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Comparative Study of The Effect of Topical Minoxidil 5% Versus Combined Fractional CO_2 Laser and Topical Minoxidil 5% in Treatment of Male Androgenetic Alopecia

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ABSTRACT

Background: Male androgenetic alopecia (MAA) is the most common hair problem among men. Androgenetic alopecia (AGA) is a non-scarring progressive miniaturization of the hair follicle with a usual characteristic pattern of distribution in genetically predisposed men and women.

Objective: To compare between the efficacy of topical minoxidil 5% alone and combined topical minoxidil 5% and fractional laser in treatment of male androgenic alopecia and detection of any side effects occurring with each line of treatment.

Patients and Methods: This prospective randomized comparative controlled study was conducted for one year on 40 patients with male androgenic alopecia attending to out Patient Clinic of Dermatology, Andrology and STDs Department, Mansoura University Hospitals. Patients were classified into two groups: Group A received minoxidil alone (minoxidil group) and group B where patients received minoxidil plus fractional CO_2 laser.

Results: In group A and B, there was a statistically significant improvement between the clinical assessment scale at baseline and after 1 month ($p<0.001$). Also, there was a statistically significant improvement between the clinical assessment scale after 1 month and after 3 months ($p=0.002$). In group A, there was a statistically significant improvement between the clinical assessment scale at baseline and after 1 month, however, there was no statistically significant improvement between the clinical assessment scale after 1 month and after 3 months. In group B, there was a statistically significant improvement between the clinical assessment scale at baseline and after 1 month, however, also, there was a statistically significant improvement between the clinical assessment scale after 1 month and after 3 months.

Conclusion: Our study revealed the superiority of combination therapy, using a fractional laser and 5% minoxidil, over 5% minoxidil alone, for the treatment of male AGA, with no serious adverse effects of treatment identified.

Keywords: Androgenetic alopecia, Topical minoxidil 5%, Fractional CO_2 laser, Topical minoxidil 5%

INTRODUCTION

Androgenetic alopecia (AGA) is a non-scarring disease with a progressive thinning of the scalp hair that follows a characteristic pattern. The pathogenesis of androgenetic alopecia involves both genetic and hormonal (androgens) factors [(1)]. 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 [(2)]. This phenomenon is caused by androgen hyperactivity and various genetic predispositions. Subsequently, hair follicles decrease in size and exhibit a reduced anagen-to-telogen ratio [(3)].

Traditionally, pharmacologic treatment of AGA targets decreasing dihydrotestosterone (DHT) and stimulating hair follicles through the use of 5-alpha reductase (5AR) inhibitors or minoxidil; however, new and experimental therapies are exploring inhibition of Janus kinase (JAK) (Regulates the activation of key hair follicle populations such as the hair germ and improves the inductivity of cultured human dermal papilla cells by controlling a molecular signature enriched in intact, fully inductive dermal papillae) and the use of platelet-rich plasma (PRP). Other therapies include laser therapy, scalp microneedling, hair mesotherapy, and hair transplantation [(4)].

There are several mechanisms by which minoxidil may promote hair growth; however, the exact mechanism of action is unclear. It has been shown both in vivo and in vitro to have a direct mitogenic effect on epidermal cells, and in vitro it prolongs the survival time of keratinocytes. In addition, topical minoxidil may oppose calcium entry into the cells, which may increase epidermal growth factors to allow hair growth [(5)]. **Rossi *et al.*** [(6)] reported stoppage of hair loss in 50% of men and hair regrowth in a small percentage of men after topical minoxidil therapy. **Jones** [(7)] suggests a dose of 1ml minoxidil twice per day. Local erythema and pruritis were reported as side effects. The drug must be continued indefinitely or hair regrowth will subside.

In 2007, low-level laser therapy has been approved by the US Food and Drug Administration and appeared to be safe and effective in treatment of male- and female-pattern hair loss [(8)].

Huang *et al.* [(9)] reported that a fractional laser-assisted drug system can be used to provide supportive

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care for patients with male androgenic alopecia, but it cannot completely replace traditional treatment methods. Rather, the technique could potentially be used in combination with conventional treatments.

The aim of this study was to compare between the efficacies of topical minoxidil5% alone and combined topical minoxidil 5% plus fractional laser in treatment of male androgenic alopecia and to detect of any side effects occurring with each line of treatment.

