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Evaluation of efficacy and safety profile of niosomal kopexil 1% lotion compared to niosomal minoxidil 2% lotion in male-pattern alopecia

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Background: Conventional topical treatments for male-pattern alopecia (MPA) have limited penetration into hair follicles and unwanted side effects, resulting in low patient compliance. We aimed to evaluate the efficacy and safety of niosomal kopexil 1% lotion compared with niosomal minoxidil 2% lotion in patients with MPA.

Methods: We conducted a prospective, double-blind, randomized clinical trial at Afzalipour Hospital of Kerman University of Medical Sciences, Kerman, Iran. Thirty participants with MPA were randomized to apply 1 ml of niosomal minoxidil 2% lotion or niosomal kopexil 1% lotion twice a day for 24 weeks. We assessed the efficacy of treatments as the percentage of change in hair density in monthly sessions compared to the baseline using a dermatoscope; we also assessed patient satisfaction and side effects.

Results: Thirty participants were enrolled, 29 of whom completed the study. The mean change in hair density was significantly higher with niosomal kopexil compared with niosomal minoxidil (23.2 ± 1.3 and 14.2 ± 0.2, respectively). The hair density increased by 57.6 ± 3.7% and 25.6 ± 4.2% in the kopexil and minoxidil groups, respectively ($P < 0.001$). Patients reported significantly greater satisfaction with niosomal kopexil than with niosomal minoxidil ($P < 0.001$). No side effects were reported in either group.

Conclusion: Despite the lower concentration, niosomal kopexil revealed significantly higher efficacy of treatment and satisfaction of patients compared to niosomal minoxidil.

Keywords: Niosomes, minoxidil, androgenetic alopecia

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INTRODUCTION

Male-pattern alopecia (MPA), also known as androgenetic alopecia, is a non-cicatricial alopecia affecting up to 58% and 73% of males in their 50s and 80s, respectively. Genetic susceptibility of hair follicles to androgens, especially dihydrotestosterone (DHT), has an essential role in the pathogenesis of MPA. To date, oral finasteride and topical minoxidil

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are the only medications approved by the Food and Drug Administration (FDA) for MPA [1].

Minoxidil is a pyrimidine derivative first used as an anti-hypertensive drug. It has low water solubility; thereby, it is generally formulated in alcohol-based vehicles, including ethanol and propylene glycol. Using minoxidil solution on the scalp usually leaves a crystal residue after evaporation of the alcoholic vehicle, causing an unpleasant feeling of hair oiliness. In addition, the alcoholic vehicle is the main cause of irritation, allergic reaction, skin dryness, pruritus, dandruff formation, and seborrheic dermatitis exacerbation. Thus, patients generally have low compliance with topical therapy, harming the efficacy of treatment with conventional minoxidil [2-4]. On the other hand, a large number of patients have no tendency to receive finasteride due to undesirable side effects such as sexual dysfunctions and mood alterations [5]. Therefore, modern therapeutic methods are required in order to find topical formulations with fewer side effects and superior efficacy.

Nowadays, nanotechnology-based formulations such as niosomes have achieved widespread popularity in dermatology. Comfortable usage, ease of storage, slow-release drug, and high stability are some of the advantages of niosomal formulations. Furthermore, due to the water-based vehicle of the niosomal structure, niosomal formulations result in neither hair greasiness nor skin irritation. Micronized particles of the active drug penetrate easily through follicular openings, directly affecting the dermal papilla cells of hair follicles. Previous studies revealed superior efficacy, fewer side effects, and higher penetration of niosomal minoxidil compared with conventional formulations [6-8].

Kopexil (trade name Aminexil) acts via a similar mechanism of action as minoxidil but has fewer side effects and greater water solubility. One disadvantage of kopexil is the poor absorption of the topical solution through the stratum corneum due to the hydrophilic structure, which results in the inferior effect of the drug on hair regrowth [9,10]. Novel drug delivery systems such as niosomes can improve drug penetration and efficacy [11]. In this clinical trial, we evaluated the efficacy and safety profile of niosomal kopexil 1% lotion compared with niosomal minoxidil 2% lotion in the treatment of MPA.

