Comparison of 1,550-nm fractional and 755-nm alexandrite picosecond laser for the treatment of acne scarring

BACKGROUND:
Acne is a highly prevalent disease and post-acne scaring has shown to have detrimental effects on a person's physical, mental, and social well-being (Purvis et al. 2006). Acne scars can be divided in general categories of hypertrophic or keloid scars, atrophic scars (icepick, rolling, Boxcar), and pigmentation alterations (redness, hypo and hyper-pigmentation). This study will focus on treatment of moderate to severe grades of atrophic acne scarring.

Both lasers in this study in this study are already FDA approved treatment modalities for acne scarring.

History 1550nm Erbium laser:

Fractional lasers are effective in treating dermatological diseases that require large treatment areas and high pulse energy, and well tolerated by patients. A non-ablative 1550-nm erbium-doped fractional photothermolysis system is widely used for clinical purposes (Cho et al. 2010). As the stratum corneum remains intact after FPS treatment and epidermal barrier function is therefore preserved, side effects and recovery time are markedly reduced, as compared to ablative lasers.

Fractionated photothermolysis invented in 2001 produces microscopic treatment zones (MTZ) of full thickness thermal damage by a mid-infrared laser. MTZs sit among the surrounding viable skin while keeping the stratum corneum intact. Each MTZ inside the skin undergoes local epidermal necrosis and collagen denaturation. Within 24 hours, the reepithelization occurs, followed by epidermal regeneration.

In 2008, Chrastil et al. investigated the efficacy and safety of second-generation 1,550-nm FPS in treatment of acne scarring (Chrastil et al. 2008). The majority of patients achieved a 50% to 75% improvement in facial and back acne scarring (18 of 29 patients). Side effects were minimal and no posttreatment pigmentary changes were noted, including within patients with Fitzpatrick Skin Types III to V. In 2009 HU et al. also investigated the effect of 1550-nm non-ablative FPS on atrophic scars, specifically within Asian patient with Fitzpatrick skin type III-IV. Good to excellent improvement was noted in 60% of the patients after 1 month, with unremarkable side effects (Hu et al. 2009).

To this date the efficacy and safety of 1,550-nm fractionated photothermolysis system has not been compared to other non-ablative lasers (Abdel Hay et al. 2016).

History 755nm picosecond laser:

A recent study investigated the safety and efficacy of a 755-nm alexandrite picosecond pulse duration laser with diffractive lens array for the treatment of facial acne scarring (Brauer et al. 2015). This laser has also been FDA approved for treatment of atrophic acne scars. The evolution from nanosecond to picosecond lasers can deliver more targeted energy, and with lower fluence, leading to fewer adverse effects. An innovative optical attachment, a diffractive lens array, has been developed that hauges distribution of energy to the treatment area. This method has a greater pattern density per pulse, and was shown in this study to improve appearance of acne scars.

In the Brauer study, patients received 6 treatments with a 755-nm picosecond laser with a spot size of 6 mm, fluence of 0.71 J/cm2, repetition rate of 5 Hz, and pulse width of 750 picoseconds in combination with a diffractive lens array, allowing for greater surface area and pattern density per pulse. This treatment produced improvement in appearance and texture at 3 months after the last treatment, with objective findings similar to those published for a series of fractional ablative laser

treatments. The study demonstrated high patient satisfaction and no significant lasting side effects among Fitzpatrick skin types I through V.

Introduction:

We will compare these two lasers in the treatment of acne scarring by performing a split faced randomized trial with three treatments over 3 months. Photographs will be taken prior to treatment and after final follow up with photographic review by blinded reviewer.

Hypotheses for this study:

1- There is no significant difference in efficacy of acne scar treatment with fractionated 1550-nm laser and 755-nm picosecond laser in combination with a diffractive lens array.

2- The 755-nm picosecond laser in combination with a diffractive lens array has superior side effect profile as compared to fractionated 1550-nm laser in treating acne scars.

PURPOSE & OBJECTIVES

Objective: To compare efficacy and safety of fractionated 1550-nm laser and 755-nm alexandrite picosecond laser in combination with a diffractive lens array, in treatment of moderate to severe acne scars.

Primary Endpoint: Improvement in acne scarring measured by photographic review. Measured by blind reviewer and quantitative 3D imaging.

