

Comparing the Efficacy of Mesotherapy to Topical Minoxidil in the Treatment of Female Pattern Hair Loss Using Ultrasound Biomicroscopy: A Randomized Controlled Trial

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ABSTRACT The efficacy of mesotherapy in the treatment of female pattern hair loss (FPHL) has not yet been evaluated. Aim of the study was to compare the initial efficacy and safety of mesotherapy containing nutritional supplements to topical minoxidil 5% solution in FPHL. 30 patients with FPHL were randomly classified into two equal groups: Group A applied minoxidil 5% lotion twice daily; Group B was injected with mesotherapy once weekly. For both groups ultrasound biomicroscopy (UBM) was performed before and at the end of the 12th week of treatment. After treatment, no significant difference was found between both groups with regard to either improvement of hair density and hair loss ($P=0.27$ and 0.056 , respectively), nor the degree of improvement of Ludwig's classification as assessed by the investigator ($P=0.210$). A significant difference was observed between both groups ($P=0.001$) with the highest degree of satisfaction in the mesotherapy group. In group A, no significant difference was found in the number of hair follicles or the diameter of the largest hair follicle ($P=0.244$ and 0.925 , respectively). In group B, a significant difference was found in the number of hair follicles ($P=0.001$), with no significant difference in the diameter of the largest hair follicle ($P=0.105$). The mesotherapy group showed more improvement with regard to the increase in the number of the hair follicles after treatment ($P=0.007$). Limitation of the study is small sample size, and relatively short duration of treatment. Mesotherapy, containing nutritional supplements only, is an effective, more acceptable to patients, and more tolerable modality compared with topical minoxidil in the treatment of FPHL.

KEY WORDS: hair fall, mesotherapy, minoxidil, ultrasound biomicroscopy

INTRODUCTION

Female pattern hair loss (FPHL) is the most common hair loss disorder in women (1). It has been defined as non-scarring progressive miniaturization of the hair follicle, usually with a characteristic pattern of distribution that occurs in genetically predisposed women (2).

Female pattern hair loss has a strikingly overwhelming psychological effect; thus, successful treatments are necessary (3). The US Food and Drug Administration (FDA) has only approved topical minoxidil 2% (4) and 5% (5) for treating FPHL. However, low patient compliance and satisfaction rates, as well as

the plethora of topical and often important systemic adverse effects have lead to a search for new treatment options (6).

Mesotherapy is a technique which involves microinjection of medications and/or vitamins into the middle layer of the skin (7). It has received a lot of publicity in the media and on the internet about its possible role in androgenetic alopecia. However, the subject is controversial in view of lack of documented evidence (8).

Ultrasound biomicroscopy (UBM) is a non-invasive imaging technique used in the examination of several skin diseases (9), including hair and scalp diseases (10).

The aim of this study was to compare the initial efficacy and safety of mesotherapy containing only nutritional supplements to a minoxidil 5% lotion in FPHL.

METHODS

This randomized controlled trial included 30 patients with FPHL. Patients were recruited from the dermatology outpatient clinic of our university over the period from October 2013 to December 2014. Diagnosis of FPHL was based on thorough history and clinical examination to exclude similar conditions, especially telogen effluvium (11). The study included female patients who were not using topical, intralesional, or systemic therapy for FPHL, hair permanent, or dyes during and 6 months before the study. Patients on medications as aspirin, warfarin, steroids, oral retinoid, hormonal or cytotoxic drugs, pregnant and lactating females, patients with high androgen levels, irregular menses, acne, or hirsutism, and patients presenting with Koebner's phenomenon, thromboembolic manifestations, low serum ferritin, and abnormal TSH were excluded from the study.

Informed written consent was obtained from each patient, and the study was approved by the Research Ethics Committee (REC) at our faculty.

