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Low Level Light-Minoxidil 5% Combination Versus Either Therapeutic Modality Alone in Management of Female Patterned Hair Loss: A Randomized Controlled Study

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Background: Female pattern hair loss (FPHL) is the most common form of hair loss in women. Nevertheless, its management represents a real challenge. Among the FDA approved therapeutic modalities for FPHL are topical minoxidil and more recently low-level light therapy (LLLT).

Aim of Work: Assess the efficacy and safety of LLLT in comparison to topical minoxidil 5% and to a combination of both therapies in the treatment of FPHL.

Patients and Methods: This study included 45 female patients with proven FPHL. They were randomly divided into three equal groups, where group (i) patients were instructed to apply topical minoxidil 5% twice daily, group (ii) patients received LLLT using the helmet iGrow® device for 25 minutes 3 days weekly, and group (iii) patients received a combination of both topical minoxidil 5% twice daily and LLLT for 25 minutes 3 days weekly for 4 months (study duration). Evaluation was done according to clinical, dermoscopic (folliscopic), and ultrasound biomicroscopic (UBM) parameters. Patient satisfaction and side effects were reported.

Results: The efficacy and safety of both topical minoxidil and LLLT were highlighted with comparable results in all parameters. The combination group (iii) occupied the top position regarding Ludwig classification and patient satisfaction. UBM and dermoscopic findings showed significant increase in the number of regrowing hair follicles at 4 months in all groups, whereas only UBM showed such significant increase at 2 months in the combination group (iii). A non-significant increase in the hair diameter was also documented in the three groups.

Conclusion: LLLT is an effective and safe tool with comparable results to minoxidil 5% in the treatment of FPHL. Owing to the significantly better results of combination therapy, its usage is recommended to hasten hair regrowth. Lasers Surg. Med. 49:835–843, 2017. © 2017 Wiley Periodicals, Inc.

Key words: female pattern hair loss; low light laser therapy; minoxidil; dermoscope; UBM

INTRODUCTION

Patterned hair loss (PHL) continues to be one of the most important hair problems affecting both sexes [1]. Female pattern hair loss (FPHL) comprises the reduction in hair density over the crown and frontal scalp with retention of the frontal hairline [2]. FPHL has a devastating psychological impact on the lives of those affected. The prompt intervention with a combination of different therapeutic modalities tends to be more efficacious than mono-therapy approach [3].

Various treatment options currently exist for the management of FPHL including; topical products, nutritional supplements, low-level laser therapy (LLLT), and hair transplantation. However, the results of such measures are mixed and have not been studied rigorously. The only Food and Drug Administration (FDA)-approved medication is topical minoxidil [4].

Low-level laser therapy is a relatively new FDA cleared device with postulated efficacy in promoting hair growth in both men and women with androgenetic alopecia (AGA) and FPHL, respectively [5]. Among various mechanisms of action, the main one hypothesized that LLLT activates epidermal stem cells in the hair follicle bulge with a shift toward the anagen phase [6,7].

The paucity of clinical trials assessing the efficacy and safety of treatment options for FPHL triggered the commencement of the present study, which aimed to evaluate and compare LLLT to topical minoxidil 5% as well

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as to a combination of both therapies in the management of such a challenging condition.

PATIENTS AND METHODS

The current randomized controlled clinical trial was conducted in Dermatology out-patient clinic, Faculty of Medicine, Cairo University. The approval of the Dermatology Research Ethical Committee (REC), Faculty of Medicine, Cairo University was obtained as well as informed written consents from all participants in the study.

Thirty adult female patients (age >18 years) with proven FPHL were enrolled in the current study. Patients were instructed to refrain from topical, intralesional, or systemic therapy for FPHL in the last 3 months prior to their inclusion. Pregnancy, lactation, signs of hyperandrogenism (hirsutism, polycystic ovaries), presence of any systemic (e.g., thyroid disorders) and/or local scalp disease, serum ferritin deficiency (<40 μg/L) [8], and the intake of medications deeming to inhibit hair growth, for example, chemotherapy were all considered as criteria of exclusion from the present study.

Confirmation of the diagnosis of FPHL was done according to criteria presented by Rasheed et al. [8].

