Official Title: Pilot Study of Early Postoperative Fractional Ablative Laser Treatment of Skin Grafts for Burns
NCT04176705
IRB-Approved Date: 12/30/20

Background:

The near and long-term functional impact of burn scars and the sequelae of skin grafting are well known[1]. The economic burden of this treatment paradigm has also been recognized – with the monetary cost of treating burn sequelae estimated as over four times that of the in-hospital stays for acute burn injury[2]. In addition to the social and psychological burden, burn scars and the contraction of skin grafts can not only limit the range of motion (with a loss of function), but also lead to skeletal deformation (**Fig. 1**). In addition, there has been increased appreciation of the incidence and importance of the impact of pruritus[3,4]. The solution to these symptomatic and functional challenges is ongoing.

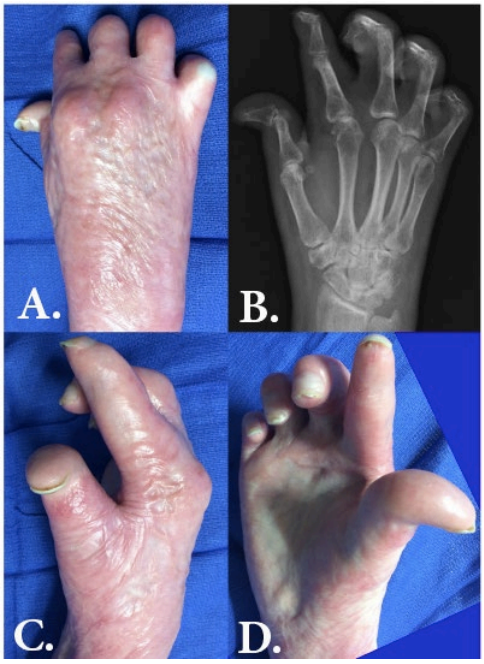


Figure 1. Disabling burn scar, resulting from combination of delayed surgical treatment and rehabilitation treatment. Fixed soft tissue deformities clinically apparent on inspection (A, C, and D) and X-ray of affected hand (B).

Modern treatment of the burn patient is multidisciplinary and a wide array of management options are available (e.g. surgical release and skin grafting, local tissue rearrangement, compression garments, laser treatments, and steroid injections) to attempt to alter scar formation[5,6]. The paradigm of burn reconstruction (often referred to as a reconstructive ladder) reflects recognition of the heterogeneity of the problem and subsequent solution. The overall strategy reflected in this metaphorical label is that the simplest solution deserves first consideration, and one proceeds to the next higher-level solution only when there is an identifiable contraindication to utilization of the first step (**Fig. 2**)[7]. The rationale for a reasoned, stepwise approach is that the risk increases as a progressively higher-level step is chosen. As an extreme example, the use of a free flap to cover a second-degree burn is illogical. The wound will predictably heal and the risk of the morbidity associated with flap loss is unacceptable. Contrast the previous extreme example with a fourth degree burn involving exposed bone of sufficient size that there is not an alternative to achieving soft tissue coverage. In the latter situation, the potential risk of free tissue transfer is logical in order to protect critical deep structures (bone, vessels, or nerves). These steps can be selected for treatment of open wounds, as well as during reconstruction. Just as there may be a better choice for coverage of an acute wound, there may also be a clear choice for improving function or appearance – while minimizing the risk to the patient. The role of the fractional CO_2 laser in modifying burn scars in not clear. Multiple authors have identified improvement in burns scars with treatment with fractional CO_2 ($FxCO_2$) laser treatment[8-13]. However, a common critique is that