METHODS

Study design

This was a prospective, double-blind, randomized clinical trial conducted at Afzalipour Hospital of Kerman University of Medical Sciences, Kerman, Iran. Participants and evaluators were blinded to the type of treatment until the end of the study.

Participants

Thirty participants with MPA aged between 18 and 40 years were enrolled in the study. Inclusion criteria were all male patients with MPA based on Norwood-Hamilton classification [12]. Exclusion criteria were patients with any other types of alopecia or systemic diseases, use of any systemic medications affecting the hair cycle, treatment of alopecia with laser therapy or topical or systemic drugs during the prior six months, or having any history of sensitivity to the drugs used.

Study intervention

Participants were randomized based on a random number table to apply 1 ml of niosomal minoxidil 2% lotion or niosomal kopexil 1% lotion twice a day for 24 weeks. Drugs were packaged in similar bottles; thus, participants were unaware of the type of therapy. Participants were instructed to gently massage the lotion and wait until it dries. Furthermore, they were asked to not wash their scalp for at least four hours after application and use the same hair products and maintain similar hair care until the end of the study. In order to evaluate the adherence of patients to treatment, they were asked to return the empty bottles at each visit.

Materials

Kopexil was gifted to us by Alborz Tejarat Yeganeh cosmetic company (Iran). Minoxidil was bought from Flamma Group (Italy). Cholesterol and polyoxyethylene (2) cetyl ether (Brij® 52) were purchased from Sigma-Aldrich (USA). All other chemicals and solvents were of analytical grade and acquired from Merck (Germany).

Preparation of niosomes

Cholesterol and Brij 52 (30/70 mol %) were dissolved in 5 ml of chloroform, and the organic solvent was removed by a rotary evaporator (Heidolf, Germany) at 70 °C. For the elimination of trace

amounts of chloroform, the lipid layers were placed in a round-bottom flask and kept in a vacuum cabinet overnight. Kopexil solution (1%w/v in deionized water) was used as the hydration medium, mixed with the above product at 70 °C for 30 min. The same procedure was carried out for the preparation of minoxidil 2% niosomal suspension, except for mixing minoxidil with the organic phase composed of chloroform and lipids. Deionized water was used as the hydration medium. Microscopic observation of the prepared niosomes revealed the formation of round and multilamellar vesicles (MLVs) without any cholesterol crystals. The viscosity of niosomal formulations was sufficiently high to prevent the administered suspensions from dropping off the scalp.

Evaluation of the response

In each participant, an area with a size of 1 cm^2 was determined and marked based on the distance from anatomical landmarks such as the tip of the nose and the lateral contour of the eyes. Subsequently, dermoscopic pictures were taken by a polarized video dermatoscope (Coscam CCL205, Sometech Cosmetic, Korea) at 10× magnification from the marked area in each follow-up session. Participants were followed up monthly during the treatment for six months. Then, terminal hairs were counted via dermoscopic pictures by two dermatologists that were unaware of the treatment groups. The satisfaction of participants at the end of the study was asked using a 10-point Likert scale and then categorized into three main groups: unsatisfied (1-3), moderately satisfied (4-6), and markedly satisfied (7-10) [13].

Safety profile

Side effects of treatment, including irritation, erythema, desquamation, skin dryness, pruritus, and hypotension, were asked during each session.

Statistical analysis

Statistical analysis was performed using SPSS 16 software (IBM, Armonk, NY, USA) by a statistician who was blind to the type of treatment. Quantitative and qualitative data were described by mean ± standard deviation and frequency (percentage), respectively. Mean changes in hair density were assessed by the independent samples t-test. The chi-squared test was used for the evaluation of the difference in participants' satisfaction. Analysis of covariance (ANCOVA) was used for the removal of confounding factors. P-values less than 0.05 were regarded as statistically significant.

Ethical considerations

This study was approved by the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.AH.REC.1398.103) and registered with the Iranian Registry of Clinical Trials (IRCT20190621043963N1). The treatment course and possible side effects of therapy were explained to all participants before commencing the study, and written informed consent was obtained.