In addition, Dermoscopic evaluation was performed by a fixed investigator for all participants using a DermLite II pro® dermoscope (3Gen, San Juan Capistrano, CA). The dermoscopic images were photographed using Samsung HD ES90 digital camera connected to a DermLite II Pro. From the dermoscopic photos obtained the number of hairs were counted and the percent of apparently thin hairs was calculated (>20% hair diameter diversity was considered AGA [9]).

The density and diameter of hair of the dermoscopic pictures were objectively assessed using (Folliscope 2.8, Lead M, Seoul, Korea). The density of hair was measured by counting the number of hairs within a 1 cm^2 area. The diameter was measured by calculating the mean value of the diameter of five hairs in this area.

Assessment of the Degree of Severity of FPHL

Patients were classified into three grades; mild, moderate, and severe according to Ludwiǵs classification where mild cases correspond to Ludwig type I, moderate cases correspond to Ludwig type II, and severe cases correspond to Ludwig type III. The categorization of patients was done by the same two investigators throughout the study.

Ultrasound Biomicroscopy (UBM)

Ultrasound biomicroscopy (UBM) was done using the Zeiss Humphrey UBM P45 plus Mode (Paradigm Medical Industries, INC) to provide high-frequency (50 MHz) ultrasonic scan images. Examination was done using a specially designed cup (24 mm diameter) that forms a water bath environment. This is filled with a viscous, sonolucent coupling fluid such as methylcellulose (1–2.5%). Normal saline was used to fill the cup after sealing the interface between the scalp and the base of the cup with 2.5% methylcellulose. The number of the hair follicles was determined by counting the number of echo-poor well defined round structures located in the reticular dermis that sometimes contained central keratin. The diameter of the largest hair follicle was measured using the segment tool in the UBM screen. These structures were either located in superficial part of the dermis (telogen phase) or deeper in the reticular dermis (anagen phase).

Patients were scheduled for UBM examination at baseline, 2 months and 4 months after the beginning of treatment. All patients were scanned by a single experienced investigator with a fixed site of examination at each visit.

Treatment Protocol

All recruited patients were randomly divided into three equal groups ($n = 15$) using the envelope concealment method. Group A: Patients were instructed to apply topical minoxdil 5% twice daily for 4 months. Group B: Patients received LLLT for 25 minutes using the iGROW® helmet device (21 Lasers Diodes and 30 LEDs, 655 nm red laser with output <5 mW CW and LED wave length range from 650 to 670 nm) every other day for 4 months. Group C: Patients received combination of LLLT for 25 minutes using the same device as group B every other day as well as topical minoxdil 5% twice daily for 4 months. All patients were evaluated at monthly intervals.

Physician Evaluation of Response to Treatment

Degree of improvement was evaluated by three blinded investigators who compared the patients' digital photos, UBM, Dermoscopic, and folliscope images at baseline, 2 and 4 months after therapy. Clinical evaluation was done according to the degree of change in Ludwig's classification as follows: If deterioration of the condition occurred, it was considered treatment failure, if the condition remained stationary (Good response), if there was improvement but still within the same Ludwig's grade (very Good response), and if the improvement resulted in a shift to a preceding grade (Excellent response). The last three responses were regarded as successful treatment.

Patient Satisfaction

The degree of patient satisfaction was determined and a score was given according to the following: Score 0: Dissatisfied (Patient feels worse than before/the same as before), Score 1: Slightly satisfied (Patient feels slightly better but still not worth it), Score 2: Moderately satisfied (Patient feels good with need for slight improvement), and Score 3: Satisfied (Patient feels optimal cosmetic result).

Side Effects

The occurrence of side effects was meticulously reported.

Follow-Up

All patients were followed up for 4 months after stoppage of therapy.

