Effect of Topical Opioid Antagonist on Diabetic Wound Healing in Rat Model

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Introduction/Purpose: Approximately 50% of the 170 million people worldwide with diabetes experience complications associated with delayed cutaneous wound healing. The current widely used treatment for DFU is topical platelet-derived growth factor (PDGF); however, it has significant side-effects. Preclinical studies have shown that a small molecular weight opioid receptor antagonist, blocks the interactions between the growth inhibitory peptide Opioid Growth Factor (OGF) and its receptor OGFr and accelerates cell proliferation and enhances angiogenesis and wound closure. The hypothesis of this research is that the topical formulation of opioid receptor antagonist is an effective therapy for healing of cutaneous wounds in diabetic rats, with healing times comparable to the standard care and will promote enhanced cell replication and accelerated angiogenesis.

Methods: Fourteen diabetic rats per group with four excisional cutaneous wounds were positioned dorsally on type 1 diabetic rats and randomly treated topically with an opioid receptor antagonist (0.03% Naltrexone), topical platelet derived growth factor (Regranex®), or placebo moisturizing cream alone. Wound closure, DNA synthesis (bromodeoxyuridine incorporation-BrdU labeling), and production of the cytokines PDGF and vascular endothelial growth factor (VEGF) were monitored.

Results: Naltrexone and Regranex® treatment resulted in more than 65% closure on days 8 and 10 respectively. On day 12, only one Naltrexone- and two Regranex-treated wounds remained (~1%), whereas the control group had 50% visible wounds. DNA synthesis in Regranex® treated wounds was 21% in comparison to vehicle-treated wounds at 28%; Naltrexone-treated diabetic wounds had 42% BrdU labeling comparable to the normal vehicle treated wounds. Naltrexone treatment significantly increased cell replication in comparison to Regranex treatment and to vehicle-only treated wounds (p<0.001). Tissue immunostained at 1, 2, and 4 days after surgery with anti-PDGF antibodies indicated that both Regranex® and Naltrexone increase PDGF+ labeling at 1 day, with Naltrexone treatment (but not Regranex®) continuing to enhance PDGF production at 4 days

Conclusion: Topical opioid receptor antagonist has been shown to enhance wound healing by increasing cell replication, accelerating angiogenesis, and matrix formation and targets an underlying pathophysiology of diabetes and enhances cell replication at all stages of wound remodeling. Topical opioid receptor antagonist is safe and effectively targets the disease-modifying pathways in this comparison study of topical platelet derived growth factor for wound closure in Type 1 diabetic rats. These data suggest that blockade of the OGF-OGFr axis, utilizing 0.03% Naltrexone is a safe and effective alternative for treatment for diabetic wounds by targeting several phases of wound repair

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