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ICG angiography predicts burn scarring within 48 h of injury in a porcine vertical progression burn model☆

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ABSTRACT

The current standard of care in determining the need to excise and graft a burn remains with the burn surgeon, whose clinical judgment is often variable. Prior work suggests that minimally invasive perfusion technologies are useful in burn prognostication. Here we test the predictive capabilities of Laser Doppler Imaging (LDI) and indocyanine green dye (ICG) angiography in the prediction of burn scarring 28 days after injury using a previously validated porcine burn model that shows vertical progression injury. Twelve female Yorkshire swine were burned using a 2.5 × 2.5 cm metal bar at variable temperature and application times to create distinct burn depths. Six animals (48 injuries total) each were analyzed with LDI or ICG angiography at 1, 24, 48, and 72 h following injury. A linear regression was then performed correlating perfusion measurements against wound contraction at 28 days after injury. ICG angiography showed a peak linear correlate (r^2) of .63 (95% CI .34 to .92) at 48 h after burn. This was significantly different from the LDI linear regression ($p < .05$), which was measured at r^2 of .20 (95% CI .02 to .39). ICG angiography linear regression was superior to LDI at all timepoints. Findings suggest that ICG angiography may have significant potential in the prediction of long-term burn outcomes.

1. Introduction

Over 175,000 burns received hospital management in the United States in 2013, with average per-patient costs of nearly, $100,000 [1]. Without early intervention, some partial thickness burns progress to full thickness injuries, exposing the patient to substantial morbidity and undergoing excision and grafting [2]. Despite multiple advances in acute treatment and surgical management, the decision to debride a burn still largely relies on the experience and visual perception of the individual surgeon [3]. Because early clinician accuracy is limited, ranging

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from 50 to 75% [4,5], it is often necessary to await burn margin declaration prior to surgical management. Delayed treatment and inaccurate diagnosis increases hospital stays, patient morbidity and increased hypertrophic scarring [6].

Without definitive treatment, current work has focused on early diagnosis of burn wound depth to optimize the management of burns. Perfusion analysis appears to be a viable modality to this end and Laser Doppler Imaging (LDI) has long been considered the gold standard of burn perfusion measurement [7,8]. Since the benchmark work of Pape et al., in which LDI was shown to predict burn depth with a 97% accuracy [9], multiple clinical and animal trials have shown that LDI can predict burn qualities at a far greater accuracy rate than visual assessment alone [10,11]. Work by members of our group and others suggests that enhanced accuracy with LDI peaks at roughly 48 h following injury, as compared to four days or more with clinical judgment alone [12]. However, as LDI demands a motionless patient and requires a significant scan time, clinical implementation remains problematic.

Indocyanine green dye (ICG) angiography has recently been presented as an alternative to LDI in burn analysis. A near infrared (800–830 nm) fluorescent dye previously FDA approved for coronary artery bypass graft patency analysis, ICG angiography is widely applied off-label in plastic and vascular surgery [13,14]. It also benefits from rapid image acquisition and movie sequence video capture. In prior work by our group, we derived an algorithm for the prediction of lateral burn progression in a validated porcine ''hot comb'' model that's effective as early as one hour after-injury [12].

While the ability of ICG angiography to demarcate horizontal burn margins is important to definitive burn management, it fails to fully characterize the utility of the technology in predicting partial to full thickness vertical burn progression. Furthermore, no technology to our knowledge is capable of predicting wound contraction and depth of scarring. We therefore sought to (1) Assess a relationship between perfusion readings using LDI and ICG angiography at early time points and 28 day burn contraction and (2) Determine the comparative efficacy of LDI and ICG angiography to determine 28 day burn scar depth.

2. Materials and methods

2.1. Study design

We performed a pilot study utilizing blinded perfusion measurements of burns created with a previously published and validated vertical progression porcine burn model [15]. All animal care and procedure protocols were approved by the Institution Animal Care and Use Research Committee (IACUC).

2.2. Animal use

All experimental procedures were performed at our Division of Laboratory Animal Research (DLAR). Twelve young female Yorkshire swine (20–25 kg) were used in this study. Animals were fed a standardized diet for several days to acclimate, and then fasted overnight before procedures. Housing and care for animals was in accordance with National Research Council guidelines [16].

2.3. Burn creation and contraction measurement

Experimental burn creation was performed using a methodology previously described by Singer et al. [15]. Burns were created using a 150 g, 2.5 × 2.5 cm^2 aluminum bar preheated in a 100 °C water bath, wiped dry prior to skin application. The aluminum bar was applied using a previously described spring-loaded device designed to maintain a controlled pressure on the skin of 2 kg/6.25 cm^2. A total of eight burns were placed at equal increments along each animal's paramedian spine, at one of four temperature/time combinations—predetermined prior to the experiment. These consisted of 6 wounds at 70 °C for 20 s, 6 at 70 °C for 30 s, 28 at 80 °C for 20 s, and 8 at 80 °C for 30 s. The non-uniform breakdown of burn intensity was to create a wide range of scar outcomes, as previously reported. The non-regular distribution of burn type on each animal was as a result of the joint requirements of ours and other studies utilizing these burn models. These other studies had aims that were incongruent to our own, and with protocols that did not alter the outcome of this study. The outline of each burn was demarcated using a black tattoo pen. Wounds were covered with a polyurethane occlusive dressing (Tegaderm^{TM}, 3 M, St. Paul, MN), before being wrapped with gauze and adhesive bandage. Dressing changes were performed daily for the first 3 days after burn, then at 7, 10, 14, 21 and 24 days. Intramuscular buprenorphine 0.01 mg/kg was administered as needed if the animals showed signs of pain and discomfort. All pigs were euthanized using intravenous pentobarbital 28 days following injury.

Wound contraction was measured via photographic assessment. Images of specific wounds were taken with a Canon Powershot Duo (Canon, Melville, NY). Changes in the surface area of each tattooed burn margin were measured using NIH ImageJ (Bethesda, MD), with percentage change attributed to wound contraction. Normalization between acquisition distances was performed using ImageJ readings of a ruler present in each image.

2.4. Scar depth measurement

Prior to euthanasia, 6 mm punch biopsies were taken from the center of each burn wound and fixed, dehydrated, and H&E stained as previously described [15]. Scar tissue depth was determined by vertical measurements from the basement membrane to the interface between scar and subcutaneous tissue (Fig. 1). Three separate vertical measurements were performed on each bisected face of the 28 d burn scar: one at the center of the image and 2 midway between the center and edge of the specimen. The average of these 6 measurement was defined as burn scar depth. All measurements were performed by a board-certified dermatopathologist (S.A.M.) blinded to burn conditions.

2.5. Perfusion analysis

LDI and ICG angiography were performed 1, 24, 48, and 72 h after burn utilizing a technique previously described in our lab