TABLE 1. Summary of the demographic and clinical data of the included patients

Variable	Group A (Minoxidil)	Group B (LLLT)	Group C (Combined)	*P*-value
Age (years)				
Range	25–39	27–45	25–49	0.207
Average ± SD	31.27 ± 5.57	35.67 ± 7.17	35.2 ± 8.86	
Onset				
Acute n, %	1, 6.7%	2, 13.3%	1, 6.7%	0.760
Gradual n, %	14, 93.3%	13, 86.7%	14, 93.3%	
Duration (years)				
Range	1–15	3–15	1–15	0.701
Average ± SD	5.4 ± 3.64	6.27 ± 3.45	5.13 ± 4.34	
Family history				
Negative n, %	5, 33.3%	8, 53.3%	6, 40%	0.529
Positive n, %	10, 66.7%	7, 46.7%	9, 60%	
Previous treatment				
Negative n, %	10, 66.7%	9, 60%	8, 53.3%	0.757
Positive n, %	5, 33.3%	6, 40%	7, 46.7%	
Pattern				
Diffuse	3, 20%	2, 13.3%	3, 20%	0.859
Frontoparital	12, 80%	13, 86.7%	12, 80%	
Ludwig n, %				
I	6, 40%	2, 13.3%	3, 20%	0.377
II	6, 40%	10, 66.7%	7, 46.7%	
III	3, 20%	3, 20%	5, 33.3%	
UBM number of follicles				
Range	13–22	6–22	6–22	0.118
Average ± SD	17.53 ± 3.48	14.8 ± 4.72	17.67 ± 4.24	
Diameter of the largest follicle (mm)				
Range	0.09–0.143	0.099–0.162	0.1–0.158	0.168
Average ± SD	0.117 ± 0.017	0.129 ± 0.019	0.128 ± 0.018	
Folliscope hair density (/cm^2)				
Range	120–175	121–175	120–180	0.888
Average ± SD	141.93 ± 19.43	145.47 ± 20.37	144.2 ± 20.42	
Hair shaft diameter (mm)				
Range	0.034–0.077	0.034–0.069	0.034–0.077	0.817
Average ± SD	0.048 ± 0.016	0.047 ± 0.013	0.05 ± 0.016	

Statistical Methods

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Kruskal Wallis test. Within group comparison of numerical variables was done using Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various

TABLE 2. Summary of UBM findings after 2 months of treatment among the three groups

	Group A (Minoxidil)	Group B (LLLT)	Group C (combined)
Number of follicles			
Range	13–24	10–24	9–25
Average ± SD	18.07 ± 3.56	15.53 ± 4.22	18.6 ± 4.44
P-value	0.301	0.166	0.025*
Diameter of the largest follicle (mm)			
Range	0.099–0.162	0.105–0.159	0.082–0.175
Average ± SD	0.129 ± 0.019	0.127 ± 0.017	0.124 ± 0.024
P-value	0.055	0.614	0.244

*$P < 0.05$ is statistically significant.

TABLE 3. Summary of UBM findings after 4 months of treatment among the three groups

	Group A (Minoxidil)	Group B (LLLT)	Group C (Combined)
Number of follicles			
Range	14–26	11–33	15–38
Average ± SD	18.67 ± 3.54	20.2 ± 6.36	27.93 ± 6.33
P-value	0.101	0.006*	<0.001*
Diameter of the largest follicle (mm)			
Range	0.1–0.158	0.105–0.151	0.1–0.197
Average ± SD	0.128 ± 0.018	0.135 ± 0.011	0.137 ± 0.024
P-value	0.061	0.123	0.862

*$P < 0.05$ is statistically significant.

variables was done using Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL) release 15 for Microsoft Windows (2006).

RESULTS

The current study included 45 adult female patients with age ranging between 25 and 49 years (34.04 ± 7.43 years) with proven FPHL. Regarding Ludwig classification their disease severity was classified as Ludwig I in 11 patients (24.4%), Ludwig II in 23 patients (51.1%), and 11 patients (24.4%) were classified as Ludwig III. They were randomly divided into three equal groups ($n = 15$) with no significant differences among the three groups regarding the demographic and clinical data (Table 1).

Clinical Assessment

Four months after the onset of treatment 31 cases (64.4%) were considered as having achieved a successful result with excellent response documented in six patients (13.3%), very good response in eight patients (17.8%) and good response in 15 patients (33.3%). Sixteen cases (35.6%) showed failed treatment.

A significant improvement ($P = 0.011$) was documented regarding the Ludwig classification. As by the end of the 4 months more than half of our cases ($n = 24$, 53.3%) were classified as Ludwig I, followed by Ludwig II in 13 patients (28.9%). Only 8 patients (17.8%) were classified as Ludwig III.