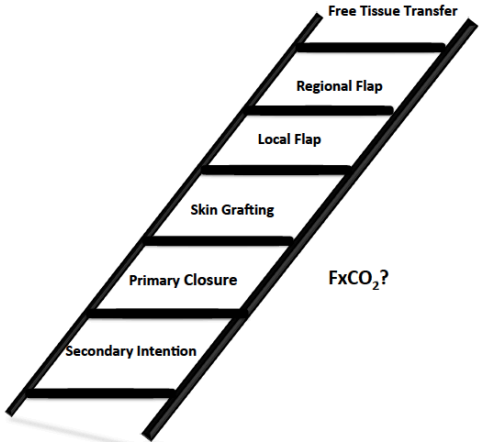


Figure 2. The reconstructive ladder (used for acute wound coverage or delayed reconstruction) is a metaphorical approach to reconstruction. Each successive step is accompanied by increasing complexity and risk. Understanding for the role of $FxCo_2$ treatment is incomplete.

measures were subjective, treatment timing and laser settings variable, and study populations were relatively small[14]. The common approach to solving these challenges is to simply focus on planning a larger study. However, we note the lasers were also deployed as a solution to a quite heterogeneous problem. A common challenge to any clinical study is identifying the condition being treated as precisely as possible. Although not commonly addressed, the term "burn scar" encompasses a heterogeneous group of pathologic skin changes associated not only with areas of burn that heal by secondary intention (forming scar), but also areas with thickened/shrunken skin grafts, hypertrophy at the seams along the edges of skin grafts, and delayed healing of skin graft donor sites with resultant hypertrophy (**Fig.3**). The scarring and contracture of split-thickness skin grafts is expected without treatment. *Human split thickness skin grafts heal with secondary contracture, and this contracture can result in decreased function*[15]. Multiple factors have been noted to affect the amount of contracture- such as the use of meshed skin grafts or graft thickness[16-18]. The timing between injury and institution of both surgical and non-surgical means of treating scars is impactful as well. Non-surgical methods of scar *prevention* are generally accepted to have increased effectiveness when applied closer to the time of injury[6]. Even in cases of simple primary closure of surgical wounds, mechanical intervention has been shown to be an effective means of decreasing scar formation, and these are applied immediately[19,20]. Similarly, there is improved effectiveness of compression garments for managing burn scars if applied closer to the time of injury[21]. These clinical observations appear consonant with animal studies of wounding which have confirmed the temporal changes in the wound environment and cellular architecture. Surgical procedures are also affected by scar characteristics. More immature scars show evidence of inflammation - greater vascularity, less pliability, and greater thickness of the tissue creates challenges that weigh against early release and graft or local tissue rearrangement (z-plasty). In summary, the choices are about the best therapy *and also* the best time. There have been clinical studies looking at the efficacy of both early versus delayed treatment strategies with $FxCO_2$ laser. However, early appears to mean a matter of months[22]. This evolution in practice has left a critical time period poorly explored, especially with regards to the potential impact on burn scars – healing split-thickness skin graft in particular. Of note, this pilot study does not seek to establish a new indication for the $FxCO_2$ laser. The FDA approves the laser in use at Wake Forest Baptist Medical Center. It is approved for use on "*surgical scars*" (we are treating the resulting scars associated with skin graft surgery). As mentioned, "burn scars" is a very inclusive term. This is precisely why we will treat only the surgical scars related to burn treatment. It is also approved for "*other soft*

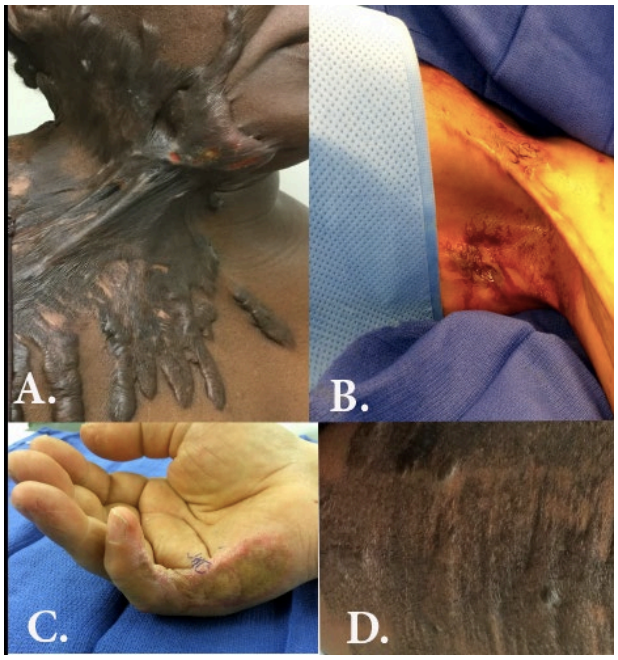


Figure 3. Examples of heterogeneity of pathology described as "burn scar". Include areas allowed to heal by secondary intention (A.), areas of contracted skin grafts (B.), scarring at the seams of supple full-thickness skin grafts (C.) and even delayed healing with hypertrophy of donor sites (D.)