PATIENTS AND METHODS

Forty patients with male androgenetic alopecia were included in this study. They were chosen from the Outpatient Clinic of Dermatology, Andrology & STDs Department, Mansoura University Hospitals from January, 2020 to January, 2021.

Ethical approval:

Mansoura Faculty of Medicine's Institutional Review Board (IRB) accepted this report (MS). An informed consent was taken before inclusion of patients into the study. Every care was taken to protect the data's privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patients diagnosed clinically and by dermoscope as androgentic alopecia with age from 25-30 years old and with bitemporal recession.

Exclusion criteria:

Patients receiving any therapy that could affect hair cycle during last three months, patients with a history of a systemic disease, history of immunocompromised status, any active local or systemic infection, connective tissue disorders, and history of allergy to any medication necessary for treatment of active psoriasis or vitiligo, unrealistic expectations and body dismorphic disorder.

All patients were subjected to the following:

- **Detailed history taking** regarding age, occupation, marital status, family history, special habits, associated psychological disturbances, associated medical or surgical condition and drug intake.
- **Detailed general and full dermatological examination** including skin, hair, nail and oral mucosa to exclude any associated disease.
- **Examination of the scalp (clinical and dermoscopically):**
- **Local clinical examination:** 40 patients with male androgenetic alopecia were included in this study. They were classified according to modified Norwood classification system **(10)**.

Dermoscopic examination of the scalp:

(1) The dermoscopy used: Dermlite3 (3 Gen, USA). It is pocket epiluminescence microscopy device with camera-compatible made to show skin with clarity and high magnification.

(2) An attachment piece: (Sony adapter) was used to connect the dermoscope to the digital camera.

(3) The camera used: Cyber-shot model DSC-W620 by Sony: 5x optical zoom lens and 16.1 - megapixel with a 28 - 140 mm focal length.

Patients were divided into 2 groups: Group A: Included 20 patients on topical minoxidil 5% for 12 weeks, and **Group B:** Included 20 patients on combined fractional laser and minoxidil 5%for 12 weeks.

Topical minoxidil group: 12 weeks of treatment with topical minoxidil 5% 6 puffs on the scalp.

Combined Fr CO2 laser and topical minoxidil:

- 20 patients received 4 sessions of fractional $C0_2$ laser (DEKA, Smart-Xide DOT, Italy), with 2-weeks interval. Topical anaethetic cream was applied under occlusion 30 minutes before the session. Fractional CO_2 laser was performed over the alopecic scalp. The treatment settings had a power of 6 watts, dot mode with spacing 550 mm, dwell time 400 ms, scanning model, smart track, single stack, square shape, ratio10/10, and size 100%. These parameters are equivalent to fluence of 0.3j/cm, density 11.9% and energy/dott 2.4 mj.
- After each laser session, the patient received topical minoxidil 5% 6 puffs on the alopecic scalp as laser beam create microscopic channels in the skin allowing deeper delivery of minoxidil. The patient was advised to apply emollient cream twice daily for 1 week after sessions.

Assessment of the efficacy of therapeutic procedure:

(1) Photographs were obtained at base-line, one and three months after the final treatment.

(2) Dermoscopy: for density of hair at base line and 3 months after final treatment.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Mann-Whitney U test was used to compare 2 independent groups. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

The main age of the cases in group A was 26.8 ± 1.7 years and the mean age in group B was 26.9 ± 1.8 with no statistically significant difference between the

two groups. The median duration of the disease was 3 years in group A with range between 1 and 9 years while in group B the duration was 2 years with range between 1 and 5 years with no significant difference between the two groups. There was 6 cases (30%) with positive family history in group A and 10 cases (50%) with positive family history in group B (Table 1).

