

STUDY PROTOCOL

Background & Purpose of the Research

Objective

The objective of the study is to examine stimulation of hair follicles in individuals with hair loss using fractional photothermolysis, which is used in wound healing and skin rejuvenation. We will assess the effectiveness of fractional photothermolysis in wound healing responses measured by hair growth.

Hypotheses

Fractional photothermolysis has been reported to increase hair growth and activate hair follicles through skin rejuvenation. We will investigate whether the proposed treatment plan will increase both the number of hairs and their density in patients with hair loss. We also aim to assess the longevity of the response of the hair follicle to the laser therapy.

Research Questions

50 subjects will be enrolled in the study and will be treated 6-10 times at 2-4 week intervals on one half of the head, and will be followed up to 24 weeks (Table 1). The other half of the head will remain untreated for comparison. Subjects will be observed for hair regrowth and thickness, and the treated area will be compared to the untreated area.

Introduction

Alopecia is also known as hair loss, and it occurs due to aging, nutritional or hormonal imbalance, or immune system etiology. It affects both males and females of different ages and races. Hair may fall out in clumps, break off leaving short stubs, or become thinner over time. The alopecia can be of a scarring or non-scarring nature. The most common form of hair loss is non-scarring, or noncicatricial, alopecia. In this case, the damage is not permanent, and although hair loss cannot be cured, it can be treated. Hair loss is usually not a sign of an underlying medical disorder. However, hair loss may affect self-esteem and cause anxiety affecting the quality of life. Scarring, or cicatricial, alopecia is a rare disorder that destroys the hair follicle and replaces it with scar tissue, resulting in permanent hair loss.

Causes

There are many genes that contribute to hair loss, so it can be hereditary. There are also other causes, including:

- Thyroid disorders
- Pregnancy
- Anemia
- Autoimmune diseases like polycystic ovarian syndrome
- Skin conditions like Psoriasis and seborrheic dermatitis

Treatment Options

Topical Minoxidil (Rogaine) and anti-inflammatory medications, such as topical and intra-lesional steroids, are used for alopecia. It is a solution that is applied directly to the scalp to stimulate the hair follicle. It slows hair loss, and some people grow new hair. Hair loss returns when the medication is stopped.

Finasteride is a prescription medicine that interferes with the production of a highly active form of testosterone that is linked to baldness. It slows hair loss. It works slightly better than minoxidil. Hair loss returns when you stop using the medicine. This prescription medication is also sometimes given to women who have been through menopause. Its role in female pattern hair loss is controversial, with both success and failure reported to occur.

Dutasteride is similar to finasteride, but may be more effective.

Hair transplants are also an option, though they are invasive and expensive. It consists of removing tiny plugs of hair from areas where the hair is continuing to grow and placing them in areas that are balding. This can cause minor scarring and possibly infection.

New Therapy

Fractional photothermolysis was originally designed as a form of laser therapy to treat wrinkles and scars. Although the link between laser treatment and hair growth is not clear and the exact mechanism still unknown, there is evidence to support that laser irradiation holds potential for the induction of hair follicles in subjects with alopecia. Laser therapy has been reported to increase hair growth and activate hair follicles. The lasers rejuvenate skin, and hair follicles are a part of skin, along with nails, so through the rejuvenation of skin, these things also get rejuvenated. Clinical examples of photo-induced hair growth include the paradoxical hair growth after laser hair removal, and hair growth after some level of wound healing by lasers has been performed. Several studies have been performed, analyzing the effectiveness of laser treatment of different settings, and researchers have observed an increase in hair numbers and density on the treatment side of the head. Improvements were most notable when the laser settings followed a low energy and high density protocol. They concluded that more research needs to be done on this topic, but fractional photothermolysis may be a new, effective way to treat different types of hair loss. The types of lasers we plan to use include Fraxel restore and Sciton Halo, a fractional hybrid laser that combines fractional erbium ablative lasers with a fractional non-ablative laser. The use of the fractional photothermolysis Fraxel laser and Sciton Halo laser have been approved by the FDA for treatment of the hands, face, and body. Fraxel received aesthetic clearance in November 2003.