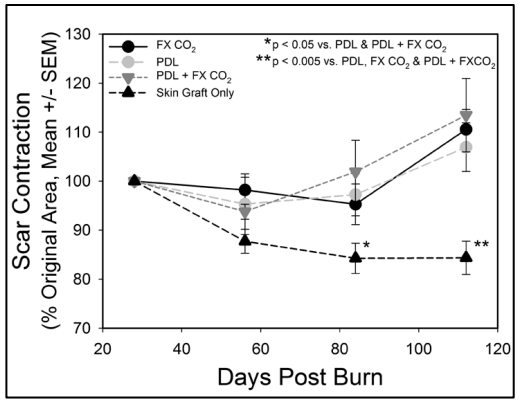


Fig 4. Split-thickness skin graft contraction (Identified as "Scar Contraction") is expressed as % original area as a function of time. In this case, the sizes of the skin grafts were normalized to day 28 (the first day of laser treatment).

tissue applications". Finally, the laser is being applied in an earlier and earlier fashion as it use has become more popular and evolved. The intent of this study is to establish safety and, perhaps efficacy, of use at a different time point.

PRELIMINARY STUDIES (Conducted at The Ohio State University)

Efficacy of Early Laser Treatment of Split-thickness Skin Grafts in a Porcine Burn Model:

Our group has documented the salutary effects of the $FxCO_2$ laser treatment on a porcine model of split-thickness skin graft applied to excised burns[23]. An unexpected finding was the improvement in eventual secondary contracture of the split-thickness skin graft (**Figure 4**.). Although we also found improvement in measures important to skin graft appearance, the finding of reduced secondary contracture is particularly important to *functional* outcomes. We have also conducted a pulse-chase study to better understand the effects of early (7 days after grafting) $FxCO_2$ treatment of split-thickness grafts in the same porcine burn model. There was no evidence of slowed healing caused by laser treatment. Healing was measured by transepidermal water loss, which is a functional measure of skin integrity (**Fig. 5**).

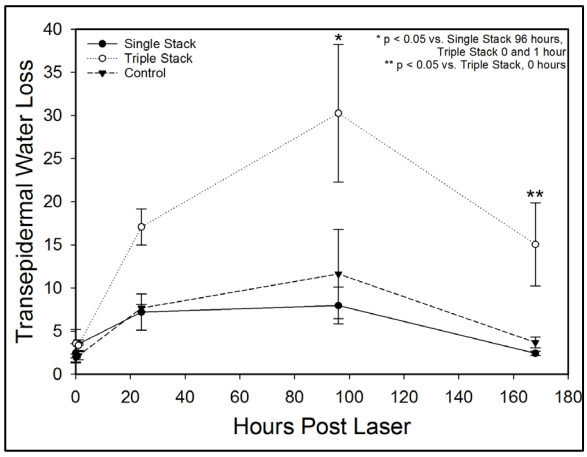


Figure 5. When the porcine split-thickness skin graft (meshed 1:1.5) is treated with single pass of 70mJ at 5% fractional coverage, wound closure (defined by transepidermal water loss) is not retarded.

Relevance to Proposed Clinical Trial:

In **Figure 3 B**, the photo is of an axillary contracture created by tension from a skin graft, which underwent the normal, expected course of secondary contracture. The photo is also intraoperative - from the surgical procedure necessary to correct the tension created by the secondary contracture. The promise offered by the porcine model findings is that such corrective surgery of contracting skin grafts may be reduced in frequency, or avoided all together. Further, the animal model offers evidence of safety.

