Methods: A 30% dorsal burn and Achilles transection was performed in C57/BL6J mice. The tendon site tissues were harvested from baseline (t0) and day 7, 42 after induction. Samples were prepared for library generation on a 10x Genomics Chromium Controller, sequenced on a Illumina HiSeq 4000, and analyzed with Cell Ranger Software for pre-processing and alignment to the mm10 genome. DRG analyses and clusters were abstracted from NIH-GEO (GSE154659). Downstream analyses including unsupervised clustering downstream analyses were performed with Seurat.

Results: We first examined candidate neurotrophins and vascular signals in nerve (DRG), finding robust upregulation of Bdnf and Vegfa. In HO, the site of injury contains many cells that may potentially respond to these signals. Indeed, in sequencing data from the pre-HO anlagen, endothelium and smooth muscle cell populations express upregulation for receptors to the nerve-derived Vegfa via Flt1/VEGFR1. This population in addition to being sensitive to the VEGFA ligand, also demonstrates upregulation of Ngrf, signifying a potential vasculo-neuro axis where a vascular signal induces endothelium/SMCs to produce neurotrophic signals. Completing the circuit, the original DRG cells and by logical extension, regenerating peripheral nerves, are highly enriched for the neurotrophin receptors: Ntrk1/TrkA (responsive to the SMC derived NGF), Ntrk2/TrkB (responsive to the nerve-autonomous BDNF), and Ntrk3/TrkC (partial combined NGF/BDNF response). This potentially signifies a feedforward loop where peripheral nerve induces angiogenesis which in return, promotes nascent nerve ingrowth in a cyclical process. Indeed, in targeted knockout of a local VEGFA source (Vegfa<sup>Prrx1</sup> mice), the injury site demonstrates parallel reduction in vascular density (77%) and reduction in nerve fiber frequency (62%) within the HO site.

Conclusions: These findings represent the first work characterizing the coordination between neurogenic and angiogenic transcription programs following extremity trauma. We demonstrate through NextGen sequencing, evidence of neuroangiogenic crosstalk following musculoskeletal/neural injury. This VEGFA/NGF axis involves vascular signaling as a potential source for additional proliferation of NGF expressing pericyte/SMCs. The presented data describe the potential nerve-driven regulation contributing to the formation of HO at the extremity that with antagonism or inhibition may lead to better treatments for aberrant extremity wound healing.

Metacarpal Subsidence Following Trapeziectomy

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Purpose: It is controversial whether subsidence after trapeziectomy prognosticates pain, poor outcomes, and need for revision. The aim of this study was to investigate the degree of subsidence following trapeziectomy and whether subsidence contributes to poor outcomes.

Methods: An IRB approved retrospective review of all patients who underwent trapeziectomy for osteoarthritis of the first carpometacarpal (CMC) joint was conducted from 2003 to 2019. Patients with available radiographic imaging greater than three months postoperatively were included. Patients with arthritis of the metacarpophalangeal joint of the thumb, arthritis of radiocarpal, distal radioulnar, and midcarpal joints were excluded. Demographic information, pain scores, and revision procedures were recorded. Conolly-Rath patient function scores were determined. Subsidence was measured by the ratio of the difference between the trapezial space (TS = distance from base of thumb metacarpal to scaphoid) preoperatively and TS postoperatively over the TS preoperatively. Patients were divided as having a high degree of subsidence (≥50%) or low degree of subsidence (<50%). Pain scores (median and interquartile range) were compared before and after surgery, as well as between high and low subsidence groups using Mann-Whitney U tests. Age was compared between the two groups using an unpaired t-test. P value <0.05 was considered significant.