The evaluation of each group separately yielded significantly better results in group C (combined) ($P = 0.001$). A significant difference regarding Ludwig classification was also documented in those who received combination therapy (group C) ($P = 0.005$).

UBM Findings

After 2 months. Regarding UBM findings among the different groups after 2 months; a significant increase in the number of hair follicles was only detected in group C, whereas the other two groups showed a non-significant increase. In addition, none of the three groups showed significant increase in the diameter of largest hair follicle (Table 2).

After 4 months. Regarding UBM finding among the different groups after 4 months a significant increase in the number of hair follicles was detected in both groups B and C. Still a non-significant increase in the diameter of largest hair follicle was documented in the three groups (Table 3).

The hair follicles induced by the combined therapy were observed at a deeper dermal level when compared to other modalities.

Dermoscopic Findings

Four months after the onset of treatment dermoscopic evaluation for all cases was performed. It showed marked reduction in the diversity of hair diameter in the three groups with no significant difference noted between the

TABLE 4. Summary of folliscope finding after 2 months of treatment among the three groups

	Group A (Minoxidil)	Group B (LLLT)	Group C (combined)
Hair density (/cm^2)			
Range	121–177	122–177	120–180
Average ± SD	142.27 ± 19.49	146.07 ± 19.76	144.33 ± 20.37
P-value	0.055	0.346	0.164
Hair shaft diameter (mm)			
Range	0.034–0.1	0.034–0.089	0.042–0.104
Average ± SD	0.05 ± 0.019	0.051 ± 0.017	0.063 ± 0.023
P-value	0.185	0.099	0.055

*$P < 0.05$ is statistically significant.

three groups. The dermoscopic images have been further analyzed through the folliscope.

Folliscope Findings

After 2 months. Regarding folliscope findings among the different groups after 2 months; a non-significant increase in the hair density was detected in the three groups. In addition, none of the three groups showed significant increase in the hair diameter (Table 4).

After 4 months. Regarding folliscope finding among the different groups after 4 months a significant increase in the mean hair density was detected in all groups. Still a non-significant increase in the hair diameter was documented in the three groups (Table 5) (Figs. 1–3).

Patient Satisfaction

A significant difference was documented between the three groups regarding the patient satisfaction level ($P = 0.027$) with the highest degree of satisfaction detected in group C (Table 6).

Correlations

No significant correlations were detected between the demographic and clinical data of the patients.

Side Effects

No major side effects were detected in any of the included patients and all the patients continued the full duration of treatment. Irritation was reported by four patients among the combined group (27%) and six patients among minoxidil group (40%) and it was self-limited. Also scalp tenderness was reported by four patients among the LLL group (27%) and by six patients in the combined group (40%). Warm sensation was reported by three patients among the LLL group (20%) and by four patients in the combined group (27%). Initial increase in the hair shedding was reported by 12 patients in the minoxidil group (80%) and by nine patients in the combined group (60%).

DISCUSSION

The efficacy of both therapeutic modalities; minoxidil and LLLT for the treatment of FPHL were reconfirmed in the present study based on clinical, dermoscopic (folliscope), and UBM assessment. There was a significant superiority demonstrated by the combination of both therapies.

Among the minoxidil treated patients, 80% showed improvement, 90% were satisfied, the UBM and the folliscope images showed increased number of hair follicles. Our results were in concordance with [10] who demonstrated that following 16 weeks of 5% minoxidil therapy, approximately 30–40% of patients showed hair regrowth. Lucky et al. [11], demonstrated that after 48 weeks minoxidil 5% twice daily was superior to minoxidil 2% and to placebo twice daily. Our follow up period was limited to 16 weeks, so our results could not be compared to theirs.

A recent study [12] highlighted the efficacy and safety of 5% minoxidil solution as a monotherapy compared to MorrF (combination of Minoxidil [5%] + Finasteride [0.1%] lipid solution). The study was conducted on male patients, unlike our female concerned study.