Patients were randomly classified into two equal groups *via* the envelope concealment method as the randomization method. Group A (15 patients) applied topical minoxidil 5% (Scalpvital®) 1 mL in two divided doses, once in morning and once at night, with proper scalp massaging for 12 weeks; Group B (15 patients) was injected intradermally with mesotherapy (BCN mesoceuticals, Institute BCN – Mesotherapy Products, Barcelona, Spain). The mesotherapy mixture contained amino acids (alanine, arginine, aspartic acid, cystine, glutamine, glycine, histidine, isoleucine, leucine, lysine, phenylalanine, proline, serine, taurine, and threonine), minerals (zinc, selenium, copper, manganese, and chrome), hyaluronic acid (1.5%), ginkgo biloba extract, and vitamins (A, C, E, and B-complex).

Injections were performed once weekly during 12 weeks of treatment. In each session, the volume injected was 2 mL, with an average of 40 injection points. After disinfection with 70% alcohol, a nappage technique was performed by intradermal injections of vertex by 0.05 mL solution/site at 1 cm intervals, at a depth of 2-4 mm, and at an angle of 30-60 using a 4 mm long 28 gauge needle (12).

Assessment of treatment response

Our primary outcomes included patient self-assessment and patient satisfaction at the end of the 12th week; patients were asked to assess the presence or absence of improvement in hair density and rate of hair loss. Each parameter was assessed as worse, no change, and improvement (13). Patient satisfaction was evaluated as previously mentioned (10).

Our secondary outcomes included a blinded investigator's assessment of the initial treatment response, UBM assessment, and any reported side-effects. Clinical improvement was assessed by comparing the patients' clinical photos at baseline and 3 months after therapy. Initial degree of improvement was assessed

Table 1. Comparison between the clinical data of both groups

Clinical variable	Group A (n=15)	Group B (n=15)	P value
Age (years)			
Range	25-45	25-40	0.177
Median, Mean±SD	36, 35.87±6.96	32, 32.47±5.87	
Duration (years)			
Range	1-15	1-10	0.659
Median, Mean ± SD	5, 6.27±4.28	5, 5.47±3.31	
Ludwig classification (N, %)			
Ludwig 1	2 (13.3%)	1 (6.7%)	0.310
Ludwig 2	11 (73.3%)	10 (66.7%)	
Ludwig 3	2 (13.3%)	4 (26.7%)	

N: number; SD: Standard deviation.

according to the grade of change in Ludwig's classification as follows: mild and moderate improvement if there was improvement that still within the same grade (type I, II, or III Ludwig's classification); good improvement if improvement resulted in changing the grade to the preceding type; or excellent improvement if improvement resulted in changing the type from type III to I or from type I or II to normal (13).

For both groups, UBM assessment was performed using the Zeiss Humphrey UBM P45 Plus Mode (Paradigm Medical Industries, INC) before and 3 months after the treatment. The inspection was performed using a specially-designed cup (24 mm diameter) that produces a water bath environment. This cup is occupied by a viscous, sonolucent connection liquid such as methylcellulose (1.0-2.5%). Normal saline was then applied to seal this cup. The number of hair follicles was determined by calculating the number of non-echogenic conical shadows reaching the epidermal entrance echo (corresponding to the hair follicles). Presence of a central keratin plug in some follicles was sonographic evidence in addition to the size and location (11). The diameter of the largest hair follicle detected in this examined area was measured using a segmented tool in the UBM screen (10,11). UBM was performed by a single experienced investigator, and the scans were obtained with the probe oriented perpendicular to the examined area in order to obtain a clear image and to eliminate bias and artifacts due to probe tilt or misalignment. This also ensured reproducibility of the images taken during the follow-up visits (in addition to marking the exact location on serial visits, a point 5 cm from the frontal hair line along the right side of the sagittal plane). The occurrence of any side-effects was accurately described.

Statistical analysis

All statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006). Data were described in terms of mean \pm standard deviation (\pm SD), median and range, or frequencies and percentages when appropriate. Comparison of numerical variables was performed using Mann Whitney U and Wilcoxon signed rank test. For categorical data, the Chi square (χ^2) test was performed. The exact test was used instead when the expected frequency was less than 5. Correlations were analysed using Pearson moment correlation / Spearman rank correlation as appropriate. P values less than 0.05 were considered statistically significant

RESULTS

Comparison between the clinical data of both groups is illustrated in Table 1. There was no statistically significant difference between both groups regarding age, disease duration, and Ludwig classification ($P=0.177$, 0.659 , and 0.310 , respectively).

