Activation of a Central Immunosuppressive Cascade Prevents Ischemia Reperfusion Injury After Acute Compartment Syndrome in a Murine Model

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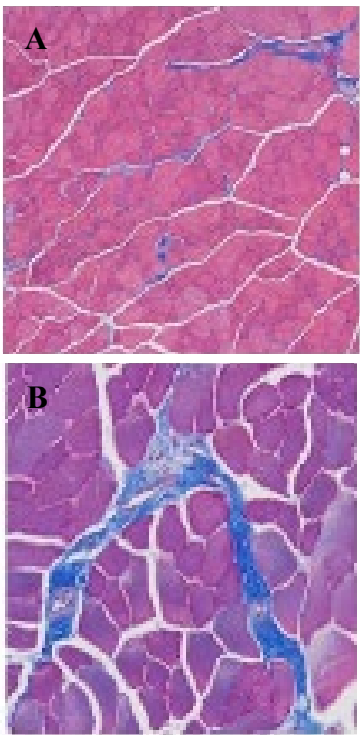
Purpose: Occurring when interstitial pressure exceeds perfusion pressure, acute compartment syndrome (ACS) results in warm ischemia and cell death due to impaired aerobic metabolism. Following surgical decompression and reperfusion of the extremity, there is a robust innate inflammatory response that results in further tissue injury due to the production of reactive oxygen species and local capillary dysfunction. In addition to prompt diagnosis and reperfusion of the compartment, therapies which limit the secondary ischemia reperfusion injury (IRI) may be helpful to improve outcomes in patients with ACS. Varenicline (Chantix™) activates a novel immunosuppressive cascade and is effective at reducing IRI in following testicular torsion and pyelonephritis. We hypothesized that varenicline administration would reduce IRI following a compartment syndrome model in a mouse.

Methods: Using an established model, warm hindlimb ischemia was induced in mature CD-1 mice by placing an orthodontic rubber band around the hindlimb for 90 minutes. In the treatment group, varenicline (1µg/gram) was administered as an intraperitoneal injection 60 minutes after the onset of ischemia. The degree of acute inflammation was quantified using Fluorescent Activated Cell Sorting, 24 hours following reperfusion. The expression of pro-fibrotic genes in the gastrocnemius muscle were evaluated 7 days following reperfusion and histologic evaluation of fibrosis with trichrome staining was performed 14 days following reperfusion of the limb.



Trichrome staining of muscle fibers 14 days following limb ischemia in animals treated with varenicline (A), N=10 and untreated controls (B), N=10 demonstrated a significant decrease in collagen deposition in animals treated with varenicline, P≤0.005.

Results: Treatment with varenicline reduced the acute leukocyte infiltrate 24 hours after reperfusion (3.08% vs 0.86%, P≤0.01, n=16). Treatment with varenicline reduced the expression of the pro-fibrotic genes (measured in relative expression) (Collagen1a1 (1.73 vs. 0.31), Collagen1a3 (1.85 vs. 0.42), Vimentin (2.11 vs 0.38) and Actin (1.82 vs. 0.56) P≤0.05, n=16 7 days following reperfusion. Histologic evidence of collagen deposition was also significantly reduced (3.45% vs. 1.89%, P≤0.005, n=20) 14 days following reperfusion in animals treated with varenicline.

Conclusions: Varenicline administration reduces acute inflammation and long-term fibrosis of the gastrocnemius muscle following warm hindlimb ischemia in a mouse.

Significance: Varenicline represents a potentially novel FDA approved adjunct to the current management of acute compartment syndrome and extremity ischemia. Administration of this medication appears to have the potential to mitigate post-injury inflammation and fibrosis which may lead to improved functional outcomes following this condition. Further studies are needed to define the optimal dosing and administration regimens.