Local Clinical Practice Cannot Provide Custom Compression Garments Sooner than 19 weeks from the time of injury:

In an effort to better understand how measures such as compression therapy were being applied at our burn center, we conducted an IRB-approved chart review to identify how long a delay exists between identification of the need for compression therapy and actual wearing by the patient. The study has been submitted for publication and a surprising 19-week delay was identified (**Table 1**).

Variable	Mean ± stdev		p-value
	Insurance	Burn Fund	
Age	37.4 ± 13.6	45.0 ± 19.9	0.152
% TBSA	9.0 ± 12.0	12.3 ± 13.5	0.189
% Partial Thickness Wound	5.4 ± 9.4	6.7 ± 8.5	0.293
% Full	3.5 ± 5.8	5.3 ± 6.7	0.100
Weeks between date of injury and date garment ordered	10.5 ± 9.7	7.6 ± 5.4	0.089
Weeks between garment ordering and delivery	8.4 ± 4.0	8.7 ± 4.2	0.771
Total number of weeks between injury and garment application	18.5 ± 11.1	16.3 ± 6.3	0.815

Table 1. A quality improvement project was translated into an IRB-approved review of the time required for patients to successfully don custom-made compression garments. A surprising delay was noted.

Relevance to Proposed Clinical Trial

The noted delay was, and is, concerning from a clinical care perspective. However, the clinicians have been unable to change the delays, as the process appears to have multiple logistical delays (therapist availability to measure, delays in ordering, delays in insurance approval, delays in fitting, delays in altering, and delays created by difficulty in contacting patient). These challenges notwithstanding, a unique opportunity has been created by the inability to offer a timely standard of care. The delay offers an acceptable and ethical justification to apply early laser treatment to patients – either as part of clinical care or a prospective study.

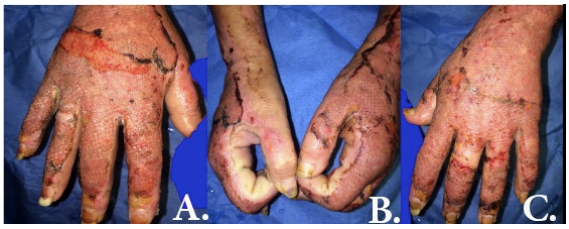
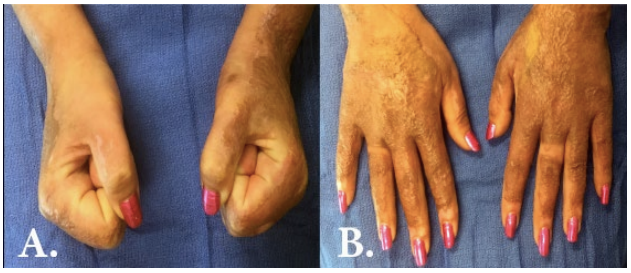


Figure 6. Skin grafts (meshed 1:1) on nearly entire dorsum of bilateral hands one day after fractional CO_2 laser treatment. No subsequent loss of graft. Displayed flexion of digits at patient maximal effort.

Limited Early Laser Treatment is Clinically Free of Complication

Due to our inability to offer a timely and effective therapy to mitigate scar formation, our surgical team at the Ohio State University has treated skin grafts with $FxCO_2$ during the period of initial hospital admission, when patients were returning to the OR for other procedures. This has been offered as empiric therapy and not part of any type of study (**Fig. 6**). With recognition of those limitations, the treatment is well tolerated, with no clinical evidence of graft injury (**Fig. 6**). Also, there is anecdotal appreciation of efficacy (**Fig. 6** and **Fig 7**). We have applied the FxCO2 laser successfully in four patients. We have seen no areas of unanticipated graft damage or loss related to its use.



Fig**ure 7.** At time of presentation for third planned laser treatment (not yet wearing compression garments). Note composite fists in A.