Comparison of patient and investigator assessment between groups

No significant difference was found between both groups with regard to the initial improvement of the hair density and hair loss after treatment ($P=0.27$ and 0.056 , respectively). Moreover, there was no significant difference between groups regarding the degree of initial improvement of Ludwig's classification after treatment as assessed by the investigator ($P=0.210$) (Table 2, Figure 1 and Figure 2).

Three months after the treatment, 7 patients (23.3%) from group B reported ideal cosmetic results,

Table 2. Comparison between both groups with regard to initial improvement of hair density and hair loss as assessed by the patient, and degree of change in Ludwig's classification before and after treatment as assessed by the blinded investigator

Clinical Variable	Group A (n=15)	Group B (n=15)	P value
Hair density (N, %)			
Improved	3 (20.0%)	2 (13.3%)	0.27
No change	10 (67.6%)	13 (86.7%)	
Worse	2 (13.3)	0 (0.0%)	
Hair loss (N, %)			
Improved	5 (33.3%)	10 (67.6%)	0.056
No change	6 (40.0%)	5 (33.3%)	
Worse	4 (26.7%)	0 (0.0%)	
Improvement of Ludwig's classification			
Good	6 (40%)	2 (13.3%)	0.210
Mild-moderate	9 (60%)	13 (86.7%)	
Excellent	0 (0%)	0 (0.0%)	

N: number



Figure 1. A clinical photo of a female patient before and after topical minoxidil showing minimal initial clinical improvement.



Figure 2. A clinical photo of a female patient before and after mesotherapy sessions showing initial clinical improvement.

11 patients (36.7%) (8 patients from group B and 3 patients from group A) were moderately satisfied, 10 patients (33.3%) (group A) were slightly satisfied, and 2 patients (6.7%) (group A) were dissatisfied. A significant difference was documented between both groups ($P=0.001$) with the highest degree of satisfaction in the mesotherapy group.

Results of the UBM study in both groups

Group A

The mean number of hair follicles increased after treatment, but it did not reach statistical significance ($P=0.244$). Moreover, there was no statistically significant difference between the diameter of the largest hair follicle before and after treatment ($P=0.925$) (Table 3, Figure 3).

Group B

There was a statistically significant difference between the number of hair follicles before and after treatment ($P=0.001$). The mean diameter of the largest hair follicle showed some increase after treatment; however, it did not reach a statistical significance ($P=0.105$) (Table 3, Figure 3).

Change in the number of hair follicles and diameter of the largest hair follicle

A statistically significant difference was found between groups regarding the increase in the number of hair follicle after treatment, with the mesotherapy group showing more increase (1.166 vs 3.211) ($P=0.007$). There was no significant difference between the groups regarding the change in the diameter of the largest hair follicle after treatment (0.094 vs 1.621) ($P=0.10$) (Figure 4).

Safety and tolerability

In group A, the reported side-effects included hypertrichosis of the face in one case (6.7%), itching in 66.7% cases ($n=10$) and scaling in 20% of cases ($n=3$). In group B, the reported side-effects were headache in 33.3% of cases ($n=5$) and pain in 66.7% of cases ($n=10$). Pain at injection sites subsided shortly after the session and lasted from several hours to up to 2 days in some cases. The headache lasted a maximum of one day and it did not occur after each session. None of our patients reported an allergic reaction to the mesotherapy cocktail.

