Study Protocol

Evaluating the efficacy of topical herbal solution on the treatment of androgenetic alopecia and comparison with Minoxidil 5%: A Double-Blind, Randomized, Clinical Trial Study

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This proposal has been reviewed and approved by the Tabriz University of Medical Sciences Ethics Committee (EC), August 8, 2018

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LIST OF ABBREVIATIONS

FDA- Food and drug administration

AGA- Androgenetic alopecia

1. STUDY OBJECTIVES:

Evaluate the effect of the topical herbal solution on the prevention and treatment of androgenetic alopecia and comparison with 5% minoxidil

2. STUDY DESIGN

This study will be done on male patients with androgenic hair loss. The patients will be selected by volunteers attending the Dermatology department of Sina Hospital and eligible individuals will be selected among them. The participants will be randomly allocated (using random number tables) to two groups; the first group will receive a 5% minoxidil topical solution, and the second group will receive a 5% minoxidil topical solution plus the topical herbal solution for 36 weeks. The hair thickness will be measured to determine efficacy at baseline, 12, 24, and 36 weeks. The patient's questionnaire self-evaluation and side effects will also be evaluated.

3. BACKGROUND AND RATIONALE

Androgenetic alopecia (AGA) is mostly caused by miniaturization of androgen-sensitive hair follicles and common form of scalp hair loss. AGA can affect the quality of life, self-confidence, and change in interpersonal and social relationships, especially among young people. AGA can be capable of affecting all races. The highest prevalence is observed in Caucasians. Finasteride and Minoxidil have been approved by the American Food and Drug Administration (FDA) for the treatment of AGA. Conventional therapy has many side effects. Herbal remedies can be more advancing than conventional when used topically on the scalp. Herbal remedies characterized by patient satisfaction, fewer side effects, and more mechanism in the treatment of AGA.

4. STUDY POPULATION

4.1 Inclusion criteria

- Men 18 to 50 years old
- Written consent
- Normal general health status
- Men who have a presentation of androgenetic alopecia (Norwood II - V).

4.2 Exclusion criteria

- Used any of topical product in the target region interfering with the study product in the last 12 months
- Within the past six months receiving of chemotherapy/cytotoxic agents
- Clinical diagnosis of alopecia areata or other non-AGA forms of alopecia

- Uncontrolled hypertension
- Any dermatological disorders in the scalp, such as fungal or bacterial infections, eczema, atopic dermatitis, seborrheic dermatitis, psoriasis, sun damage, skin cancer
- Hormonal diseases, such as thyroid disorders and diabetes.
- Smokers
- Liver and kidney disease
- History of hair transplants
- History of surgical correction of hair loss on the scalp
- Subject having dyed, bleached hair, or with a permanent wave before study start.
- No written consent

4.4 Recruiting/Screening

- The dermatologist will select subjects presenting to the Department of Dermatology Clinic at the Sina hospital who meet the inclusion criteria. Those expressing an interest to participate in the study will contact for a verbal explanation of the protocol by an investigator.
- Written announcements for participation in the study will also be posted on the internet and around the Tabriz University of Medical Sciences, School of Medicine, School of Pharmacy, and School of Dentistry. Volunteer participants will come for a screening visit. If they meet inclusion/exclusion criteria, the participant will consent.
- Consent for participation will be obtained in writing by signature on a consent form by the study staff. Before consent, the consent will be read by the subject, and the subject will be encouraged to ask any questions for clarification. A copy of the subject's signed consent form will be retained in the study file.

4.3 Criteria for terminating study participation

- Subject wishes to stop being in the study
- Subjects are not eligible based on inclusion/exclusion criteria
- Adverse events occur that, in the opinion of the investigator, but the subject at increased risk and it is not in the best interest of the subject to continue the study

5. STUDY PROCEDURES

5.1 Screening visit

- Subjects who meet the inclusion/exclusion criteria will be enrolled, and written informed consent will be obtained.
- The subject's demographic data, medical history, duration and onset of AGA, and current usage of any topical or systemic drug for the treatment of AGA will be recorded.

5.2 Treatment Visit

- In addition to oral explanations, participants will be given written instructions on how to use solutions and storage conditions.
- Subjects will not be permitted to apply their usual hair cosmetics products and will be requested not to alter their usual routine hair care during the study period.
- Subjects will be instructed to avoid the use of any prescripted and/or nonprescription therapeutic agents for preventing hair loss or hair growth during the study period.
- Baseline hair thickness will be taken, and every three months, it will be repeated. For reproducibility, the target location on the scalp, where the hair thickness will be measured over time, consist of Intersecting three distances from the fixed anatomical locations.

Treatment randomization

Before the study begins, a random number table will be generated (in 1:1 ratio) for each study participant according to the subject number. The number will indicate whether treatment or control will be taken on the study groups. “0” represents a 5% minoxidil topical solution whereas “1” represents a 5% minoxidil topical solution plus the topical herbal solution.