RESULTS

Thirty participants were enrolled, among whom 29 completed the study. One patient in the kopexil group withdrew from the study after the first session because of the desire to receive systemic therapy. The per-protocol population was used to describe the demographic features and evaluate the efficacy of treatments. The two groups were similar at baseline in terms of age but differed regarding the MPA stage according to the Norwood-Hamilton classification (Table 1).

Table 1. Clinical and demographic of participants at baseline

Variable	Niosomal kopexil group	Niosomal minoxidil group	*P*-value
Age, years (mean ± SD)	30.5 ± 2.9	28.2 ± 3.1	0.606
Hamilton- Norwood stage, n (%)			
Stage I	1 (7.1)	1 (6.7)	
Stage II	1 (7.1)	4 (26.6)	
Stage III	3 (21.4)	3 (20)	
Stage IV	5 (35.7)	3 (20)	0.024
Stage V	1 (7.1)	2 (13.3)	
Stage VI	2 (14.2)	1 (6.6)	
Stage VII	1 (7.1)	1 (6.6)	

Abbreviations: SD, standard deviation;

Efficacy of treatment based on mean change in hair density

In the second session, both treatment groups showed a decline in hair density compared to baseline; this reduction was greater with niosomal minoxidil than with niosomal kopexil (1.7 ± 0.5 versus 0.3 ± 0.6, respectively). The mean change in hair density was significant in both treatment groups during treatment sessions ($P < 0.001$); however, this change was significantly greater in the kopexil group than in the minoxidil group (23.2 ± 1.3 versus 14.2 ± 0.2, respectively) (Table 2). Regarding the significant differences in the stage of alopecia and hair density at baseline between the two groups, analysis of covariance (ANCOVA) was used to remove the confounding effects of these factors; however, a significant difference persisted.

Mean change in percentage of increased hair density

By the end of the study, hair density increased by 57.6 ± 3.7% and 25.6 ± 4.2% in the niosomal kopexil and niosomal minoxidil groups, respectively ($P < 0.001$) (Table 2).

Patient satisfaction

Regarding patient satisfaction, significantly more patients were markedly satisfied with niosomal kopexil (50%) compared with niosomal minoxidil (6.7%) (Table 3).

Safety profile

No patient complained of irritation, pruritus, dandruff formation, or any other side effects during the treatment course in either group.

DISCUSSION

Minoxidil is a prodrug that is converted to its active metabolite by the sulphotransferase enzyme located in the outer root sheath of hair follicles. The drug activates potassium channels and increases blood flow and oxygenation in the peripilar areas by stimulating the synthesis of nitric oxide and increasing the levels of vascular endothelial growth factor (VEGF) in the dermal papilla. It also stimulates dermal papilla cells by increasing prostaglandin E_2 and inhibiting prostaglandin D_2. Furthermore, it prolongs the anagen phase of hair via anti-apoptotic effects on dermal papilla cells mediated by β-catenin

Table 2. Efficacy of treatment based on mean change from baseline in hair density and percentage of increased hair density during treatment visits

Variable	Niosomal kopexil group	Niosomal minoxidil group	*P*-value
Mean change from baseline in hair density			
Session 2	-0.3 ± 0.6	-1.7 ± 0.5	0.074
Session 3	3.5 ± 0.1	1 ± 0.6	0.008
Session 4	7.9 ± 0.4	4.2 ± 0.4	0.001
Session 5	13.3 ± 1.2	7.6 ± 0.1	<0.001
Session 6	19.5 ± 1.3	11.2 ± 0.5	<0.001
Session 7	23.2 ± 1.3	14.2 ± 0.2	<0.001
P-value			
Mean change from baseline in percentage of increased hair density			
Session 2	-6 ± 1.3	-3 ± 1.9	0.096
Session 3	7.1 ± 2.8	2.2 ± 1.3	0.033
Session 4	16.4 ± 2.4	8 ± 3.8	0.001
Session 5	27.1 ± 3.2	13.9 ± 5.9	<0.001
Session 6	39.8 ± 4.3	20.1 ± 6.5	<0.001
Session 7	57.6 ± 3.7	25.6 ± 4.2	<0.001
P-value	<0.001	<0.001	