Table 3. Results of ultrasound biomicroscopy (UBM) study in both groups

	Group A (n=15)		P value	Group B (n=15)		P value
	Before treatment	After treatment		Before treatment	After treatment	
Hair follicles number (Range, Median, mean \pm SD)	8-30 14, 16.13 \pm 6.95	9-40 17, 19.67 \pm 8.09	0.244	7-30 12, 13.80 \pm 6.45	11-49 23, 24.87 \pm 9.12	0.001*
Largest hair follicle diameter (mm) (Range, Median, mean \pm SD)	0.10-0.19 0.14, 0.13 \pm 0.028	0.09-0.20 0.13, 0.13 \pm 0.028	0.925	0.09-0.18 0.12, 0.12 \pm 0.019	0.11-0.16 0.13, 0.13 \pm 0.015	0.105

N: number; SD: Standard deviation; *P value significant at <0.05

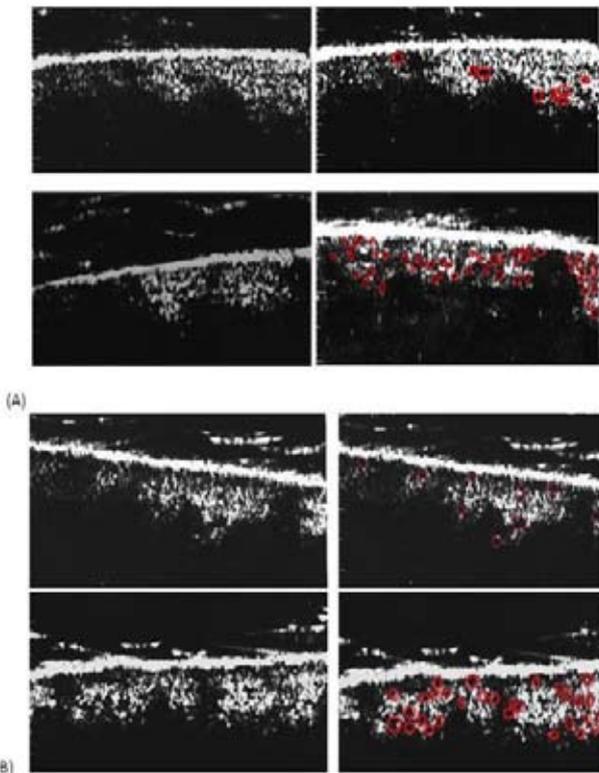


Figure 3. Ultrasound biomicroscopy (UBM) images in both groups before (top images) and after (bottom images), hair follicles are outlined in red. Red circles refer to the site of the hair follicles for measurement of their number and diameter. (A) A female patient in the topical minoxidil group; (B) A female patient in the mesotherapy group.

DISCUSSION

In the present pilot study, the initial efficacy of both therapeutic modalities, topical minoxidil 5% and mesotherapy for the treatment of FPHL, was confirmed both subjectively and objectively.

Although the results of UBM assessment in the minoxidil group revealed no significant initial clinical improvement, there was an improvement in Ludwig's classification and some of the patients reported initial improvement in their hair density and rate of hair loss. UBM can provide an objective assessment of the clinical improvement. UBM pictures the hair follicles at the reticular dermis and enables earlier detection of re-growing hair follicles (10). The lack of significant ultrasonographic results in the current study may be related to the low number of patients involved or to the duration of treatment, which was 12 weeks long, due to being limited by the cost of medications; moreover, it would have been better to measure the median or mean of diameters of a greater number of hair follicles rather than just one.

There are several studies in literature on the efficacy of topical minoxidil in the treatment of FPHL

(14-18). What differentiates our study from the previous works is the use of an objective tool, ultrasound biomicroscopy, in the evaluation of hair regrowth after treatment. Most of the previous studies relied on the patient's and investigator's assessment of the condition, in addition to villous hair count in some studies (15).

The ultrasonographic results of group B (mesotherapy group) revealed a significant initial clinical improvement by showing an increased number of hair follicles after treatment. However, no significant improvement was found in the diameter of the largest hair follicles after treatment. This lack of significant improvement could be explained by the short treatment duration and the assessment of a single hair diameter. These ultrasonographic findings were matched the results of both the patient's self-assessment and the investigator's judgment.