Blinding

Dermatologist and the randomized subjects will be blinded to the subject’s allocation. It is necessary to use blinded treatment in order to reduce potential bias during data collection and evaluation of study outcomes.

5.3 Follow-up visits

- **3 and 6-month follow-up visit**

- Hair thickness will be measured via a digital micrometer.
- At each follow-up visit, adverse events will be recorded.

- **9-month follow-up visit**

- Hair thickness will be measured via a digital micrometer.
- Adverse events will be recorded.
- Subjects will complete a self-assessment questionnaire.

6. DATA COLLECTION AND REPORTING

6.1 Primary Outcome Measures

Hair thickness via a digital micrometer will record for each subject by a blinded investigator at the treatment visit (before treatment) and during the three months, six months, and 9-month follow-up visits.

6.2 Secondary Outcome Measures

1. Patients self - assessment questionnaire of improvement and overall satisfaction scores will be performed at the 9-month follow-up visit (the end of the study).
2. At each follow-up visits, adverse events will be recorded

7. STUDY EQUIPMENT

7.1 Digital micrometer to determine hair diameter will be used.

7.2 pH meter to measure the pH of the solutions will be used.

8. DATA DISCLOSURE AND SUBJECT CONFIDENTIALITY

The information that will be generated from this research project will be kept confidential. Information about subjects that will be collected during the research will be put away, and no-one but the investigations will be able to see it. Any info about subjects will have a number on it instead of their name. Only the researchers will know what their number is, and we will lock that information up with a lock and key. Data generated as a result of this study will not be shared with or given to anyone except the food and drug administration and Tabriz University of medical sciences Ethics Committee (EC), upon their request**.** The information from this study, if published in scientific journals or presented at scientific meetings**,** we will not be sharing the identity of the subjects in the research**.**

9. EFFICACY ASSESSMENT

Efficacy Assessment will be done based on the primary and secondary outcome measures mentioned above.

10. SAFETY ASSESSMENT

Any procedure has potential risks. According to the herbal origin, the topical herbal solution does not hold any chance of dangerous reactions or systematic disease. The threat from the use of topical solutions may include scalp itching, scalp dryness, and headache. The procedures used in this study may cause all, some, or none of the risks and side effects listed. Each study participant will be informed about the occurrence of these adverse events, and phone numbers will be given for answering any questions. Telephone contact with the investigator will be available 24 hours per day, seven days per week. Treatment for adverse events will be per standard of care from a dermatologist in the Department of Dermatology.

11. STATISTICAL ANALYSIS PLAN (SAP)

The statistical analysis will be performed using SPSS software 25 (SPSS Inc., Chicago, IL, USA). The normalcy of continuous data will be checked using the Kolmogorov-Smirnov Test. Mean (SD) will be calculated for all normally distributed continuous variables, e.g., age, duration of disease, hair diameter, etc. The unpaired (independent) t-test and paired t-test will be applied to compare the mean of hair diameter between two study groups and within

groups, respectively. For differences between self-assessment questionnaires, the Mann-Whitney test will be performed. At or before the time of the Week 0 administration, subject demographics, hair diameter, and duration of AGA will be summarized. All statistical tests will two-side and will perform at a significance level of p-value < 0.05.

12. STUDY SITES

Tabriz University of Medical Science
Azadi St., Dermatology Clinic, Sina hospital, Tabriz, Iran

13. ETHICAL CONSIDERATIONS

13.1 Human Subjects Protection

The EC must be notified of the completion of the study. After study completion or termination, a final report must be provided to the EC to close the study. The investigator must maintain an accurate and complete record of all submissions made to the EC, including a list of all reports and documents submitted. Adverse events are reported to the FDA. This clinical trial study will conduct in according to the Declaration of Helsinki.

13.2 Consent Form

Before study entry, written informed consent must be given from each subject. A copy of the subject's signed consent form must be retained in the study file.

13.3 Protocol Amendments

All changes must be submitted to the EC Protocol modifications that impact subject safety, or the EC must approve the validity of the study before initiation.

13.5 Use of Information and Publication

The Principal Investigator or sub-investigator may publish the results of this study in conjunction with appropriate scientific and medical personnel.

Appendix-1: Informed Consent Form (ICF)

Study title: Evaluating the efficacy of topical herbal solution on the treatment of androgenetic alopecia and comparison with Minoxidil 5%: A Double-Blind, Randomized, Clinical Trial Study

Name of the participant: _____
Name of the Principal (Co-) Investigator: _____
Name of Organization: _____

PART I: Information Sheet

I am going to give you the information and invite you to participate in this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Androgenetic alopecia (AGA), the most common type of hair loss, the drugs that are currently used to help people with AGA are not as good as we would like them to be. There is a new drug that may work better. The main reason we are doing this research is to discover if the new herbal solution is better than minoxidil, which is currently being used.

Type of Research Intervention

This research will involve the topical solutions that you will use on your scalp as well as the follow-up visits to the dermatology clinic at Sina hospital.

