GDNF-Blended Chitosan Nerve Guides Promote Both Motor and Sensory Regeneration

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Statement of Purpose: Insufficient expression of neurotrophic factors at the injury site is known to be a causative factor in deterring complete peripheral nerve regeneration. Glial cell line-derived neurotrophic factor (GDNF) has been shown to be a potent trophic factor for both motor and sensory neurons. GDNF has also been shown to play a major role in enhancing nerve re-myelination and repair after nerve injury. Previously, we have demonstrated an increase in functional recovery by utilizing unblended chitosan nerve guides to bridge severed peripheral nerves. For this study, chitosan nerve guides blended with GDNF and laminin were investigated for use in a completely transected peripheral nerve injury, with both functional and sensory recovery assessment.

Methods: Chitosan nerve guides were fabricated using previously published methods.(1) Addition of 2μg/ μm^2 GDNF and laminin were blended within the 2% chitosan solution. Rat groups (n=18 per group) included, chitosan/laminin/GDNF (G), chitosan/laminin (L), autograft (A) and resection (U), were sacrificed at 6, 9 and 12 weeks. Functional testing via video gait analysis occurred weekly and behavioral assessment via von Frey sensitivity testing occurred at the 12 week time point. At sacrifice, nerve guides were extracted for histological analysis and Gastrocnemius muscle weight was measured.

Results and Discussion: The addition of GDNF within the chitosan nerve guides promoted both functional and sensory recovery. The GLC group showed an increase in functional improvement when compared to the unblended chitosan nerve guides, which was significantly higher at the terminal stance phase angle as compared to the unblended chitosan nerve guides. In normal rats, the terminal stance phase has a maximum angle value, but after sciatic nerve injury the terminal stance angle value decreases significantly. As recovery occurs the angle value increases significantly over time. This causes the ipsilateral foot to improve its shock absorbing properties while the body weight is transferred from the ipsilateral foot to the ipsilateral toe. In our study, GLC angle values increases considerably from the 2^{nd} to the 12^{th} week indicating increased muscle strength. Muscle weights for the GLC group indicated decreased atrophy and restoration of functional strength, compared to the unblended chitosan group. After six weeks, the muscle weight values had a significant correlation between the terminal stance angle values for both GLC and LC groups ($r = 0.986$, $p = 0.0001$ and $r = 920$, $p = 0.009$). A significant correlation was not seen for the C, A and U groups. During behavioral testing, GLC group promoted sensory nerve regeneration as sensory perception was comparable to pre-surgery threshold levels. Additionally, the results indicated that sensory assessment of GLC was not significantly different from its contralateral non-surgical leg, while CL, U and A were all significantly less sensitive as compared to their contralateral leg. As axonal connections are re-established sensory nerve regeneration increases and decreased resistance to applied force is displayed. Thus, this typical increased sensitivity was not seen for the LC, C and U groups even after 12 weeks, indicating decreased axonal connections. However, for the GLC group at 12 weeks, a decreased resistance to applied stimuli and increased sensitivity was observed. This indicates that axonal connections were re-established through the nerve guide leading to an increase in muscle strength and sensory nerve regeneration.

Figure 1. Assessment of Video Gait Analysis at 8 Weeks. (N=Normal Rat Angle).

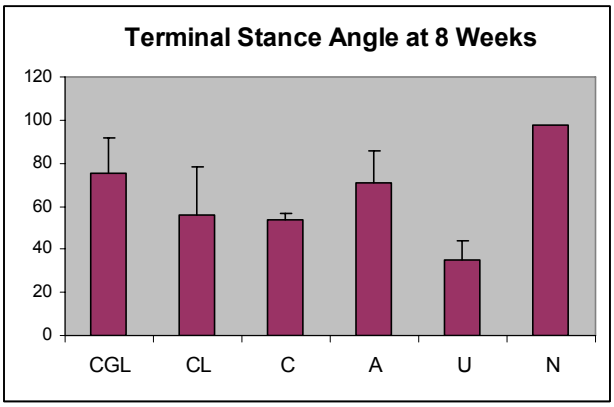
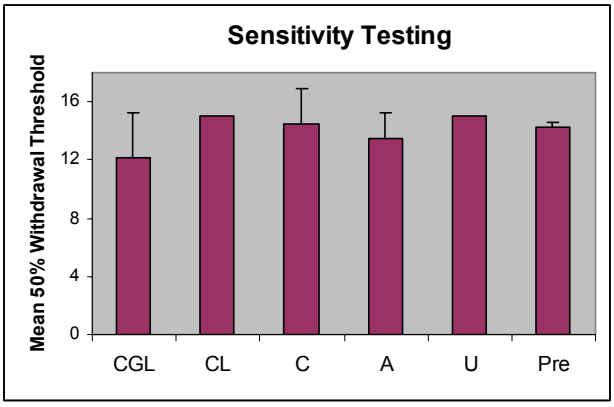


Figure 2. Animal Sensitivity at 12 Weeks via Von Frey Testing. (Pre = Pre-Surgery Threshold)



Conclusions: Thus, this study demonstrates that GDNF-blended chitosan nerve guides promotes both motor and sensory regeneration, displaying that GDNF is a powerful neurotrophic factor. However, optimal release needs to be further investigated to improve regeneration to pre-injury levels.

Reference: (1) Patel et al, Tissue Eng 12: 2006.