reconstruction for predicting flap success. Based on this, the delayed group was further divided into two groups: 4–9 days and 10–90 days. Demographics, flap characteristics and outcomes were compared using Chi-square and one-way ANOVA. Multivariate logistic regression was performed to determine whether timing of reconstruction independently predicts complications and flap failures, controlling for injury-related and operative factors.

RESULTS: The mean age was 38.8 years (range 18–83) and 76% of patients were male. 77 free flaps (21.5%) were performed ≤ 3 days after initial injury, 233 (65.1%) were performed within 4–90 days and 48 (13.4%) flaps were performed after 90 days. There was significant difference in the presence of arterial injury between the groups (64.2% early vs. 46.6% delayed vs. 67.6% late; p=0.014) and timing within cohort. Univariate analysis demonstrated no association between time to coverage and rates of partial flap failure (p=0.11), total flap failure (p=0.44), takebacks (p=0.79) or major complications (p=0.14). Multivariate logistic regression analysis demonstrated that flaps performed within 3 days after injury had decreased risk of major complications (OR 0.40, p=0.04), trend towards decreased risk of partial flap failures (OR 0.13, p=0.06) and any flap failures (OR 0.41, p=0.10) compared to flaps performed between 4–90 days. Our ROC curve demonstrated day 10 to be the optimal day for predicting flap success (AUC=0.56). Multivariate logistic regression analysis demonstrated that flaps performed ≤ 3 days vs. 4–9 days had no differences in major complications (OR 0.40, p=0.04), partial flap failure (p=0.92) or total flap failure (p=0.35). In contrast, flaps performed 10–90 days from injury compared to ≤ 3 days had increased risk of major complications (OR 2.67, p=0.002) and total flap failure (OR 3.40, p=0.03).

CONCLUSION: Early free flap reconstruction performed within 3 days of injury had superior outcomes compared to the delayed (4–90 day) group, consistent with Godina’s original findings. However, as an update to his paradigm, this ideal early period of reconstruction can be safely extended to within 10 days of injury without an adverse effect on outcomes.

Large Gap Peripheral Nerve Repair in a Non-Human Primate Model: Improving Outcomes Utilizing Photochemical Tissue Bonding (PTB) with Acellular Nerve Allograft (ANA)

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PURPOSE: Segmental peripheral nerve deficits are challenging injuries associated with poor outcomes. While these injuries afflict civilians (e.g. Boston Marathon bombing), they have become increasingly prevalent in combat trauma since the advent of improvised explosive devices. Standard of care large-gap (>3cm) reconstruction requires nerve autograft. Alternatives are sought in clinical scenarios where donor limb is not available (e.g. multiple extremity trauma) or donor site morbidity (e.g. painful neuroma formation, loss of function) makes autograft use suboptimal. A variety of alternatives have been proposed including allografts and conduits. Photochemical tissue bonding (PTB) as an alternative to traditional suture neurorrhaphy has been extensively studied in the rodent sciatic nerve model. PTB carries several advantages: reduction of needle trauma, prevention of axonal escape, and a water-tight seal to contain neuroregenerative factors and exclude inflammatory invasion. We report a non-human primate study which recapitulates human anatomy, allows for objective quantitative functional outcomes testing, electrophysiology and histomorphometry. The purpose of this study is to evaluate whether PTB can elevate the performance of acellular nerve allograft (ANA) to that of standard of care autograft/suture.

METHODS: Nineteen rhesus macaques underwent 4cm proximal radial nerve defect creation in the right upper
extremity, the radial nerve transected proximally at the humeral spiral groove, distally prior to the branch to brachioradialis. The radial nerve was selected as it is responsible for an isolated function with no input from other nerves. Three repair techniques were evaluated: n=6 autograft/suture, n=6 ANA/suture, n=7 ANA photosealed in place with light-activated human amnion wraps (PTB). An objective functional outcome test was conceived using an apparatus that accurately measured the degree of wrist extension as a function of time after surgery. Electromyography (EMG) was performed at 0, 120, 240, and 365 days (euthanasia). Histomorphometry and muscle mass retention were analyzed at euthanasia.

