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The Northwestern Abdominoplasty Scar Model: A Novel Human Model for Scar Research and Therapeutics

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Summary: There is a growing interest in the development and evaluation of therapeutic agents that improve the cosmetic appearance of scars. Existing nonhuman animal models to study scarring, while valuable, have well-acknowledged limitations, as it is accepted that the biology of human scarring differs significantly from scarring in other species. Moreover, human clinical trials of scarring require large numbers of subjects to achieve statistical power and are plagued by inherent intersubject variability because of the complex nature of wound healing in human beings. As a better alternative, we have developed the Northwestern Abdominoplasty Scar Model—a novel human clinical model that permits analysis of up to 20 cutaneous scars in a single subject and allows for not only visual scar comparison, but also histologic and molecular analyses of factors involved in scarring and wound healing. We have utilized this model in 5 early phase clinical trials designed to test the safety and efficacy of a variety of scar therapeutics without any complications to date. The model not only is applicable to scar therapeutics, but also can be utilized for other applications, such as the testing of implantable biomaterials, injectable products, therapies such as lasers, or even for in vivo study of wound healing processes in humans. *(Plast Reconstr Surg Glob Open 2016;4:e867; doi: 10.1097/GOX.0000000000000857; Published online 23 September 2016.)*

Over 100 million surgical incisions occur yearly, and a significant number of these heal with widened, dyspigmented, hypertrophic, or keloid scars.[1] In addition to pruritus and pain, severe scars can result in restrictive contractures and debilitating functional impairments. Importantly, poor scars have underappreciated adverse psychological effects, including negative self-image, depression, and unfavorable social interactions.[2,3]

A variety of in vitro and in vivo models have been put forth to investigate scarring and test therapeutics. Currently, the most accepted models include the Red Duroc porcine model[4–6] and the rabbit ear hypertrophic scar model.[7–9] However, these models have well-known limitations and an uncertain correlation to human scars.[10–12]

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We have developed a human abdominoplasty in vivo scar model, the first of its kind, to allow scar therapeutics testing on a large number of scars on a single patient. Up to 20 discrete 2-cm full-thickness incisions are created in the area of skin to be removed in a planned abdominoplasty. Incisions are made in parallel columns such that each incision has a mirror image on the contralateral side, allowing analysis as matched pairs to control for minor variations in tension due to location. During wound healing, investigational therapies are applied topically or intradermally to a subgroup of these scars, with the remaining scars on the same pannus serving as controls. Scar position and design can be varied as needed. Should there be concern about interference between treatment effects of adjacent scars, fewer scars spaced further apart can be utilized while maintaining the mirrored matrix design.

Scar analysis is possible at various time intervals after treatment. Biopsies permit histology and molecular analysis of mRNA and proteins of interest, including fibrogenic factors such as transforming growth factor beta and other cytokines involved in wound healing. The ability to provide *objective data* on the severity of scarring represents

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a distinct advantage over existing human models that permit visual analysis alone.

We have performed 6 clinical scarring and wound healing trials with our model to date, with observation lasting for up to 3 months before participants undergoing abdominoplasty. This can be extended to longer periods if needed. A total of 33 subjects have participated in trials with no adverse events. All studies were approved by the Northwestern University Institutional Review Board.

As an example of the type of investigation possible using the model, one study we have conducted was a phase 2, randomized, double-blind, within-subject controlled trial evaluating efficacy of a proprietary pharmaceutical delivered via intradermal injection to ameliorate scarring. Incisions were created in the office by the senior author (R.D.G.) after diffuse infiltration of the abdominal skin and subcutaneous tissue with dilute local anesthetic and closed using simple interrupted 4-0 Prolene sutures (Fig. 1). All hemiabdomens were randomized to receive injection with either the investigational drug or a dilution-matched placebo in a double-blinded fashion. Columns of treated incisions were further randomized to high or low dose. Dosing schedules varied, with injections repeated as often as every 2 weeks for a total of 10 weeks before harvesting of tissue for analysis during the abdominoplasty at week 13. At weeks 4 and 8, the lateral most incisions were biopsied for mRNA analysis and histology. Efficacy was determined by evaluation of blinded photographs taken at week 13 before the abdominoplasty (Figs. 2, 3), which were rated by an expert panel using a visual analog scale and an Investigator Scar Global Rating. All experimental scars were removed during abdominoplasty (Fig. 4).

The importance of thorough informed consent cannot be overemphasized when employing this model. Patients are counseled fully on risks of minor skin incisions, including infection, bleeding, and pain. Specific local and systemic risks of therapeutics are discussed at length utilizing an Institutional Review Board–approved study-specific consent form. Treatment of any complications is covered with study funds at no cost to the patient, and the option always remains to proceed early to abdominoplas-

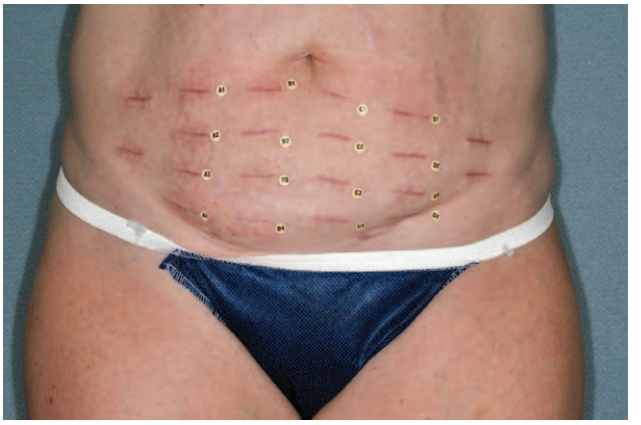

Fig. 2. Appearance of scars on patient's abdomen after 12 weeks of healing. Note the ability to compare mirror image incisions in the various rows.