The efficacy of minoxidil could be attributed to its ability to increase the cutaneous blood flow, stimulate the vascular endothelial growth factor and other hair growth promoters in dermal papilla [13]. It also increases angiogenesis, enhances cell proliferation, and DNA synthesis [14]. Moreover, it might enhance hair growth by increasing the production of prostaglandin E2 (PGE2) *via* stimulation of prostaglandin endoperoxidesynthase-1 [15].

In addition, it has been shown that minoxidil shortens the telogen phase, extends the anagen phase and increases the size of shrinking follicles [16], as well as maintains and thickens preexisting hair [11]. All those mechanisms of action could offer an explanation to the beneficial effect exerted by minoxidil in FPHL. In the current study 20% of the minoxidil treated patients were non responders. This could be attributed to either the relatively short duration of the study (16 weeks) or due to them having an endogenous defect in the sulfotransferase enzyme present in the outer root sheath of the hair follicle.

This enzyme is the one responsible to convert minoxidil into its active form, minoxidil sulfate that stimulates hair follicles [17,18]. Recently, three studies [19–21] pointed out the importance of testing for minoxidil response given the lengthy treatment time required to ascertain individual efficacy of minoxidil. They performed Sulfotransferase assay test which yielded an accuracy of 95.9% in ruling out

TABLE 5. Summary of folliscope finding after 4 months of treatment among the three groups

	Group A (Minoxidil)	Group B (LLLT)	Group C (combined)
Hair density (/cm^2)			
Range	150–220	170–220	190–235
Average ± SD	191.53 ± 18.23	195.53 ± 14.71	207.2 ± 12.97
P-value	<0.001*	<0.001*	<0.001*
Hair shaft diameter (mm)			
Range	0.042–0.077	0.042–0.104	0.042–0.124
Average ± SD	0.05 ± 0.016	0.063 ± 0.023	0.064 ± 0.029
P-value	0.099	0.118	0.078

*$P < 0.05$ is statistically significant.

Fig. 1. A: Female patient (35 years old) in the minoxidil group: pre (baseline: Ludwig grade II) and post (4 months after treatment: Ludwig grade I = excellent response), B: Female patient (34 years old) in the LLLT group: pre (baseline: Ludwig grade III) and post (4 months after treatment: Ludwig grade II= excellent response), C: Female patient (38 years old) in the combined group: pre (baseline: Ludwig grade II) and post (4 months after treatment: Ludwig grade I = excellent response).

non responders to minoxidil. This demonstrated the clinical utility of minoxidil response testing prior to initiation of prolonged therapy for AGA, which would aid in minimizing potential side effects and the expense of using an ineffective drug.

LLLT treated patients showed evident response as well, where 90% of patients were improved and 90% were satisfied. The UBM and the folliscope findings revealed significant increase in the number of hair follicles after four months. The detected improvement achieved by LLLT