Relevance to Proposed Clinical Trial

Safety is an essential concern of any proposed clinical trial. Although the experience of treating skin grafts at 6-10 days after surgery is limited at our Burn Center, it is promising. Establishing safety with an appropriately monitored study is an important unmet need. However, the preliminary data and qualitative observations are supportive that the study can be done safely.

PROPOSED PILOT STUDY.

This pilot study is being conducted to establish safety, however we will make multiple measures to measures of efficacy as well. We hypothesize that human split-thickness skin grafts will safely respond similar to the porcine model when treated with the $FxCO_2$ laser and have significantly less secondary contracture than control sites.

Overall Strategy

The great majority of laser studies have addressed treatment of established scars. Ideally, treatment modalities could be moved into the acute period of injury, to shorten the recovery time of thermal burns by decreasing the time to maximum recovery, and mitigate scar formation. The current study will address the impact on treatment of skin grafts applied in the treatment of acute burn wounds. Preliminary work completed by our team has confirmed that the red Duroc porcine model is a good model of hypertrophic scar formation in humans, and early use of the $FxCO_2$ on split-thickness skin grafts decreased secondary contracture. Further, we have identified a period of 19 weeks between the time custom-made compression garments are ordered and actually applied with benefit to the patient. We have identified a "therapeutic donut hole" in which we have no efficacious alternative to offer until about 19 weeks. In these patients who had larger burn returning to the OR for additional procedures, we were able to offer $FxCO_2$ treatment as a "salvage" therapy. With this, we have demonstrated safety for the skin graft and anecdotal efficacy. We propose a pilot study to prospectively demonstrate safety in a controlled study and attempt to establish efficacy of early (post grafting day 6-10) $FxCO_2$ laser treatment of split-thickness skin graft applied in the treatment of burn injuries.

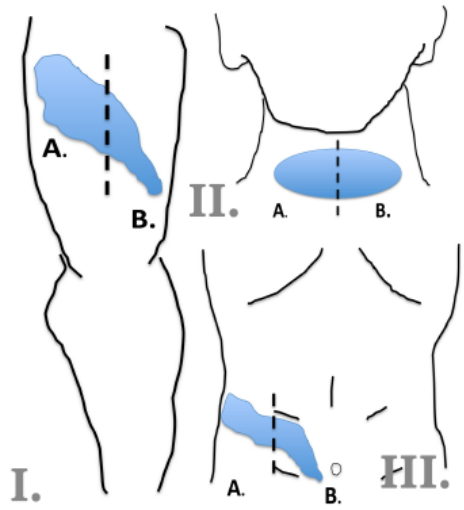


Figure 8. Sites will be randomized such that the choice between treatment and control will be between A.(Right, cephalad, or lateral) and B. (left, caudad, or medial). Extremities include the feet. To avoid confusion regarding medial/lateral we will invoke convention of assuming body is in anatomic position (i.e. arms extended to the side with palms facing in direction of forward gaze of the patient.

Patient Eligibility

All patients who are to undergo skin grafting procedures for acute treatment of thermal burns will be screened for enrollment. Although, split-thickness skin grafts placed for reconstruction or coverage of non-burn injuries should be expected to heal and respond to treatment in a similar fashion to grafts on acute burn wounds, this study will seek to limit these variables and is focused on offering benefits to the acutely injury patient. Only patients with grafts placed over at least $100cm^2$ will be approached for inclusion in the study so as to minimize any paracrine effect that might result from non-treated grafts in proximity of treatment areas. The $100cm^2$ need not be contiguous. That is to say, two smaller areas totaling 100cm2 can be used. Sites will be randomized to laser/no laser. If there is a single site of sufficient size, it will be divided in to two, roughly equivalent surface area segments with the midpoint along the long axis of the limb/hand/foot/neck/torso (**Fig. 8**). For site assignment purposes we will assume the classic anatomic position with patient assumed to be in a standing position, gaze forward, hands to sides with palms facing the direction of gaze. Areas will be labeled: A.(Right, cephalad, or lateral) and B. (left, caudad, or medial). In order to attempt to assess the same three locations at each site, a tracing of each site will include a tracing of three, individual locations about 1 cm in (approximately) in diameter (**Fig. 9**). Any measures done at the time of treatment visits will be done prior to any therapeutic intervention. Both sites will have lidocaine 4% topical anesthetic cream (Ferndale Laboratories, Ferndale MI) applied as thin layer and left for 30-45 minutes to minimize discomfort (after any measurements have been taken). The area to be treated (A. vs. B.) will be randomized with opening of an