Table (1): Distribution of studied patients according to their personal characteristics (n=40)

Personal characteristics	Group A (n=20)	Group B (n=20)	Test of significance
Age (years) Mean ± SD Median (min-max)	26.8 ± 1.7 26.5 (25 – 30)	26.9 ± 1.8 27 (25 – 30)	t=0.27 p=0.78
Duration of disease (years) Mean ± SD Median (min-max)	3.75 ± 2.09 3 (1 – 9)	2.75± 1.37 2.0 (1.0 – 5.0)	z=1.58 p=0.11
Family history	**No. (%)**	**No. (%)**	
Positive Negative	6 (30%) 14 (70%)	10 (50%) 10 (50%)	X^2=1.67 p=0.19

t: Student t test z=Mann Whitney U test X^2= Chi-Square test

The mean pretreatment number of terminal hairs in the minoxidil-treated group was 98.15 ± 27.58/cm^2 while in the minoxidil + fractional laser therapy-treated group was 96.12 ± 22.16/cm^2 with no statistically significant difference between the two groups (p=0.258). At 1 month follow up, the mean number of terminal hairs in the minoxidil + fractional laser therapy-treated group was 120.23 ± 31.15/cm^2, which was statistically significantly higher as compared to the minoxidil-treated group (113.28 ± 30.04/cm^2) (p=0.021).

At 3 month follow up, the mean number of terminal hairs in the minoxidil + fractional laser therapy-treated group was 131.18 ± 34.10/cm^2, which was statistically significantly higher as compared to the minoxidil-treated group (121.2 ± 30.92) (p< 0.001).

There was a statistically significant increase in the number of terminal hairs in the two studied groups along the duration of follow up, but the mean percentage of increase was higher in the minoxidil + fractional laser therapy-treated group (36.5%) as compared to the minoxidil group (23.5%) (Table 2).

Table (2): Comparison of terminal hair per cm^2 in the two studied groups along the duration of follow up

Duration of follow up	Group A (Minoxidil group) (n=20)	Group B (Minoxidil + Fractional laser therapy group) (n=20)	P value
Pretreatment	98.15 ± 27.58	96.12 ± 22.16	0.258
1 month follow up	113.28 ± 30.04	120.23 ± 31.15	0.021*
3 months follow up	121.2±30.92	131.18 ± 34.10	< 0.001**
Mean percentage of change at last follow up	23.5%	36.5%	
Repeated measures ANOVA	F= 6.842 P1< 0.001**	F= 11.019 P2< 0.001**	

F: Repeated measures ANOVA, P value: Comparing between group A and group B

*: Statistically significant (p< 0.05), **: Highly statistically significant (p≤0.001)

Before treatment, peripilar sign was detected in 40% in the minoxidil-treated group while it was detected in 45% in the minoxidil + fractional laser therapy group, with no statistically significant difference between the two groups (p=0.242). At 1 month of follow up, peripilar sign was detected in 30% in the minoxidil-treated group while it was detected in 20% in the minoxidil + fractional laser therapy group, with no statistically significant difference between the two groups (p=0.068). At 3 months of follow up, peripilar sign was detected in 25% in the minoxidil-treated group while it was detected in 10% in the minoxidil + fractional laser therapy group, with statistically significant difference between the two groups (p=0.039) (Table 3).

Table (3): Comparison of peripilar sign in the two studied groups along the duration of follow up

Duration of follow up	Group A (Minoxidil group) (n=20)	Group B (Minoxidil + Fractional laser therapy group) (n=20)	P value
Pretreatment	8 (40%)	9 (45%)	0.242
1 month follow up	6 (30%)	4 (20%)	0.068
3 months follow up	5 (25%)	2 (10%)	0.039*

F: Repeated measures ANOVA P value: Comparing between group A and group B

*: Statistically significant (p< 0.05)

**: Highly statistically significant (p≤0.001)

In group A at the base line, all cases were classified as negative according to the clinical assessment scale. After 1 month, 3 cases (15%) were negative, 8 cases (40%) showed mild improvement and 9 cases (45%) with moderate improvement. After 3 months, 1 case (5%) was negative, 4 cases (20%) showed mild improvement, 9 cases (45%) showed moderate improvement and 6 cases (30%) showed significant improvement. There was a statistically significant difference between the clinical assessment scale at baseline and after one month in all grads except for significant improvement. There was a statistically significant difference between the clinical assessment scale at baseline and after three months in all grads except for mild improvement. Also there was a statistically significant difference between the clinical assessment scale after 1 month and after three months in the significant improvement scale (Table 4).

Table (4): Comparison of clinical assessment scale change at baseline, 1 month and 3 months follow up periods among group A.