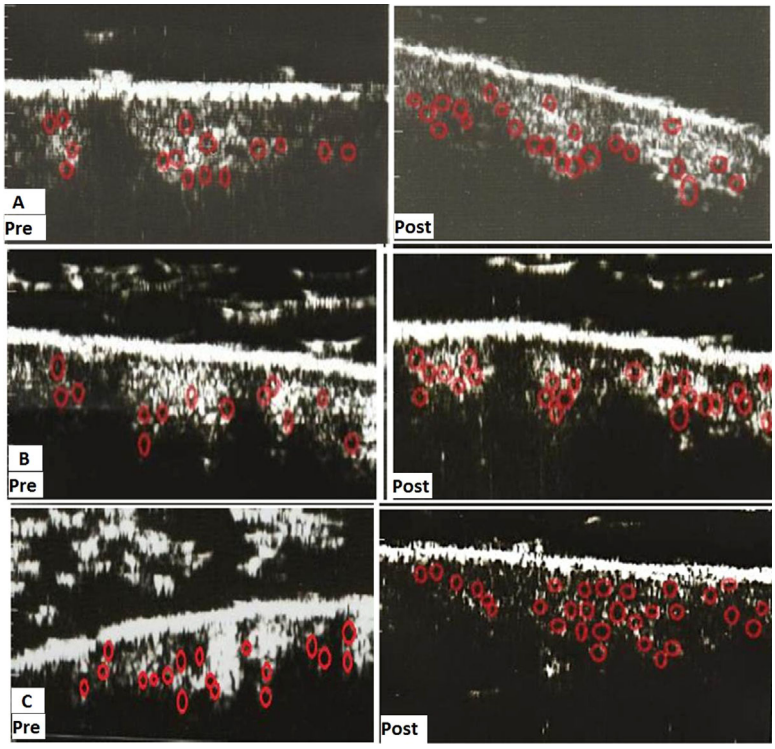

Fig. 2. A: UBM images of 40 years old patient in the minoxidil group: pre (baseline) and post (4 months after treatment), B: UBM images of 39 years old patient in the LLLT group: pre (baseline) and post (4 months after treatment), C: UBM images of 29 years old patient in the combined group: pre (baseline) and post (4 months after treatment). Red circles refer to the site of the hair follicles for measurement of their number and diameter. All three groups showed significant increase in the number of hair follicles and a non-significant increase in diameter.

in the current study was in agreement with others. Back in 2003, Santino and Markou evaluated the HairMax LaserComb®, which was used for 5–10 minute on alternating days for 6 months in patients with AGA [22]. It yielded significant increase in hair growth in both the temporal and vertex areas, respectively, in both sexes. Santino and Markou reported no statistical analysis unlike our study [22]. Another difference is that iGROW® used in the current study is not only LLL but also has light emitting diode.

Leavitt et al., conducted a study where participants were instructed to use a LLLT comb for 15 minutes three times a week for 26 weeks [23]. Results showed a significant increase in terminal hairs in the LLLT group compared to controls. Significant improvement was also documented by Jimenez et al., in which laser comb was used three times a week for 26 weeks [24].

On the other hand, our results were contradicted by Avram and Rogers, who investigated the use of LLLT for hair loss in seven patients (6 females and 1 male) for 20 minutes twice weekly over a period of 3–6 months [25]. All results for vellus hair counts, terminal hair counts, and hair shaft diameter were not statistically significant.

The efficacy of LLLT could be attributed to its ability to stimulate epidermal stem cells in the hair follicle bulge, shift the follicles into anagen phase, induce protein synthesis that triggers cell proliferation and migration, and tissue oxygenation [6]. The ability of LLLT to induce vasodilation and increase blood flow has been reported [26], thus benefiting patients with FPHL.

Patients in combined group occupied the top position with respect to physicians' assessment, where 90% of cases showed improvement and 100% of the patients were satisfied. A significant difference regarding Ludwig classification was only documented in this group and the UBM findings showed significant increase in the number of hair follicles after 2 and 4 months, while the folliscope images revealed significant increase in hair density after 4 months only, similar to the other two groups. This difference could be explained by the fact that UBM visualizes the hair follicles at the reticular dermis whereas the folliscope captures images of hair shafts above the skin surface. In addition, detection of acceleration of nerve regeneration, wound healing, and other cellular processes is a common feature of UBM, hence enabling earlier demonstration of re-growing hair follicles.

In the current study, the use of UBM and folliscope provided an objective assessment of the improvement. Few studies have utilized the folliscope to assess hair density and thickness [27].