Exploratory Objective: Comparing side effects of the different lasers.

Exploratory Endpoint: measure side effects by patient reported adverse events.

PARTICIPANT ELIGIBILITY
INCLUSION CRITERIA
Men and women with Fitzpatrick skin types I through V and facial acne scarring of grades III-IV (moderate to severe), who are able to give consent, will be enrolled. Both sides of the participants' face should have similar amount and severity of acne scarring. Participants will be over 18 years old. Patients have to be otherwise healthy without a history of skin cancer, keloidal scarring, localized or active infection, immunodeficiency disorders, and light sensitivity.

EXCLUSION CRITERIA
Patients have to be overall healthy without a history of skin cancer, keloidal scarring, localized or active infection, immunodeficiency disorders, and light sensitivity. Per PI discretion, any serious medical condition that may interfere with the study. In addition, patients who have been taking isotretinoin for a period of 6 months before treatment will be excluded.

JUSTIFICATION REQUIREMENTS FOR INCLUSION OF VULNERABLE POPULATIONS
Pregnant women are not excluded from this study and we will not perform pregnancy tests during the study. Neither laser device used in this study has shown risks during pregnancy or to the fetus.

Acyclovir is the only systemic medication used in this study to prevent herpetic outbreaks after laser treatments. Acyclovir is category B in pregnancy.

CDC studies have indicated that "Based on comparisons with birth defects surveillance data maintained by CDC, the registry findings summarized in this report indicate no increased risk for birth defects among infants born to women exposed to acyclovir during pregnancy". Source is the CDC website at:

https://www.cdc.gov/mmwr/preview/mmwrhtml/00022071.htm

Recruitment:
Patients recruited will all be current patients of U of U dermatology department. We will send out an email to all current dermatologists within the department asking for referrals to this study. If they have patients with acne scarring who are interested in participating in this study, they will refer the patients to the study by providing the PI and sub-investigator with patient's name and university ID number. There will also be a flyer about the study available in the dermatology clinics of the U of U. The patient's medical record will then be reviewed by the PI or sub-investigator in order to determine if patient meets inclusion criteria. A recruitment letter (see documents sections), will then be mailed to the potential participants signed by the PI. The letter will give a brief description of the study, and contact information for opting out or asking for more information. Letter will let possible participants know that they will be called by the PI or sub-investigator to invite them to an introductory visit during which they will be given details about the study and their eligibility will be determined by the PI. If the patients are interested in participating in the study at this visit, they will be asked to sign the consent form (see documents section).

STUDY PROCEDURES
Screening visit- this visit takes place anytime between one week to 6 months prior to initiation of treatments at week zero. Participants will be screened based on inclusion and exclusion criteria, Fitzpatrick skin type will be determined, and full details of study are explained. If participation is desired, patients will sign the consent form at this time. Prescription may be given for oral acyclovir and topical triamcinolone.
Treatment phase
Week 0:

- Baseline full face photographs taken
- Laser treatment #1 to both sides of the face (R and L sides of the face are each treated with one of the two study lasers based on randomization)
- Review post-laser standard-of-care skin care with participants (sun avoidance, sunscreen use, moisturizer use)
- Complete VAS pain assessment (see documents attached)
- Prescription given for oral acyclovir and topical triamcinolone per protocol

Week 4:

- Full face photographs taken
- Review and evaluation of any adverse events from previous session and complete assessment of adverse events form (see attached documents)
- Laser treatment #2 to both sides of the face (R and L sides of the face are each treated with one of the two study lasers based on randomization)
- Review post-laser standard-of-care skin care with participants (sun avoidance, sunscreen use, moisturizer use)
- Complete VAS pain assessment (see documents attached)
- Prescription given for oral acyclovir and topical triamcinolone per protocol

Week 8:

- Full face photographs taken

- Review and evaluation of any adverse events from previous session and complete assessment of adverse events form (see attached documents)
- Laser treatment #3 to both sides of the face (R and L sides of the face are each treated with one of the two study lasers based on randomization)
- Review post-laser standard-of-care skin care with participants (sun avoidance, sunscreen use, moisturizer use)
- Complete VAS pain assessment (see documents attached)
- Prescription given for oral acyclovir and topical triamcinolone per protocol

Week 24:

- Full face photographs taken
- Review and evaluation of any adverse events or serious adverse events
- Complete physician assessment of improvement of acne scarring (see documents attached)
- Participants fill out final satisfaction survey (see documents attached)

STUDY TREATMENT

Both laser treatments are FDA approved for acne scarring and both are considered as part of standard of care of acne scarring. The procedures that are for research purposes only are:

- blinding the participant to which side of face receives which laser
- randomization of which side of face receives which laser
- review of clinical photos by blinded dermatologist

STATISTICAL CONSIDERATIONS

Analysis method will be based on the following table:

Outcome	When measured	Analysis Method
VAS pain score after each treatment	After each treatment	T test to compare means across laser type at each time point. Repeated measures mixed effects models to compare effects across study.
Equivalence across laser type.	Final visit at 24 weeks (3 moths post final laser tx)	One sided t test for non-inferiority or equivalence.
Proportion Satisfied or Extremely Satisfied		Verify that there is no stat. sig dif between laser types, Then using score of side with lowest satisfaction test if proportion is different from 0 or proposed placebo effect.
Mean of scores from 3 physician evaluators on improvement in texture and overall appearance	Week 24 photos (3 months post final treatment)	T test to compare means across laser type. Repeated measures mixed effects models to compare effects across all study timepoints.

All analyses will be conducted using SAS software version 9.4. All test will be two-sided with an alpha level of 0.05 with the exception of the non-inferiority analysis which will be a one-sided test with and alpha level of 0.025.

Power and Sample Size

Sample size estimation is based on the primary aim of patient-reported scar improvement. The goal of the study is to show non-inferiority of the two types of laser treatments. Cho (2009) found that the mean difference in patient satisfaction scores (scores ranged from 0 to 3) across the two laser treatments was -0.75 with a standard deviation of 0.71 Using this standard deviation of 0.71 to power for a non-equivalence test, it was found that a sample sizes of 8 achieves 80% power to detect non-inferiority using a one-sided t-test.

Results from PASS software:

Power	N	Non-Inferiority Margin (-NIM)	Actual Difference (D)	Significance Level (Alpha)	Beta	Standard Deviation (S)
0.80388	18	-0.500	0.000	0.02500	0.19612	0.710

If the goal is to establish non-inferiority of the new laser to the old, 18 subjects are needed. The assumption is that there is no difference in the two lasers, but the investigator is willing to accept a margin of inferiority of 0.5. Allowing for a 10% dropout rate, 20 subjects would need to be enrolled. The investigator would also like to establish that either laser type achieves a certain proportion of good or excellent results on subjective assessment. Assuming that the two methods are equivalent, we want to determine if the effect of either side would be better than a placebo effect or a much less effective treatment. The following table gives scenarios of detectable difference if 18 subjects complete the study for a two-sided test at alpha = 0.05.

With 18 subjects completing the study and a power of 0.80 the following differences between those rating either laser treatment as satistfied or very satisfied could be detected:

% satisfied/ext. satisfied if no effect (as compared to an ineffective or no treatment)	% satisfied/ext. satisfied if an effect	Detectable difference
0.0500	0.2339	0.1839
0.1000	0.3318	0.2318
0.1500	0.4126	0.2626
0.2000	0.4839	0.2839
0.2500	0.5487	0.2987
0.3000	0.6085	0.3085
0.3500	0.6640	0.3140
0.4000	0.7158	0.3158
0.4500	0.7641	0.3141
0.5000	0.8090	0.3090

STUDY DESIGN: This is a Prospective, Blinded, Split-faced, comparative study using a blinded assessor.

SAFETY MONITORING
Safety monitoring for this study will be performed by PI, Dr. David Smart. Data and events that will be monitored include:

- Immediate side effects from laser treatments will be monitored and recorded, such as redness, edema, blistering, hyperpigmentation, pain.
- Risks of the both types of lasers used are similar and include redness, swelling, hyperpigmentation (temporary darkening of your skin), scarring, crusting, bacterial skin infection, cold sore reactivation, and blistering of the skin.

Participant Withdraw Criteria
Participants may withdraw at any time during the trial.

Study Modification or Stopping Criteria
The study could be stopped or modified if there are severe or irreversible unforseeable side effects of the two laser treatments used.