baseline after applying anova test, (p value 0.001, df 23.29) increase was statistically significant (Table 8, 9 & Figure 8).

Figure 7. Comparison of mean value of average hair thickness at each visit.

Figure 8. Mean value of number of hair at every visit.

Table 9. Efficacy of combination group

<table>
<thead>
<tr>
<th>Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>31.65</td>
<td>30.52</td>
<td>37.43</td>
<td>40.21</td>
<td>0.0001 (f 12.30)</td>
<td>Significant</td>
</tr>
<tr>
<td>Number of Hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.036</td>
<td>0.041</td>
<td>0.046</td>
<td>0.051</td>
<td>0.0001 (f -55.52)</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Table 10. Comparison of side effects of treatment in both the groups

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>5% Minoxidil</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dryness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Burning</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No side effects</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

Side effects like pruritus were seen in 2 patients and erythema was seen in 1 patient in minoxidil group. In
6. Discussion

Factors such as occupation, marital status, religion and economic status do not play a major role in the manifestation of disease.

In the present study mean age of patients with AGA was 34 years. There were 17 (36.9 %) patients in age group of 31-35 years, which formed majority of the study population which was comparable to study done by C L Goh in which mean age was 33.7 years. In study done by Shin et al21 mean age was 37.77 years.

In a population based study of 1005 subjects done by Dr DS Krupa Shankar22 mean age was 37 years.

In the present study mean duration of hair loss in patients of AGA was around 3 years which was comparable with study of Sehgel et al23 who reported 72% of male patients having less than 4 years duration of AGA.

In the present study family history was present in 80 % males which was comparable with study done by Smith and Wells24 in which 82% men had positive family history of AGA. Ellis et al25 reported that 81.5 % of significantly bald sons had bald father.

Sehgel et al23 reported 87 % of male patients had positive family history. A family history of baldness was present in 48-5% of men in study done by Paik et al26.

In the present study Grade IV was the most common grade of alopecia and grade VI was least common which was comparable to study done by Hamidreza Pazoki-Touroudi27 grade III alopecia was most common.

In the present study difference in the results were attributed to ethnic and racial differences in prevalence of AGA.

In this study group during follow up

At visit 1 (1 month after starting treatment) mean values of number of hair decreased by 4.26 % from the baseline. At visit 2 (3 months after starting treatment) mean values of number of hair increased by 18.54 % from the baseline. At visit 3 (6 months after starting treatment) mean values of number of hair increased by 27.74 % from the baseline.

The increase in mean values of number of hair from the baseline was significant in this group. In the present study increment of number of hair was seen by 3 months after treatment.

In study done by Price, Menefee, and Strauss22 number of hair increased by 35 % at 3 months after treatment and 15% at 6 months after treatment.

The values in the above studies were different from the present study as the results were evaluated at different durations from baseline.

This suggests that there is lot of ethnic difference in treatment response to minoxidil in patients of androgenetic alopecia.

In this study group during follow up

At visit 1 (1 month after starting treatment) mean values of average thickness of hair increased by 11.11
% from the baseline. At visit 2 (3 months after starting treatment) mean values of average thickness of hair increased by 25 % from the baseline.

At visit 3 (6 months after starting treatment) mean values of average thickness of hair increased by 38.8 % from the baseline.

The increase in average thickness of hair was significant in this group.

In the present study increment of thickness of hair was seen by 1 month after treatment.

In study done by Shin et al21 average thickness of hair increased by 5 % at 18 weeks after treatment.

Difference in the results was due to different study durations used for evaluation of the results as compared to present study.

Mean values of number of hair increased by 27.74 % and average hair thickness increased by 38.8 % in this group.

The comparison of increment of above parameters was insignificant compared to combination group.

In the present study topical minoxidil 5% was effective in increasing number and thickness.

6.2 Group 2: Combination of Topical Minoxidil 5%, Tretinoin 0.01% and Azelaic Acid 1.5%

In this study group average age of patients was 35 years which was less compared to study done by Shin et al21 in which mean age was 39 years.

In this study group grade IV of alopecia was found to be most common followed by grade III and grade I, V, VI were least common. In study done by Shin et al21 grade III was most common grade of AGA.

In this study group during follow up

At visit 1 (1 month after starting treatment) mean values of number of hair decreased by 3.57 % from the baseline.

At visit 2 (3 months after starting treatment) mean values of number of hair increased by 18.3 % from the baseline.

At visit 3 (6 months after starting treatment) mean values of number of hair increased by 27.04% from the baseline.

In the present study it was observed that even in combination group there was decrease in hair count after 1 month of therapy, tretinoin and azelaic combination did not have an added advantage of preventing telogen effluvium caused by minoxidil.

The increase in mean values of number of hair from the baseline was significant in this group. In the present study increment of number of hair was seen by 3 months after treatment. In study done by Shin et al21 number of hair increased by 14 % at 18 weeks in patients after applying combination of minoxidil 5% lotion and tretinoin 0.01 % lotion once daily. The difference in the results in above studies from the present study may be due to difference in the duration for evaluation of results from the baseline and difference in frequency of application of the drug.

Bazzano et al28 reported in 58 % of the male and female patients, who were treated the twice daily with tretinoin 0.025% solution, had at least 20% increase from baseline hair count at 12 months.

In this study group during follow up

At visit 1 (1 month after starting treatment) mean values of average thickness of hair increased by 13.8 % from the baseline.

At visit 2 (3 months after starting treatment) mean values of average thickness of hair increased by 27.7 % from the baseline.