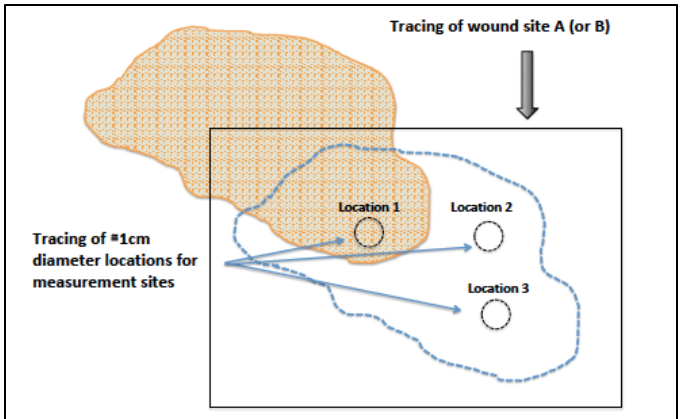


Figure 9. Tracings will be obtained of the perimeter of each site. On the first set of tracings, we will mark three locations (approximately 1 cm in diameter) that will be used to help identify the same areas for subsequent measures and surveys.

evelope with assignment to treatment arm after the test sites have been identified. The treatment area will then be cleaned with chlorhexidine gluconate solution 4.0% w/v (Mölnlycke Healthcare, Norcross, GA). $FxCO_2$ laser treatment will then be completed with 5% fractional coverage and 70-mJ fluence setting (percentage of the total surface area ablated and the energy delivered in each micro-beam –respectively). We will apply triamcinolone acetonide (Bristol-Myers Squibb, Princeton, NJ) at a concentration of 20mg/ml immediately after treatment to both laser and no-laser sites - as this is often reported and there is some speculation that this may be part of the reason improvement is noted.
For aftercare, patients will be instructed to apply a thin layer of an over-the-counter moisturizing cream such as Lubriderm® (Johnson and Johnson, Skillman, NJ) or Aveeno® (Johnson and Johnson, Skillman, NJ).

Study Intervention and Group Assignment

Sites will be labeled A and B in accordance with **Figure 8**. For each patient, one site will be randomized to receive laser treatment and the other will be the control. The study statistician will generate a permuted block randomization scheme (three blocks of 5 cells). Treatment assignments will be delivered on-demand following confirmation of eligibility, patient consent, and identification of test sites.

Study Outcome Assessment

Measurements of scar properties, as illustrated in **Fig. 10**, will be made at the time of each treatment (immediately prior to treatment) and at two additional follow up time points. To assess changes in scar development and maturation in the control and treatment sites, scar appearance and properties will be assessed at each clinic visit using non-invasive methods and measurements. Scars will be photographed at each session with a scale bar and color palette in each photograph so all images can be balanced to the same lighting conditions. Scar area at sites A and B will be traced onto transparent sheets and quantified using computerized planimetry following the same methodology used for our porcine studies[23]. The planimetry will also be used to digitally estimate graft loss (if any). To assess erythema and pigmentation, a Mexameter (Courage + Khazaka, Cologne, Germany) will be used to quantify the color of the treated and control scar. Scar biomechanics, pliability, elasticity and viscoelasticity, will be quantified using a BTC-2000(SRLI, Franklin, TN) as this instrument was shown to have the greatest inter- and intra-user reliability in our prior human studies. Scar height and roughness will be quantified using a mold/casting technique using Aquasil Ultra XLV dental impression material (DENTSPLY International, Milford, DE) followed by mold imaging and quantitative analysis. In addition, the VSS and POSAS (Observer Scale only) will be performed by the research team members for scar color, mechanics, height and roughness. These measurements will be collected at each clinic visit (every 1.5-3 months). This data collection strategy has been optimized in adult burn patients at OSUWMC (IRB protocol #2016H0250) and requires no more than 25 minutes per patient.

