The Effect of Sensory Denervation on Fracture Healing
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Introduction: In orthopaedic trauma care, it has long been observed that fractures associated with a peripheral nerve injury lead to impaired fracture healing. This study investigates the relationship between a pure sensory nerve denervation and healing of a standardized femur fracture. Although it is unclear exactly how nerves interact with bone growth and repair, some clinical observations and genetic diseases point to possible neuro-osseous interactions. Fractures associated with a concomitant head injury have higher non-union rates and a higher incidence of heterotrophic ossification. Serum from rats with a CNS injury has been shown to be mitogenic to mesenchymal stem cells in vitro[1]. Congenital insensitivity to pain with anhidrosis (CIPA) is a rare genetic disorder characterized by insensitivity to pain and autonomic instability. This disease is caused by a mutation in gene encoding the high-affinity nerve growth factor (NGF) receptor, tyrosine receptor kinase A (trka). In addition to the multiple neurological deficits, these patients demonstrate slow fracture healing, and are prone to bone abnormalities such as scoliosis and atypical slipped capital femoral epiphysis[2]. Although there is some evidence for this neuro-osseous interaction, it is poorly understood. The purpose of this study was to examine the effect of selective sensory denervation on fracture healing.

Materials and Methods: Skeletally mature adult male Lewis rats were used. The rats, aged approximately 16 weeks and weighing 300g were assigned to one of two groups. Group 1, the experimental group (n=28), received a capsaicin injection adjacent to the anterior and posterior femur 7 days prior to intramedullary rod insertion and fracture. Capsaicin is a highly selective neurotoxin and destroys the sensory unmyelinated C fibers[3]. Group 2, the control group (n=28), did not receive capsaicin injections. All animals underwent intramedullary rod placement and fracture with a well-established fracture model[4]. Four time points: 3 days, 7 days, 14 days, and 6 weeks after intramedullary rod insertion and fracture were studied in each group. These time points were chosen to look at the early inflammatory phase, the endochondral ossification phase and the late remodeling phase of bone healing, respectively. Real Time Polymerase Chain Reaction (RT-PCR) was performed for the 3, 7, and 14 day groups for gene expression of TrkA, ERG-1, TGF-β1, BMP-2, BMP-4 and BMP-7. Micro CT was performed on live animals 5 weeks after fracture. Biomechanical testing using a previously described three point bending technique[5] was performed for the 6 week groups.

Results: Three dimensional reconstructions of micro CT data were reviewed by a blinded orthopedic surgeon and a significant difference was found between experimental and control groups. Examples are included (Images 1 and 2). Maximal cross-sectional area and relative density for each fracture callus in the control and sensory denervated groups were computed as was an equivalent cross-sectional area and density in uninjured femurs for comparison purposes (Figures 1 and 2). An apparent difference was observed with both measures. Further results from RT-PCR, biomechanical testing, and quantification of micro CT data will be presented.

Discussion: These preliminary results demonstrate the deleterious effect of sensory denervation on fracture healing. This is a step toward a deeper understanding of the numerous factors that influence fracture healing and will add to an important body of knowledge. We expect further data to show specific genes that are affected by the sensory denervation leading to further research and possible treatments. It is possible that genes such as Trka, ERG-1, TGF-β1, BMP-2, BMP-4 and BMP-7 affect fracture healing and are affected by sensory innervation or lack thereof. This information is especially important for diabetics and other patients with impaired sensory nerve function. It also lends further evidence of the importance of preserving sensory nerve function during surgery.

References

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