At visit 3 (6 months after starting treatment) mean values of average thickness of hair increased by 41.6 % from the baseline.

The increase in mean values of average thickness of hair was significant in this group.

In the present study increment of thickness of hair was seen by 1 month after treatment. In study done by Shin et al21 thickness of hair increased by 5 % at 18 weeks in patients after applying combination of minoxidil 5% lotion and tretinoin 0.01 % lotion once daily. In this study group mean values of number of hair increased by 27.04 % and average hair thickness increased by 41 % from baseline in this group.

The increase in mean values of number of hair and average thickness of hair was significant in this group.

The comparison of increment of above parameters was insignificant compared to minoxidil group. In the present study combination of Minoxidil 5%, azelaic acid 1.5 %, tretinoin 0.01 % was effective in increasing number of hair and average thickness of hair.

In the present study combination therapy was equally effective to minoxidil monotherapy in treatment of AGA.

In study done by Shin et al21 it was proven that efficacy and safety of combined 5% minoxidil and 0.01% tretinoin administered once daily are equivalent to those of conventional 5% minoxidil administered twice daily for the treatment of AGA.

Different frequency of application of drugs (once daily) can be factor for difference in the results in above study as compared to present study in which combination drug was applied twice daily.

Different time duration for evaluation of results (18 weeks) as compared to 6 months in the present study can be a factor for difference in the results.
Different racial and ethnicity factor can be a factor for difference in the results from the present study.

In a study done in Iran MHEC containing 3 hair growth promoters (minoxidil 12.5%, azelaic acid 5%, betamethasone-17-valerate 0.025%) seemed to be effective in hair loss treatment, more potent than minoxidil 5% alone, without intolerable adverse effects and was to be considered for AGA patients who do not respond well to minoxidil alone.

There was a drastic improvement in cosmetic scalp coverage with the use of tretinoin (58% with tretinoin 0.025% alone; 66% with tretinoin 0.025% combined with 0.5% minoxidil) in a study done by Bazzano et al.

Different concentration of azelaic acid 5% and tretinoin 0.025% in above study can be a factor for difference in results from the present study.

Different time duration for evaluation of results, 24 in both the above studies weeks as compared to 6 months in the present study can be a factor for difference in the results from the present study. Different racial and ethnicity factor can be a factor for difference in the results of the above studies from the present study.

Side effects like pruritus were seen in 2 patients & erythema was seen in 1 patient in minoxidil group. In combination group side effects like pruritus was seen in 2 patients and erythema, dryness, burning were seen in 1 patient. However, symptoms were mild in all cases and the patients were able to continue application of the drugs. Side effects were not significantly associated with treatment in both the study groups.

In study done by Shin et al 5 five patients in the test group (minoxidil 5% and tretinoin 0.01%) and four patients in the control group (minoxidil 5%) complained of scalp itching or pricking.

It was observed that minoxidil mono therapy group was more effective in increasing number of hair than combination group (27.74% in minoxidil group and 25% in combination but the difference in the increment was not statistically significant.

It was observed that combination group was more effective in increasing in average thickness of hair than minoxidil monotherapy group (41% in combination group and 38.8% in minoxidil group) but the difference in the increment was not statistically significant.

The patients were satisfied with scalp coverage in both the groups.

Most of the studies are carried out in different parts of the world; ethnicity is a factor while comparing results of therapy.

Some patients with androgenetic alopecia might respond better to therapy of any sort, and others respond more slowly and less completely this factor should be considered while comparing the results.

Minoxidil sulfate is the active metabolite that stimulates hair follicles. The conversion of minoxidil to minoxidil sulfate is catalysed by sulfotransferase enzymes, which exist in scalp. There are individual variations in scalp sulfotransferase levels. Patients with better response to topical Minoxidil were found to have greater level of enzyme activity. Different study duration for evaluation of results can be a factor for difference in results. Different frequency of application of medications can be a factor for discrepancy in results. As there are very few comparative studies proving efficacy of combination of tretinoin and azelaic acid with minoxidil versus minoxidil monotherapy world wide and also in Indian population more studies are invited to prove their efficacy.

In present study combination therapy (minoxidil 5%, azelaic acid 1.5% and tretinoin 1.5%) was equally effective to minoxidil 5% mono therapy in treatment of AGA. The present study strengthens the evidence that topical minoxidil 5% mono therapy is an effective treatment for androgenetic alopecia and dermoscope is a very useful tool in patients of androgenetic alopecia.

7. Conclusions

To conclude, in the present study:

- Topical minoxidil monotherapy 5% was effective treatment for androgenetic alopecia. Drug was effective in increasing hair number and thickness. Drug was safe with minimal side effects.
- Combination of topical minoxidil 5%, tretinoin 0.01% was effective treatment for androgenetic alopecia. Combination of topical minoxidil 5%, azelaic acid 1.5%, tretinoin 0.01% was effective in increasing hair number and thickness. Combination of topical minoxidil 5%, azelaic acid 1.5%, tretinoin 0.01% was safe with minimal side effects.
- Both topical minoxidil and combination of topical minoxidil 5%, azelaic acid 1.5%, tretinoin 0.01% were equally effective in treatment of AGA.
- Combination therapy had no added advantage over minoxidil monotherapy.

8. Recommendations

As there are very few comparative studies of minoxidil monotherapy versus combination of minoxidil, tretinoin and azelaic acid in treatment of AGA as well as role of topical tretinoin and azelaic acid in androgenetic alopecia more studies are invited worldwide as well as in Indian population.
9. References