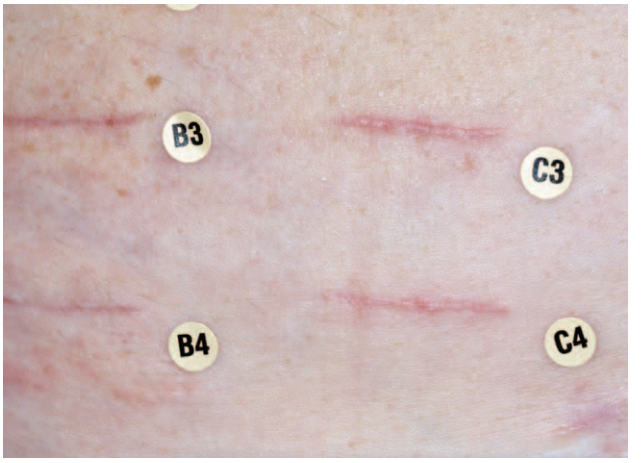

Fig. 3. Close-up view showing a comparison of mirror image scars, B3/C3 and B4/C4, randomized to either placebo or treatment at 12 weeks.

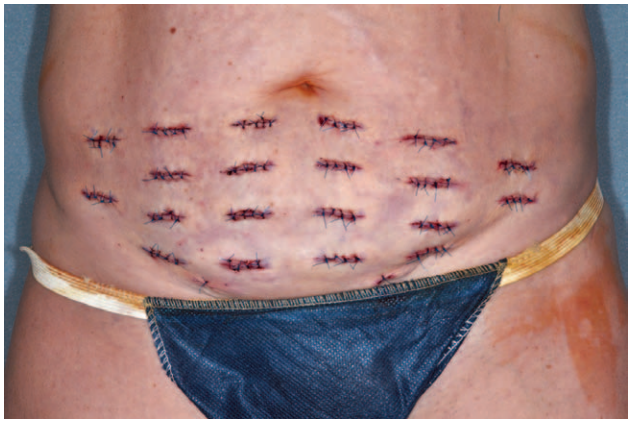

Fig. 1. Abdominoplasty scar model utilized to test intradermal injection therapy to modulate scarring. Appearance of patient's abdomen immediately after creating incisions.

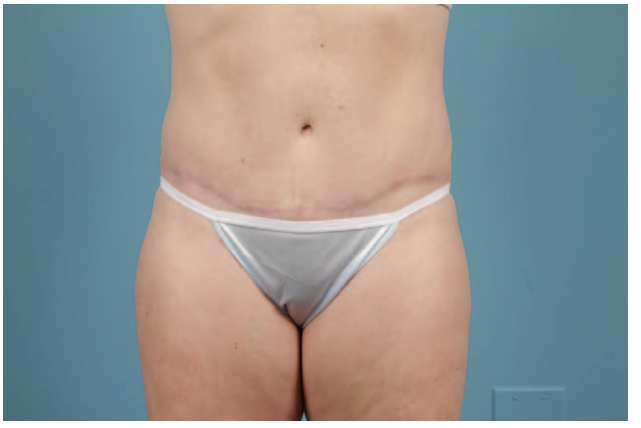

Fig. 4. Seven-month postoperative appearance after undergoing abdominoplasty shows removal of all experimental scars.

ty to excise local wound complications. The time course of the study is made explicit, as is the number and timing of wound biopsies planned. Patients understand that should they choose not to ultimately undergo abdominoplasty, they will be left with scars on their abdomen. Patients receive a free abdominoplasty as compensation for study participation.

The Northwestern Abdominoplasty Scar Model offers a number of distinct advantages for clinical trials. Human scar studies limited to evaluation of 1 or 2 scars per patient are subject to inherent intersubject variability despite good study design. Furthermore, variables such as skin tension, thickness, and anatomic location can result in highly disparate scars within a single patient. This variability is mitigated in our model through analysis of many position-matched incisions on a single patient. Utilization of a model in which only 1 or a few scars are evaluated per subject can require over 100 experimental subjects to achieve statistical significance, posing a significant hurdle in terms of cost.[11] Our model allows for the analysis of 100 scars with only 5 experimental subjects, resulting in substantial cost savings. The incisional matrix design also allows for randomization of study drug and placebo administration along with multidose and multifrequency combinations within a single patient. Furthermore, as abdominoplasty is a commonly sought procedure, we have found enrollment of subjects in trials to be a relatively fast and easy process, avoiding the challenges of lengthy recruitment periods that can plague other experimental designs. Importantly, ethical concerns of leaving a permanent investigational scar on the subject are eliminated by removal of all scars during abdominoplasty, leaving only a lower midline scar related to the initially sought cosmetic procedure.

Our model has potential for use in a number of experimental applications in addition to scarring. It is ideal for the testing of implantable biomaterials in a human milieu, as it allows their harvest for both gross and histologic analysis. Other potential applications of the model are to test responses to injectable filler materials and novel modalities such as energy-delivering therapeutics. We believe the model will find wide applicability for evaluating the efficacy of therapeutics within human subjects, which remain the most clinically relevant model of healing and scarring.

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