Δ Carbon Monoxide Releasing Molecule-3 (CORM-3) Protects the Skeletal Muscle in a Porcine Model of Compartment Syndrome

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Purpose: Acute limb compartment syndrome (CS), a devastating complication of musculoskeletal trauma, results in muscle necrosis and cell death. Fasciotomy, to decompress all affected compartments, remains the only gold standard treatment, but must be performed within a 6- to 8-hour surgical window. Recently, carbon monoxide (CO), liberated from the carbon monoxide releasing molecule-3 (CORM-3), has been shown to protect microvascular perfusion and reduce inflammation in a rat model of CS. The purpose of this study was to test the effect of CORM-3 in a preclinical setting, using a large animal model of CS (pig). The ultimate goal is the development of a rational pharmacologic adjunctive treatment for CS, capable of prolonging the surgical window, and reduce the morbidity and disability in patients.

Methods: Pigs were anesthetized with isoflurane, intubated, and had a femoral artery line put in for invasive cardiovascular monitoring/blood sampling. They underwent 6 hours of intracompartment pressure (ICP) elevation by infusing saline enriched with bovine serum albumin (0.4 g/L) into the anterior compartment of the right hind limb. CORM-3 (or its inactive counterpart, iCORM-3) was administered systemically (2 mg/kg, IV) at fasciotomy, and the muscle was allowed to reperfuse for 3 hours. Subseq[ently, tissue perfusion (orthogonal polarized spectral imaging), cellular injury (ethidium bromide [EB]/bisbenzimide [BB] staining ratio) and apoptosis (FLIVO/BB staining ratio) were assessed in the skeletal muscle of all pigs. In parallel, systemic polymorphonuclear leukocyte (PMN) activation (L-012 assay) was assessed at various time points during CS and reperfusion in all animals.

Results: Elevation of hind limb ICP for 6 hours resulted in significant microvascular perfusion deficits (44 ± 1% continuously perfused capillaries in CS vs 76 ± 4% in sham, $P < 0.001$; 39 ± 3% nonperfused capillaries in CS vs 13 ± 2% in sham, $P < 0.001$), increased tissue injury (EB/BB of 0.31 ± 0.07 in CS vs 0.17 ± 0.03 in sham, $P < 0.05$), apoptosis (FLIVO/BB of 0.26 ± 0.06 in CS vs 0.13 ± 0.03 in sham, $P < 0.05$), and activation of leukocytes in the systemic circulation (14.7 relative luminescence units/106 PMNs in CS vs 1.0 ± 0.1 in baseline, $P < 0.001$). Systemic application of CORM-3 (but not iCORM-3) at fasciotomy was able to increase the number of continuously perfused capillaries (68 ± 3%, $P < 0.001$), decrease the number of nonperfused capillaries (25 ± 3%, $P < 0.05$), diminish tissue injury (EB/BB of 0.13 ± 0.04, $P < 0.05$), apoptosis (FLIVO/BB of 0.12 ± 0.03, $P < 0.05$), and completely block the systemic leukocyte activation (3.9 ± 0.3 relative luminescence units/106 PMNs, $P < 0.001$).

Conclusion: Administration of CORM-3 at fasciotomy offered protection against CS-induced microvascular perfusion deficit, tissue injury, and systemic leukocyte activation. The data suggest the potential therapeutic application of CORM-3 to patients at risk of developing CS.

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See pages 47 - 108 for financial disclosure information.