These lasers do not meet the definition of a significant risk device because we do not believe that they present a potential for serious risk to the health, safety, or welfare of a subject. Side effects that have been reported from use with these lasers include redness and tenderness in the area that it was applied, and these side effects don't last more than a couple days. They do not impair human health.

In the paper "Fractional Photothermolysis Laser Treatment of Male Pattern Hair Loss" by Dr. Kim, WS and Dr. Kim, BJ, simulation of hair growth with fractional photothermolysis in animal and human subjects was observed, and confirmed on histological specimens. 20 male subjects were treated over 5 sessions at 2 week intervals using laser settings of 5 mJ and a density of 300 spots/cm². Photos and biopsies taken showed increased hair growth and density. Previous studies, as listed in the references section, have shown the effectiveness of fractional photothermolysis in inducing hair growth in people with different types of hair loss conditions. The limitations of these studies are the small numbers of patients, which has prompted us to perform our study.

Primary Outcome Measures:

- Change in the amount of hair loss (we will count before, and compare treated/untreated again at the end of the study for all primary outcome measurements)
- Change in the density of the hair
- Regrowth of new hair

Secondary Outcome Measures: Change in the quality of life

List up to ten relevant references/articles to support the rationale for the research:

1. Kim, WS, HI Lee, JW Lee, YY Lin, SJ Lee, BJ Kim, MN Kim, KY Song, and WS Park. "Fractional Photothermolysis Laser Treatment of Male Pattern Hair Loss." *Dermatologic Surgery* (2011): 41-51.
2. Lee, G.-Y., Lee, S.-J. and Kim, W.-S. (2011), The effect of a 1550 nm fractional erbium–glass laser in female pattern hair loss. *Journal of the European Academy of Dermatology and Venereology*, 25: 1450–1454. doi:10.1111/j.1468-3083.2011.04183.x
3. Bae, J. M., Jung, H. M., Goo, B. and Park, Y. M. (2015), Hair regrowth through wound healing process after ablative fractional laser treatment in a murine model. *Lasers Surg. Med.*, 47: 433–440. doi:10.1002/lsm.22358
4. Gold MH, ed. Update on Fractional Laser Technology. *The Journal of clinical and aesthetic dermatology*. 2010;3(1):42-50.

5. Mlacker, Stephanie, Adam Souhail Aldahan, Brian James Simmons, Vidhi Shah, Colin Andrew Mcnamara, Sahal Samarkandy, and Keyvan Nouri. "A Review on Laser and Light-based Therapies for Alopecia Areata." *Journal of Cosmetic and Laser Therapy* (2016): 1-13.
6. Gupta, A.K., Carviel, J. & Abramovits, W. *Am J Clin Dermatol* (2016). doi:10.1007/s40257-016-0230-4
7. Tierney, E. P., Kouba, D. J. & Hanke, C. W. Review of fractional photothermolysis: treatment indications and efficacy. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 35, 1445-1461, doi:10.1111/j.1524-4725.2009.01258.x (2009).
8. Sherling, M. et al. Consensus recommendations on the use of an erbium-doped 1,550-nm fractionated laser and its applications in dermatologic laser surgery. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 36, 461-469, doi:10.1111/j.1524-4725.2010.01483.x (2010).
9. Town, G. & Bjerring, P. Is paradoxical hair growth caused by low-level radiant exposure by home-use laser and intense pulsed light devices? *Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology* 18, 355-362, doi:10.3109/14764172.2016.1157373 (2016).
10. Cho, S. et al. Clinical effects of non-ablative and ablative fractional lasers on various hair disorders: a case series of 17 patients. *Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology* 15, 74-79, doi:10.3109/14764172.2013.764436 (2013).

Research Procedures

The duration of participation in the study will be 24 weeks. The treatment period is 12 weeks, and the continuation period is 12 weeks.