Clinical assessment scale	Baseline (n=20) No. (%)	After 1 month (n=20) No. (%)	After 3 months (n=20) No. (%)	Test of significance (MC)
Negative	20 (100%)	3 (15%)	1 (5%)	P1<0.001* P2<0.001* P3=0,60
Mild	0	8 (40%)	4 (20.0%)	P1=0.001* P2=0.106 P3=0.17
Moderate	0	9 (45%)	9 (45%)	P1=0.006* P2=0.006* P3=1.0
Significant	0	0	6(30%)	P1=1.0 P2=0.007* P3=0.007*

MC for MC Nemar test P1: comparison between baseline and 1 month P2: comparison between baseline and 3 months P3: comparison between 1 month and 3 months ∗ Indicating statistically significant result
0: negative +1: Mild + 2: Moderate +3 significant

In group B at the base, line all cases were classified as negative according to the clinical assessment scale. After 1 month, 11 cases (55%) were negative, 3 cases (15%) were with mild improvement and 6 cases (30%) were with moderate improvement. After 3 months, 4 case (20%) were negative, 9 cases (45%) were with mild improvement, 6 cases (30%) were with moderate improvement and 1 case (5%) was with significant improvement. There was a statistically significant difference between the clinical assessment scale at baseline and after one month in the negative and moderate improvement. There was a statistically significant difference between the clinical assessment scale at baseline and after three months in all grads except for significant improvement. Also, there was a statistically significant difference between the clinical assessment scale after 1 month and after three months in the negative and mild improvement grads (Table 5).

Table (5): comparison of clinical assessment scale change at baseline, 1 month and 3 months follow up periods among group A.

Clinical assessment scale	Baseline (n=20) No. (%)	After 1 month (n=20) No. (%)	After 3 months (n=20) No. (%)	Test of significance (MC)
Negative	20 (100%)	11(55%)	4 (20%)	p1=0.0006* p2< 0.001* p3=0.02*
Mild	0 (0.0%)	3 (15%)	9(45%)	p1=0.23* p2=0.0006* p3=0.0038*
Moderate	0 (0.0%)	6 (30%)	6 (30%)	p1=0.007* p2=0.007* p3=1.0
Significant	0 (0.0%)	0 (0.0%)	1 (5.0%)	p1=1.0 p2=1.0 p3=1.0

MC for MC Nemar test P1: comparison between baseline and 1 month P2: comparison between baseline and 3 months P3: comparison between 1 month and 3 months ∗ indicating statistically significant result
0: negative +1: Mild +2: Moderate +3 significant

There was statistically significant difference in the clinical assessment scale between the cases in group A and group B at 1 month and 3 months of treatment (p=0.02 and 0.04) respectively. The percentage of improvement was higher in group A (Table 6).

Table (6): Comparison of clinical assessment scale at baseline, 1 month and 3 months follow up periods between group A & B.

Clinical assessment scale	Group A (n = 20) No. (%)	Group B (n = 20) No. (%)	Test of significance
At baseline 0	20 (100%)	20 (100%)	……
After 1 month No Mild Moderate Significant	11(55%) 3 (15%) 6 (30%) 0	3 (15%) 8 (40%) 9 (45%) 0	MC P = 0.02*
After 3 months No Mild Moderate Significant	4 (20%) 9(45%) 6 (30%) 1 (5.0%)	1 (5%) 4 (20.0%) 9 (45%) 6(30%)	MC P = 0.04*

MC for Monte Carlo test, P value significant if ≤0.05

Regarding the side effects in the two studied groups, initial shedding was detected in 75% in the minoxidil-treated group that was statistically significantly higher as compared to the minoxidil + fractional laser therapy-treated group (45%) (p=0.001). Irritation was detected in 25% in the minoxidil-treated group and in 20% in the minoxidil + fractional laser therapy-treated group, with no statistically significant difference between the two groups (p=0.254). Erythema was detected in 10% in the minoxidil-treated group and in 20% in the minoxidil + fractional laser therapy-treated group, with no statistically significant difference between the two groups (p=0.071). Dandruff was detected in 15% in the minoxidil-treated group and in 10% in the minoxidil + fractional laser therapy-treated group, with no statistically significant difference between the two groups (p=0.267) (Table 7).