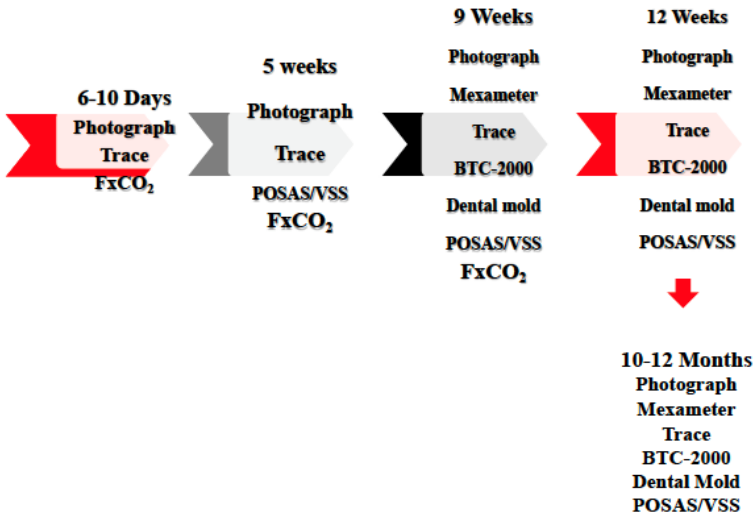


Figure 10. Prior to each of three successive laser treatments, measures will be taken. Photography, done at each visit, will be important to assessing qualitative graft changes, including monitoring for graft loss. Surveys will be given at the visit following a laser treatment (to asses for adverse events). As the graft continues to heal, we expect measureable differences, color measurements (Mexameter), biomechanical measurements (BTC-2000), and casts with dental impression material will be taken.

Clinical End Points: The primary endpoint for this pilot study is the contracture of scar (skin grafted) surface area at 90 days post-grafting. A significant reduction in secondary graft contraction in the treatment group compared to the control group would prompt the design of a multi-center confirmatory trial. Secondary endpoints include scar roughness, biomechanics as measured by stiffness and elasticity, redness measured by erythema each examined at 90 days post-grafting and VSS/POSAS scores along with patient reported satisfaction. Additional secondary endpoints will include the examination of each measurement at mentioned above at 1 year post-grafting to examine longer term healing.

Patient Eligibility: Eligible patients are non-emergent, patients with full-thickness burns who were seen at Wake Forest Baptist Medical Center and are scheduled for treatment with autografts for burn injury. Inclusions criteria: ages 18- 89, autograft site of at least 100cm^2 (not involving the head, neck, hands, buttocks or perineum). All non-burn diagnosis (i.e. chronic wound, Steven-Johnsons/TEN, etc.) prisoners, pregnant women, and patients younger than 18 years will be excluded.

Patient Identification: To screen for eligible patients, the operating room schedules and surgeons' calendars will be reviewed by the clinical research coordinator (CRC), and the three burn surgeons will aid in identifying any potentially eligible adult (age 18-89) patient who is to undergo skin grafting of a full-thickness burn. After identification, study team personnel will then screen the patient for eligibility, by review of clinical information.

Patient Recruitment: Once eligible patients are identified, a qualified research team member will approach the patient and offer the opportunity to learn more about participation in this study. If the patient is willing, then the qualified research team member will proceed to complete the informed consent and enrollment process. This will be completed at the conclusion of clinical care, to avoid any duress from the pain of wounds left open to the air. In the clinic, the process will be conducted in the patient's exam room. Similarly, inpatients will also be consented in the quiet of their hospital room so as to allow them time to carefully consider the details of the study and ask questions.