Participant selection

You are being asked to participate in this study because you satisfy our eligibility criteria which are:

- Men 18 to 50 years old
- Normal general health status
- Presentation of androgenetic alopecia (Norwood II - V)
- Have not been used any of topical product in the target region interfering with the study product in the last 12 months

Voluntary Participation:

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue, and nothing will change.

Right to withdraw:

You do not have to take part in this research if you do not wish to do it. You have the right to withdraw from this study at any time during the study without giving any reasons. However, you should talk to the research team before stopping the treatment.

The study design

All the topical solutions in the study will be divided into two groups. You will be receiving one of the solutions. The solutions will be randomly assigned to receive any one of the treatments. Randomization improves the scientific quality of research. Neither you nor we must know which of the two drugs you are given. This information will be in our files, but we will not look at these files until after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results.

Study Procedures:

Since we do not know if the new AGA drug is better than the currently available drug for treating AGA, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance.

The research takes place over nine months in total. During the study, you make three visits to the hospital. The plan, scheduled visits involve visits at 12, 24, and 36 weeks. At the end of nine months, the research will be finished.

Once you are enrolled in the study, you will be required to follow the instructions. You will apply 1 mL of solution at morning and evening intervals to the thinning hair areas of the scalp for 36 weeks. You will not be permitted to use your routine hair cosmetics products and will be requested not to alter your regular hair care during the study period.

You will not be allowed the use of any prescripted and nonprescription therapeutic agents for preventing hair loss or hair growth during the study period. Furthermore, you will not be allowed to take any medications other than the ones prescribed by the investigator. If you need to take some treatment, you must consult the investigator before taking that treatment.

You may have to come to the hospital for examination and investigations apart from your scheduled visits if required.

Cost to the participant

You will not be required to pay for the medications. In case of any adverse event occurring due to the study medications, treatments are free and will be per standard of care from a dermatologist in the Department of Dermatology.

Side Effects

Some of the common adverse effects of topical solutions on the scalp:

- Itching, redness or irritation at the scalp
- Unwanted hair growth elsewhere on the body
- Temporary hair loss

Risks

By participating in this research, you may be at higher risk than you would otherwise be. There is, for example, a risk that your disease will not get better and that the new medicine does not work even as well as the old one. While the possibility of occurrence this happening is very low, you should still be aware of the option.

Benefits

If you participate in this research, you will have the following benefits: the treatment benefit and free investigations. There may not be any benefit for you, but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit in providing safe, cost-effective, and readily available to treatment AGA.

Cost to the participants

You will not pay any fees for interventions. In case of any adverse event occurring due to the study medications, you will be provided per standard of carefree treatment at the department of dermatology, Sina hospital.

Reimbursements

If you would like to participate in this study, you will not give any gifts, money, or travel grants.

Confidentiality and Sharing the results

The information that will be generated from this research project will be kept confidential. Information about subjects that will be collected during the research will be put away, and no-one but the investigations will be able to see it. Any info about subjects will have a number on it instead of their name. Only the researchers will know what their number is, and we will lock that information up with a lock and key. Data generated as a result of this study will not be shared with or given to anyone except the food and drug administration and Tabriz University of medical sciences Ethics Committee (EC), upon their request**.** The information from this study, if published in scientific journals or presented at scientific meetings**,** we will not be sharing the identity of the subjects in the research**.**

Whom to Contact

If you have any questions about the study procedure, you may ask them now or later, 24 hours per day, seven days per week, even after the study has started. If you wish to ask questions then, you may contact any of the following:

Farid Masoud, 09036859062, faridmasoud@gmail.com

Yousef Javadzadeh, 09143112969, javadzadehy@yahoo.com

This proposal has been reviewed and approved by Tabriz University of Medical Sciences Ethics Committee (EC), which is a committee whose task it is to make sure that all research procedure are protected from harm. If you would like to find more about the EC, contact Tabriz University of Medical Sciences, Daneshgah Street, P.O. Box 5165687386).

PART II: Certificate of Consent

- I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it, and any questions that I have asked have been answered to my satisfaction. I voluntarily consent to participate as a participant in this research.
- I have been explained in a language understandable to me, the nature of the treatment, its expected benefits, and possible side effects, and I am willing to undergo any necessary investigations.
- I have informed that for academic and scientific purposes, pictures of my scalp will be photographed before and after the study.
- I, at this moment, permit the investigators to release the information obtained from me, as a result of participation in this study, to the sponsors, regulatory authorities, government agencies, and ethics committee. I understand that they may inspect my original records.
- I am aware that I will have to come to Sina hospital for follow up at least three times over 36 weeks (weeks 12, 24, and 36) for the proper conduct of the study.
- I am aware of my right to opt-out of the study any time during the course trial without having to give the reason for doing so.
- My signature on this form indicates that I:
  - Have carefully read and understood the information provided in this form
  - Have been explained the nature of this study and give my consent for inclusion in the study.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

Statement by the researcher

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. The purpose of the study

2. The risks and benefits of the study

3. Instructions on how to use the topical solutions

4. Schedule to follow-up visits

I confirm that the participant was allowed to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year