Table (7): Comparison of side effects in the two studied groups

Side effects	Group A (Minoxidil group) (n=20)	Group B (Minoxidil + Fractional laser therapy group) (n=20)	P value
Initial shedding	15 (75%)	9 (45%)	0.001**
Irritation	5 (25%)	4 (20%)	0.254
Erythema	2 (10%)	4 (20%)	0.071
Dandruff	3 (15%)	2 (10%)	0.267

P value: Comparing between group A and group B
**: Highly statistically significant (p≤0.001)

DISCUSSION

In the current study, the mean age of the studied patients was 26.8 ± 1.7 years versus 26.9 ± 1.8 with no significant difference between the two groups (p=0.78). Similarly, a previous study by **Salah *et al.*** [11] on 45 Egyptians with male androgenetic alopecia (MAGA) whose ages ranged from 21 to 45 years with a mean of 31.48 ± 6.62 years. All patients had a positive family history. In the same way**,** the study conducted by **Kaya Erdogan *et al.*** [12] showed that the mean age for AGA onset was 19.51 ± 2.87 years. This age distribution supports the view of **Wang *et al.*** [13] and **Harries *et al.*** [14] who stated that almost all patients with PHL have an onset prior to the age of 40 years.

In the present study, there were 6 cases (30%) with positive family history in group A and 10 cases (50%) with positive family history in group B. This comes in agreement with **Arias-Santiago *et al.*** [15] who showed that among patients with AGA included in their study, 84.11% had a family history of AGA versus 19.1% of the control subjects (P=0.0001). The results of high ratio of AGA in relatives of patients was explained by **Lolli *et al.*** [16]**, Pirastu *et al.*** [17] and **Rojas- *et al.*** [18] who documented that both maternal and paternal genetics appear to be involved in the inheritance of PHL and the mode of this inheritance is best viewed as polygenic.

In the instant study, the mean pretreatment hair density in the minoxidil-treated group was 122.8 ± 10.67/cm^2 while in the minoxidil + fractional laser therapy-treated group was 120.19 ± 9.85, with no statistically significant difference between the two groups (p=0.324). At 1 month follow up, the mean hair density in the minoxidil + fractional laser therapy-treated group was 149.9 ± 15.64/cm^2, which was statistically significantly higher as compared to the minoxidil-treated group (140.56 ± 14.81) (p=0.038). At 3 months follow up, the mean hair density in the minoxidil + fractional laser therapy-treated group was 166.17 ± 19.39/cm^2 which was statistically significantly higher as compared to the minoxidil-treated group (154.07 ± 17.44) (p=0.010). There was a statistically significant increase in the mean hair density in the two studied groups along the duration of follow up, but the mean percentage of change was higher in the minoxidil + fractional laser therapy-treated group (38.3%) as compared with the minoxidil group (25.8%). In **Huang *et al.*** [9] study, hair density improved in both groups, but the improvement was much more in the combined group than in the growth factor group and the hair shaft diameter also noticeably increased after the treatment. The findings of the present study are in concordance with **Yu *et al.*** [19] at baseline where there were no significant differences in hair count (P > 0.05) or hair thickness (P > 0.05) between the FRM (Fractional Radio Frequency) plus minoxidil combined-therapy side and the minoxidil monotherapy side. At follow-up 1 month after the final FRM treatment, both sides had significant improvements in hair count (P < 0.001) and hair thickness (P < 0.001). Mean hair count increased by 66% on the combined-therapy side and 37% on the monotherapy side, while mean hair thickness increased by 34% and 27%, respectively. The combined-therapy side therefore had a higher degree of improvement than the monotherapy side in both mean hair count (P = 0.01) and mean hair thickness (P = 0.02). **Salah *et al.*** [11] found a significant increase in the mean number of hairs after treatment in each group, where it was the most significant in the combined patient group, then in the fractional group, and then in the minoxidil group. However, there was no significant difference in comparing the 3 groups after treatment.

In the current study**,** the mean pretreatment number of vellus hair in the minoxidil-treated group was 47.6 ± 13.14/cm^2 while in the minoxidil + fractional laser therapy-treated group was 48.12 ± 12.75/cm^2 with no statistically significant difference between the two groups (p=0.189). At 1 month follow up, the mean number of vellus hair in the minoxidil + fractional laser therapy-treated group was 35.17 ± 8.49/cm^2, which was statistically significantly lower

as compared to the minoxidil-treated group (40 .35 ± 9.14/cm^2) (p=0.045). At 3 months follow up, the mean number of vellus hair in the minoxidil + fractional laser therapy-treated group was 27.46 ± 6.017/cm^2, which was statistically significantly lower as compared to the minoxidil-treated group (35.4 ± 7.33/cm^2) (p=0.017). In agreement with the results of the present study, **Salah *et al.*** [11] found a statistically significant decrease in the number of vellus hair in the two studied groups along the duration of follow up, but the mean percentage of change was higher in the minoxidil + fractional laser therapy treated group (42.9%) as compared to the minoxidil group (25.6%).