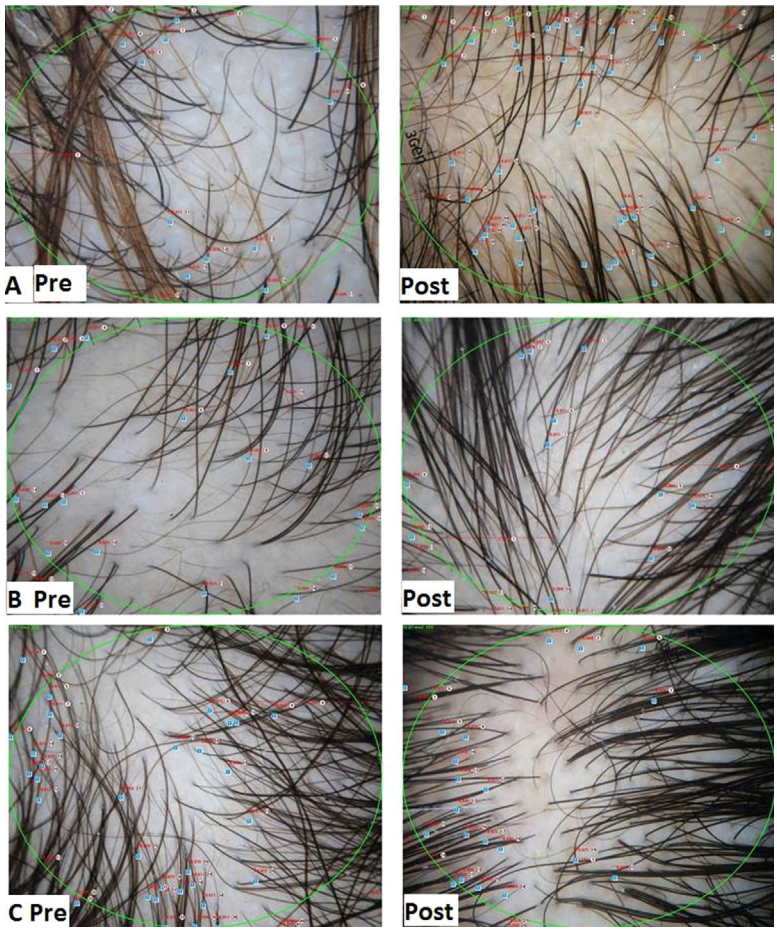

Fig. 3. A: Folliscope image of a female patient in minoxidil group: pre (baseline) and post (4 months after treatment), B: Folliscope image of a female patient in LLLT group: pre (baseline) and post (4 months after treatment), C: Folliscope image of a female patient in combined group: pre (baseline) and post (4 months after treatment). All three groups showed significant increase in hair density (blue dots) and a nonsignificant increase in hair diameter (red dots) (magnification: ×50).

Patients were followed up for an additional period of 4 months. Relapse was observed among two patients in the LLLT group and one patient in the combined group after cessation of LLLT in both groups. Accordingly, maintenance of LLLT should be considered as its effect seems to be temporary like minoxidil.

All the modalities used were safe and no major side effects were detected in any of the included patients. Irritation was reported by three patients among the combined group (30%) and four patients among minoxidil group (40%) and it was self-limited. This side effect was previously reported with minoxidil therapy [13].

Furthermore, scalp tenderness was reported by three patients among the LLLT group (30%) and by four patients in the combined group (40%). A warm sensation was reported by two patients in the LLLT group (20%) and by one patient in the combined group (10%). Both sensations were self-limited and resolved after cessation of the sessions. These incidents were also reported by Jimenez et al. [24]. The warm sensation could be attributed to the

TABLE 6. Patient satisfaction level among the three groups

Satisfaction	Group A (Minoxidil) (%)	Group B (LLL) (%)	Group C (combined) (%)
0	3, 20	3, 20	0, 0
1	6, 40	7, 46.7	2, 13.3
2	5, 33.3	4, 26.7	6, 40
3	1, 6.7	1, 6.7	7, 46.7

vasodilation and increase in the blood flow induced by the LLLT [26].

Initial increase in the hair shedding was reported by eight patients in the minoxidil group (A) (80%) and by six patients in the combined group (C) (60%). This could be explained by transient hair shedding caused by minoxidil during the first month of treatment, due to the synchronization of the hair cycle caused by stimulation of telogen follicles to re-enter the anagen phase [28]. Those patients reported decrease in the hair shedding after 2–3 months and this also could be explained by normalization of the hair cycle within a few weeks to months with continuation of minoxidil use [28].

Hair follicles which received combined therapy (group C) were observed to occupy deeper dermal level in UBM images compared to those in the other two groups (groups A and B). This finding might explain the potential benefit of combination therapy over monotherapy in FPHL, as inducing hair regrowth at a deeper level, thus hair follicles are more firmly anchored with probable higher sustainability.

All groups did not show significant increase in hair diameter by either UBM or folliscope images. However, the minoxidil group (A) demonstrated almost significant increase (P-value = 0.05). Larger scale studies would further elucidate this observation.

Low-level laser is an effective and safe tool for the treatment of FPHL. It is comparable with a slight upper hand over minoxidil 5%. The combination of both techniques seems to be preferable as one would benefit from all mechanisms of action in such a distressing disease.

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