Table 3. Patient satisfaction with treatment at the end of the trial

Satisfaction grade	Niosomal kopexil group	Niosomal minoxidil group	*P*-value
Unsatisfied	0 (0)	8 (53.3)	<0.001
Moderately satisfied	7 (50)	6 (40)	
Markedly satisfied	7 (50)	1 (6.7)	

activation [2-4,14]. Major disadvantages of topical minoxidil solution are restricted penetration of drug to hair follicles and unwanted side effects due to the alcoholic-based vehicle; thereby, using innovative drug delivery systems in order to optimize topical drug absorption and minimize side effects of treatment is always demanded [6-11]. Kopexil is nearly similar to minoxidil in its mechanism of action; however, it has fewer side effects due to its greater water-solubility. Furthermore, it inhibits peripilar fibrosis via the inhibition of the lysyl hydroxylase enzyme. Nonetheless, it has limited skin permeability with relatively poor efficacy compared to minoxidil [9,10].

To date, several nanotechnology-based strategies, including lipid nanoparticles and vesicular nanoparticles, have been used to enhance minoxidil's efficacy. Niosomes are vesicular nanoparticles that have ion-ionic surfactant-based structures. Application of niosomal minoxidil leads to sustained delivery of the active drug through stratum corneum and follicular openings into the target organ. A higher percentage of penetration of niosomal formulation results in greater accumulation and deposition of the drug into the dermis and target organ [6-8]. Mali *et al.,* in an in vitro study, revealed a high percentage of permeation with niosomal minoxidil (43.68 ± 4.7%). Furthermore, a greater percentage of deposition within the dermis was reported with niosomal minoxidil compared to the conventional form (17.21% versus 2.26%, respectively) [15]. Another in vitro study by Balakrishnan *et al.* demonstrated a higher percentage of drug accumulation within the skin with niosomal minoxidil compared to the conventional form (1.03 ± 0.18%–19.41 ± 4.04% versus 0.11 ± 0.03%–0.48 ± 0.17%) [8]. Meymandi *et al.*, in a randomized clinical trial, revealed a significantly greater increase in hair density with niosomal minoxidil 2.5% solution compared with conventional minoxidil 2.5% solution (28.18 ± 11% vs. 14.22 ± 5.23%, respectively). Furthermore, a significantly marked improvement in patients' self-assessment was achieved with the niosomal formulation compared with the conventional form (53.5% versus 4.4%, respectively). In the current study, 2% niosomal minoxidil triggered a 25.6 ± 4.2% increase in hair density from baseline—approximately similar to the Meymandi *et al.* study [16]. However, the percentage of increased hair density in the niosomal kopexil 1% group was markedly higher (57.6 ± 3.7%).

Afsharpour *et al.,* in one pilot study, demonstrated a significant increase in hair density with both niosomal forms of minoxidil and kopexil and the conventional form of minoxidil. However, they reported no statistical difference between treatment groups due to the small sample size and short duration of treatment [9].

Several methods can be used to enhance transdermal drug delivery. Some researchers used ablative techniques such as microneedling, fractional carbon dioxide laser, and fractional radiofrequency to augment the absorption and efficacy of minoxidil. Combination therapy resulted in better outcomes than monotherapy [13,17,18]. In the current study, niosomal formulations were used to improve transdermal drug delivery. The outcomes were promising and minimized the overall treatment costs without causing local side effects. Moreover, there was no need for microneedling in every session.

Our study limitations were the small sample size, lack of follow-up, and lack of assessing the treatment efficacy by other objective markers such as hair weight, hair diameter, and other dermoscopic markers of MPA. Therefore, further studies with large sample sizes are required to confirm the efficacy of these niosomal drugs as monotherapy or combination therapy with other treatment modalities of MPA.

CONCLUSION

While both niosomal formulations had favorable outcomes with no side effects, niosomal kopexil had superior efficacy and led to greater patient satisfaction than niosomal minoxidil.

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None.

Authors contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Saman Azizi, Maryam Khalili, Rezvan Amiri, Abbas Pardakhty and Mahin Aflatoonian. The first draft of the manuscript was written by Mahin Aflatoonian and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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