Study Design

Study Design (Table 1)

- 50 subjects will be enrolled in the study for 6-10 visits total.
- Each subject's head will be divided into half depending on the pattern of hair loss.
- Subjects will randomly be split in half and assigned to one of two groups- one will receive treatment with the Fraxel DUAL 1550 laser and the other will receive the Halo by Sciton laser.
- At the beginning of every visit, vital signs will be taken for every subject.
- A quality of life questionnaire will be given to the subject to fill out prior to starting the treatment for that visit.
- We will determine what part of the head will get the laser therapy depending on the pattern of hair loss. We will take precise measurements of the area so it can be located at the next visits. Measurements (coordinates) will be taken from mid-pupillary line to the hair loss region, and from superior margin of the ear attachment to the hair loss region. The x-coordinate will be the distance in centimeters from the superior margin of the ear attachment to the region, and the y-coordinate will be the distance from the mid-pupillary line to the region. These coordinates will allow us to locate the precise location on the patient's head that the laser was applied at every visit.
- The area that will receive the laser will be square in shape and will be 3x3 cm.
- Subject will have half their head treated via fractional photothermolysis using either the Fraxel DUAL 1550 or Halo by Sciton Laser. The other half will be left untreated.
- Treatment settings will be as followed: 1550 nm wavelength, 7 mJ energy, 8 laser passes, 120 spots/cm², treatment level 3 which is 9% coverage.
- The subjects will be asked to come in for visits every 2-4 weeks.
- Photographs will be taken of the treated and untreated areas during each visit.
- The hairs will be counted at each visit on both the treated and untreated areas.
- Screening will last 24 weeks. There will be 6 visits and they will be 2 weeks apart. So the treatment period will last 12 weeks. Everyone will come in 6 weeks later (week 18 since screening) for an assessment visit, and again another 6 weeks later (week 24 since screening) for a final assessment visit.

The study results will be based on quantifying hair on photographs. Digital photographic assessments of hair density over fixed scalp area, hair shaft with, and hair darkness will be obtained. A small area of the scalp will be chosen, where images will be obtained with high power photography and dermoscopy. This will allow for hair counts to be obtained. The first endpoint is to see if we can appreciate an increase in hair number or density using optical imaging modalities. The second endpoint is to identify any features of hair follicles that separate normal versus alopecia. These features can be follicle size, number, or tissue environment. Based on

what we find, we might be able to quantify these results. In addition, quality of life questionnaire will be used, and it is a statistically proven Skindex questionnaire designed for skin diseases. (Table 2).

STATISTICAL ANALYSIS PLAN

We hypothesize that a significant change can be noted with respect to the primary outcomes if the density of hair increases by 25% in 16 weeks per cm^2 (with a standard deviation of ± 25). A significant change can be noted with respect to the secondary outcomes if the quality of life score increases by 25% in 16 weeks as well.

We will use a paired t-test to compare treated and non-treated areas with respect to the primary outcome of interest, taking into account that the control and treatment are paired because they belong to the same person. We are taking away subject to subject differences by making each person their own control. We will look at average and standard deviation.

The paired t test will be used to examine whether the treated part is significantly different the non-treated part.

Secondary analyses of primary outcomes could include the factor of age, degree of hair loss, size of hair loss treated area, and race. We will examine confounding factors such as these that have potential to be important to this study. By analyzing these factors, we will see whether or not we need to control for them in follow up studies.

Sample size was determined using power analysis for paired t-test. Based on the results of previous papers, the mean difference between treated and untreated areas was set at 25 hairs/ cm^2 , with a standard deviation of 25. With 50 subjects, we have 93% power, which will allow for our results to be statistically significant. This is assuming that the effect size is half of a standard deviation, at a significance level of .05. This analysis was done using a 2-sided paired t-test. In literature, the range of hair density is approximately 100-120/ cm^2 in patients experiencing hair loss, and we consider 25% increase in 16 weeks as biologically significant.