Patient Sample Size and Rationale: As this is a pilot study in humans, we used preclinical data from our porcine burn model to inform the choice of sample size. For a full clinical study we estimate a need to enroll 29 patients. We acknowledge we may not have a large enough sample size to measure significant improvement. However, the data obtained will aide in the more accurate calculation of the needed sample size for further human studies. In addition, the prospective documentation of safety will increase our competitiveness for funding for a full study. For this pilot study we propose enrolling only 15 patients – the number at which we would have conducted an interim analysis and assess safety if we were to proceed with enrollment of 29 patient s (current estimate for full study). The primary endpoint that we will assess is the scar area at 90 days post-grafting. We will conduct analysis for efficacy after the patients have each reached 90 days post-grafting using the spending function of Lan and Demets[24]. There is not an accepted standard for the measure of graft loss or an expected "percent take". Some have proposed to use less than or greater than 50% of graft loss reflecting the difficulty[25]. In an effort to proceed in a conservative fashion, an adverse safety outcome (namely graft loss not evident by physical changes visible on Day 7-10 photographs, will be defined as a 5% or greater, laser-associated graft loss with a rate in patients of 15% or greater deemed unacceptable. In a previous study of burn patients with heterogeneous types of scars, it was noted that those treated with $FxCO_2$ were most likely to complain of postoperative pain (8/42 patients, or 19%), followed by reports of fever (2 out of 42 patients, or 4.8%), development of hypopigmentation (2/42 or 4.8%), rash (1/42, or 2.4%), or blistering (1/42, or 2.4%)[26].

Statistical Plan and Data Analysis

The primary endpoint of the full trial is the burn scar area at 90 days post-grafting. For the primary analysis, we will compare the log transformed area of the scar for the treatment wounds to the control wounds. We will use linear mixed effects models that will adjust for fixed effects of the baseline wound surface area grafted (prior to the occurrence of any significant contracture) and treatment center. A random effect will be

included in the model for each patient to account for dependence between the treatment and control sites. The primary analysis will follow intention to treat principles and will be conducted at the two-sided 0.05 level[27,28].

Secondary objective endpoints include scar roughness, biomechanics as measured by stiffness and elasticity, redness measured by erythema each, examined at 90 days post-grafting. Secondary analyses will follow the same general framework as outlined for the primary analysis. Outcome variables may be log transformed to satisfy necessary distributional assumptions for the analysis. Secondary subjective endpoints are the VSS and POSAS scores at 90 days post-grafting. These endpoints will be analyzed within the same framework as described for the other primary and secondary endpoints. In addition, we will examine all endpoints at 1 year post-grafting to characterize the effects of treatment on longer term healing.

We will also conduct exploratory longitudinal analyses of the primary and secondary endpoints. Since we will observe each endpoint at multiple visits across time, we will use longitudinal mixed effects models to explore the healing profile across time for both the treatment and control group.

For efficacy, analysis will be interested in assessing the primary endpoint through the error spending function approach described by Lan and Demets[24,29]. For safety, an adverse safety outcome will be defined as a 5% or greater, laser-associated graft loss with a rate in patients of 15% or greater deemed unacceptable. If there are 6 adverse safety outcomes within the first 15 patients, we will terminate the study due to an unacceptable safety risk to patients.

Data Collection

Data will be collected on Case Report Forms (CRF) and individual SD cards (for photographs) kept with the CRF for each individual patient. These CRFs and SD cards will be stored in the locked office of the CRC and in a locked file cabinet.

Data and Safety Monitoring Committee

A Data Safety and Monitoring Committee (DSMC) will be formed and will meet every 6 months throughout the period during which patients are being recruited and experiencing follow-up. The DSMC will review data provided by the primary study statisticians and other study staff involved in data management and analysis. The committee will consist of Martin Avery, MD(a trauma surgeon at WFBMC, Molly J. Thompson, PhamD (Specialty Practice Pharmacist – Critical Care at the Ohio State University), and Rachel Penny PA (PA at the Ohio State University - experienced with appearance of grafts, laser patient care, and clinical trials. All unexpected non-serious adverse events and serious adverse events relating to participation in the study will be reported verbally and in writing to the local IRB and the study PI.. The verbal report will occur within 48 hours of the occurrence. The written report of a serious adverse event (e.g., death or life-threatening adverse event) will be reported within 7 days.

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