In the current study**,** the mean pretreatment number of terminal hairs in the minoxidil-treated group was 98.15 ± 27.58/cm^2 while in the minoxidil + fractional laser therapy-treated group was 96.12 ± 22.16/cm^2 with no statistically significant difference between the two groups (p=0.258). At 1 month follow up, the mean number of terminal hairs in the minoxidil + fractional laser therapy-treated group was 120.23 ± 31.15 which was statistically significantly higher as compared to the minoxidil-treated group (113.28 ± 30.04/cm^2) (p=0.021). At 3 months follow up, the mean number of terminal hairs in the minoxidil + fractional laser therapy-treated group was 131.18 ± 34.10/cm^2, which was statistically significantly higher as compared to the minoxidil-treated group (121.2 ± 30.92/cm^2) (p< 0.001). There was a statistically significant increase in the number of terminal hairs in the two studied groups along the duration of follow up, but the mean percentage of change was higher in the minoxidil + fractional laser therapy-treated group (36.5%) as compared to the minoxidil group (23.5%). **Salah *et al.*** [11] found a significant increase in the thickness of thin and thick hairs after treatment in the combined patient group and the fractional group, but in the minoxidil group only the thin hair thickness increased. However, there was no significant difference in comparing between the 3 groups after treatment.

In the present study**,** before treatment, peripilar sign was detected in 40% in the minoxidil-treated group while it was detected in 45% in the Minoxidil + Fractional laser therapy group, with no statistically significant difference between the two groups (p=0.242). At 1 month of follow up, peripilar sign was detected in 30% in the minoxidil-treated group, while it was detected in 20% in the minoxidil + fractional laser therapy group, with no statistically significant difference between the two groups (p=0.068). At 3 months of follow up, peripilar sign was detected in 25% in the minoxidil-treated group while it was detected in 10% in the minoxidil + fractional laser therapy group, with statistically significant difference between the two groups (p=0.039). Conversely, **Salah *et al.*** [11] found peripilar sign in all the patients before and after treatment. However, there was a significant difference between the 3 groups; it was more present in the fractional group than in the other 2 groups after treatment. Other study noted that the peripilar halo varied from brown to white color. Although there was no specific relationship detected in the occurrence of brown peripilar sign and the stage of hair loss, there was a positive correlation between the white peripilar sign and the progressing stage of AGA besides its duration [20].

In the current study, the clinical assessment scale change among group A (Minoxidil alone) was as follow: After 1 month, 3 cases (15%) at grade 0, 8 cases (40%) at grade +1 and 9 cases (45%) at grade +2. After 3 months, 1 case (5%) at grade 0, 4 cases (20%) at grade +1, 9 cases (45%) at grade +2 and 6 cases (30%) at grade +3. There was a statistically significant improvement between the clinical assessment scale at baseline and after 1 month (p<0.001). Also, there was a statistically significant improvement between the clinical assessment scale after 1 month and after 3 months (p=0.002). In the same line, **Panchaprateep and Lueangarun** [2] showed that hair growth in patients on oral minoxidil was clearly observed in the global photographic assessment, with a 100% improvement (score > + 1 or + 1–40% improvement) on the vertex area at 24 weeks. An improvement scale score of + 2 (moderate increase, + 41–70% improvement) and 3 (large increase, > + 70–100% improvement) were reported in 93.3% of patients in the vertex and 73.3% of patients in the frontal area. Similarly, in a previous study by **Suchonwanit *et al.*** [21] for the monotherapy with minoxidil 5%, hair density increased from 97.25 ± 15.91/cm^2, at baseline, to 133.77 ±19.42 hairs/cm^2,at 24weeks(p= 0.001), with the hair diameter increasing from 51.16 ± 14.53 to 65.32 ± 16.42μm, respectively (p=0.002).