RESULTS: Average loss of wrist extension was 88.3±8.2° after radial nerve defect creation. Autograft group animals recovered 82.0° of extension by 7 months. Wrist extension recovery was modestly slower, as expected, in the ANA groups, however, by 8 months the ANA/PTB group recovered 63.0° of extension with no difference in recovery of baseline EMG amplitude as compared to controls (Avance/PTB=75.81% vs. autograft/suture=65.06%). If recovery follows current trajectory, we expect ANA/PTB to demonstrate equivalent outcomes to the autograft/suture group at one year.

CONCLUSION: This radial nerve defect model improves upon existing animal models by allowing for large nerve gap testing in a primate model more analogous to the clinical large nerve gap injury in humans. ANA/PTB group functional recovery lagged modestly behind autograft/suture (by as long as 8 weeks) but is approaching equivalence at 8 months. EMG recovery is similar at 8 months. This preliminary data confirms PTB as a promising technique to improve outcomes of large nerve gap reconstruction in combination with autograft (previously demonstrated) and with acellular nerve allograft.

The Role of Burn Tissue and Denatured Small Leucine Rich Proteoglycans in the Activation of the Toll-like Receptor 4 Pathway

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PURPOSE: Hypertrophic scar (HTS), a common and significant consequence of burn injury to deep dermis with prolonged inflammation, causes reduced range of motion, intense pruritis, heat intolerance, and cosmetic problems. It does not respond well to current treatment options. HTS formation is a dynamic, complex process that involves interactions between multiple factors such as fibroblasts, extracellular matrix molecules, inflammatory cells, cytokines, growth factors, and chemokines. Toll-like receptors (TLRs) are innate immune receptors that respond to microbes to initiate innate immunological defense, and detect and initiate tissue repair after injury. They are expressed in immune cells, gingival, synovial and dermal fibroblasts. Activation of toll-like receptor 4 (TLR4), a proinflammatory pathway, has been suggested to be associated with HTS by responding to extracellular matrix (ECM) and endogenous cellular ligands to promote inflammation. Small leucine-rich proteoglycans (SLRPs) such as decorin, biglycan, fibromodulin, and lumican, are molecules involved in wound healing that modify the ECM by altering fibroblast proliferation, collagen organization, and growth factors. We hypothesized that the endogenous molecules released from damaged burn tissue could activate the TLR4 pathway in dermal cells, which may lead to a cascade of fibrogenic growth factors and collagen deposition following the activation of resident fibroblasts. Therefore, in this study, we determined the role of burn tissue and denatured SLRPs in the stimulation of the TLR4 pathway in vitro, to elucidate immunological mechanisms preceding HTS.

METHODS: Burn tissues, including eschar and exudate, were collected from patients (n=8) at the University of Alberta Hospital. A normal skin sample was collected from a patient who underwent abdominoplasty, as a control. Total cells were isolated from solid tissue by collagenase-digestion. HEK-Blue hTLR4 cells, human embryonic kidney cells that were co-transfected with human TLR4, MD-2 and CD14 co-receptor genes and are used to determine activation of the TLR4 pathway, were treated with the solid tissue, exudate, cells, denatured SLRPs decorin and biglycan, and bacterial lipopolysaccharide (LPS) as a positive control. Secreted embryonic alkaline phosphatase (SEAP) assay was used to measure NF-κB activation as an indicator of TLR4 activity.

RESULTS: HEK-Blue hTLR4 cells treated with solid tissue, exudate, and burn tissue-isolated cells showed higher TLR4 activity compared to untreated cells. Burn site microbiology and days post-burn injury are clinical patient factors that influenced TLR4 activity. Normal skin tissue stimulated TLR4 pathway to some extent, possibly due to...