Results: One-hundred-eighty-six patients, who underwent 211 primary trapeziectomies, were included. The average age at the time of surgery was 61 years (range 18-86). Eighty-five percent of patients were female. Average follow-up was 38.2±31.9 months (range 3-146.5 months). Metacarpal subsidence was present in all patients after trapeziectomy (average 58.0±20.8%). There was no
significant difference in age (p=0.49), pre-op (p=0.19) or post-op (p=0.72) pain between patients with high and low subsidence. Sixty-eight percent of patients had high subsidence (69.2±13.6%). The average age was 60±10.6 years (range 18-86 years) and 80.9% were female. Pain decreased significantly from 6 (5-8) to 1 (0-2)(p<0.001) after surgery. Based on Connolly-Rath scores 25.7% had good, 48.7% fair, and 25.7% poor outcomes. Thirty-two percent of patients had low subsidence (34.6±12.1%). In this group, the average age was 61±8.7 years (range 37-84 years) and 87.4% were female. Pain decreased significantly from 7 (6-9) to 0 (0-3) (p<0.001) in this group and there were 8.9% good, 33.9% fair, and 57.1% poor outcomes. There were 7 revisions in 5 patients (revision rate 3.3%). There was one male and 4 female patients. All patients were right-handed. Right side was revised in 3 cases and left side in 4. In this cohort, after primary trapeziectomy, the average subsidence was 76.7±24.0% (range 33.1%-100%). In 4 cases, the trapezial space increased after revision surgery (subsidence decreased from 72.0±28.0% to 56.9±0.1% after revision); in 1 case the subsidence increased (from 59.2% to 70.2%). One hundred percent subsidence persisted in 2 cases. Three patients had good outcomes, 1 fair, and 3 poor outcomes based on Connolly-Rath scores after revision.

Conclusions: Post-trapeziectomy, pain scores improved significantly in patients with both high and low subsidence. While all patients subside after surgery, it is rare that subsidence is symptomatic and requires revision.

Purpose: Major amputations of the lower extremity, specifically through and below the knee, are morbid procedures requiring general anesthesia typically followed by high doses of postoperative opioids. Many are performed on highly comorbid, chronic wound patients with a potential for increased opioid use following surgery. Given the current opioid epidemic, perioperative narcotic-reduction strategies are paramount. Our center instituted a protocol for major amputations that includes continuous regional anesthesia, for intraoperative and postoperative pain control, and targeted muscle reinnervation (TMR) nerve transfers to mitigate long-term pain. The aim of this study was to analyze the impact of continuous regional anesthesia and TMR on early postoperative opioid requirements after major lower extremity amputation at our limb salvage center.

Methods: We retrospectively reviewed our center’s below-knee and through-knee-amputations from 2017-2019 for utilization of regional pain catheters and TMR nerve transfers. Opioid usage as morphine milligram equivalents (MMEs) was tracked for the first seven postoperative days. Baseline opioid dose was defined by the documented opioid use one day before amputation. Patients were categorized into one of four groups, based on whether regional pain catheter and/or TMR were used. Kruskal-Wallis testing was used to assess baseline opioid use between groups. Bivariate linear regression was used to assess postoperative opioid use of each group compared to the control group. Logistic regression analysis was conducted to examine association between TMR and changes in opioid use postoperatively versus baseline.

Results: 198 patients were reviewed. 95 patients received perioperative regional anesthesia, of which 81 underwent TMR. 103 patients did not receive regional anesthesia, of which 30 underwent TMR. Average baseline opioid use was 40.6 MME in patients treated with TMR and regional anesthesia, 60.2 MME with TMR and without regional anesthesia, 28.7 MME without TMR and with regional anesthesia, and 132.6 MME without TMR and regional anesthesia (p=0.0004). Multivariate analysis showed that undergoing TMR, without regional anesthesia, significantly decreased postoperative opioid use by 111.7 MME, compared to the control group (p=0.006). Use of regional anesthesia, with TMR, provided an additive effect, significantly decreasing postoperative opioid use by 124.3 MME, compared to control (p<0.0001). Interestingly, regional anesthesia without TMR decreased postoperative opioid use by 93.4 MME, but without significance (p=0.08).