In the current study, the clinical assessment scale change among group B, at the baseline, all cases were at grade 0 according to the clinical assessment scale. After 1 month, 11 cases (55%) at grade 0, 3 cases (15%) at grade 1 and 6 cases (30%) at grade 2. After 3 months, 4 cases (20%) at grade 0, 9 cases (45%) at grade 1, 6 cases (30%) at grade 2 and 1 case (5%) at grade 3. There was a statistically significant improvement between the clinical assessment scale at baseline and after 1 month (p<0.001). Also, there was a statistically significant improvement between the clinical assessment scale after 1 month and after 3 months (p=0.02). Similarly, **Salah *et al.*** [11] found a significant increase in the mean number of hair after treatment in the 3 groups, where it was most significant in the combined patient group (P = 0.001). There was a significant increase in the count of thick hairs after treatment in all the groups, where it was most significant in the combined patient group (P = 0.001). There was a significant increase in the count of thin hairs after treatment in the combined group (P = 0.001). There was a significant increase in the thickness of thick hairs after treatment in the combined group (P = 0.042).

Also **Suchonwanit *et al.*** [21] found a significant improvement in hair density and diameter, from baseline, for the combination therapy. Also, hair density increased from 96.58 ± 16.52, at baseline, to 147.12 ± 18.19 hairs/cm^2, at 24 weeks (p= 0.001), with the hair diameter increasing from 50.93 ± 13.59 to 67.28 ± 15.63μm, respectively (p= 0.001).

The efficacy of non-ablative fractional Er: Glass laser for the treatment of AGA was first reported by **Kim *et al.*** [22] who conducted a pilot study of 20 men who received treatment every 2 weeks, for a total of five treatments, with clinical improvement in hair density and growth rate reported, without any serious adverse events. At the onset of the current study, according to clinical assessment scale, all the cases in the two groups were at grade 0. After 1 and 3 months, there was a statistically significant improvement in the clinical assessment scale in group B when compared to group A) (p=0.02 and 0.04, respectively). In a previous study, twenty-eight men were enrolled to determine the efficacy and safety of hair growth factors combined with ablative carbon dioxide (CO_2) fractional laser therapy in MAA. The outcome was significantly better in the combined group than in the growth factor group alone (investigator assessment, p=0.018) [9]**.** Similarly, **Suchonwanit *et al.*** [21] found that the mean difference of the change in hair density, from baseline, was significantly higher for the combination than monotherapy at treatment weeks 16 (p=0.042), 20 (p=0.001), and 24 (p= 0.004). Furthermore, for the hair diameter, the mean difference of the change, from baseline, was significantly higher for the combination than monotherapy at treatment week 20 (p= 0.032) and 24 (p= 0.034).

Regarding the side effects in the present study, initial shedding was detected in 75% in the minoxidil-treated group that was statistically significantly higher as compared to the minoxidil + fractional laser therapy-treated group (45%) (p=0.001). Irritation, and dandruff were more detected in minoxidil-treated group than in the combined group (25% vs 20%, 15% vs 10% respectively) with no statistical significance. Also erythema was more detected in the combined group (20%) than in the minoxidil group (10%) with no tactical significance. In agreement with the results of the current study, there is no report of serious adverse events regarding fractional Er: Glass laser for hair loss treatment in previous studies [21, 23]**.** Patients in **Suchonwanit *et al.*** [21] study felt tolerable pain and a sensation of warmth during laser treatment. Mild adverse effects, such as erythema, itching, and scaling, occurred with both treatments and resolved spontaneously within a few days. Parallel to this**,** no serious AEs (Adverse Events) were encountered by **Yu *et al.*** [19] during the treatment term. Pain during the FRM treatment was well tolerated by all participants, with an average pain score of 3.63 ± 1.38. Transient pinpoint bleeding was observed during FRM treatment. Mild erythema occurred at the FRM-treated site and resolved within 24 h. No erosion or breakage of hair shaft was noted on the FRM-treated side. Eight participants reported dandruff on the drug-applied area of the scalp.

CONCLUSION

Our study revealed the superiority of combination therapy, using a fractional laser and 5% minoxidil, over 5% minoxidil alone, for the treatment of male AGA, with no serious adverse effects of treatment identified. Laser-induced photothermolysis and the formation of effective routes for transdermal drug delivery are possible mechanisms explaining the superiority of clinical outcomes for the combination therapy. Fractional laser therapy, either combination with topical agents or monotherapy, can be considered as a promising option for the treatment of AGA.

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