To the best of our knowledge, there were no previous reports in the literature on the effect of mesotherapy injections on FPHL, including the use of nutritional supplements only. Moftah *et al.* (19) evaluated the efficacy and safety of mesotherapy using

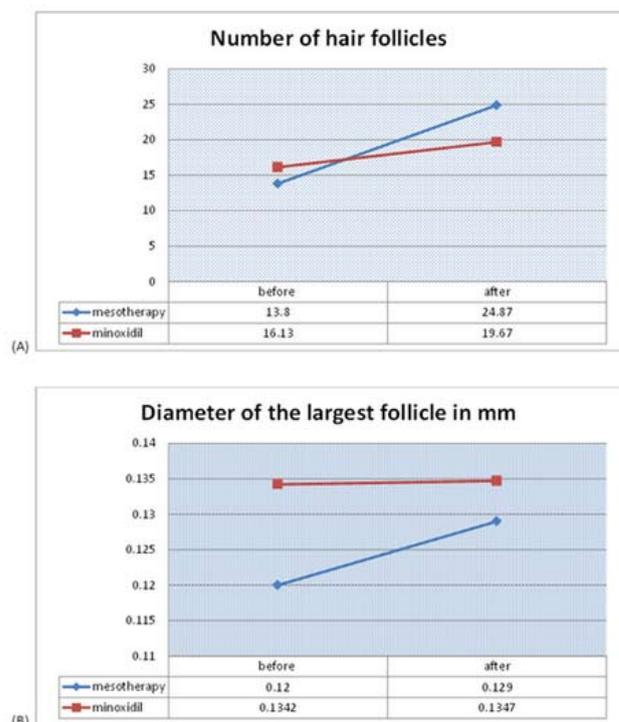


Figure 4. Comparison between both groups before and after treatment. (A) Change in the number of the hair follicles, showing non-significant change in the minoxidil group ($P=0.244$) and a significant increase in the mesotherapy group ($P=0.001$); (B) The diameter of the largest follicle, showing no change in the minoxidil group ($P=0.925$) and a non-significant change in the mesotherapy group ($P=0.105$).

a dutasteride preparation in the treatment of FPHL. However, they used commercial preparation, which contained dutasteride together with other vitamins, because it was the only preparation available in the Egyptian market that contained dutasteride at the time of study commencement. They attributed improvement in hair quality as assessed by the patient to biotin, pyridoxine, and pantothenic acid present in the formulation used, as they are known to improve hair color, texture, and thickness as previously reported by Boccaletti *et al.* (20).

There were no statistically significant findings when comparing the groups (topical minoxidil 5% vs mesotherapy) regarding initial clinical improvement, change of the number of hair follicles, and the diameter of the largest hair follicle before and after treatment, apart from the increase in the number of hair follicles after treatment, which was better in the mesotherapy group.

In both groups, we observed a discrepancy between patient self-assessment in those who were not completely satisfied and the improvement of their condition as judged by the investigator who observed initial improvement as monitored by the degree of change in Ludwig's classification. This might be related to the impact of the disease on the psychological and social activities of patients, thereby reducing their quality of life (QoL) (1). Patients were more satisfied with the mesotherapy modality, which might reflect the preferred psychological role of mesotherapy in many patients irrespective of the agent used (21).

The side-effects in the mesotherapy group in this study were minimal and tolerable, a finding which was consistent with previous studies (19,22). However, serious side-effects such as multifocal scalp abscess with subcutaneous fat necrosis and scarring alopecia as complications of scalp mesotherapy (23) were not detected in the current study.

The limitations of the current study included the low number of cases, relatively short duration of treatment due to the cost of the medications, lack of another objective tool "such as dermoscopy/folliscope/histopathology" to validate the method of counting hair numbers and measuring hair diameter, and the inability of the available UBM machine to precisely locate the superficial venous plexus which could have facilitated the calculation of hair follicles in each phase (anagen/telogen). Future studies considering these limitations are strongly recommended.

CONCLUSION

Mesotherapy with vitamins and minerals only is an effective, more acceptable to patients, and more tolerable modality compared with topical minoxidil 5% in the treatment of FPHL.

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