Paper - Basic Science

Paper Session: Polytrauma

Possible Therapeutic Application of CORM-3-Derived Carbon Monoxide in Acute Limb Compartment Syndrome

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Purpose: Acute limb compartment syndrome (CS), a potentially devastating complication of musculoskeletal trauma, results in muscle necrosis and cell death. Ischemia and inflammation both appear as contributing factors leading to microvascular dysfunction and parenchymal injury. Currently, surgical fasciotomy to decompress the muscles and restore perfusion remains the only treatment. Systemic application of carbon-monoxide-releasing molecule-3 (CORM-3) in animal models of CS has shown benefits when given in conjunction with open fasciotomy; however, CORM-3 without fasciotomy has never been tested. The objective of this study was to assess the effects of CORM-3 in CS without surgical intervention and to identify whether CORM-3 could extend the surgical window after its administration. The ultimate goal is the development of a pharmacologic treatment for CS.

Methods: 28 male adult Wistar rats were randomly assigned into 3 groups: sham (no CS, n = 6), CS (with inactive CORM-3, iCORM-3, n = 12), and CS+CORM-3 (10 mg/kg IV, n = 12). CS was induced by elevation of intracompartmental pressure (ICP) to Δp between diastolic blood pressure and ICP of <20 mm Hg through an infusion of isotonic saline into the anterior compartment of the hind limb, maintained for 2 hours. CORM-3 or iCORM-3 was then injected and animals were allowed to recover from anesthesia. Microvascular perfusion (% continuously perfused, intermittently perfused, and non-perfused capillaries), cellular injury (ethidium bromide:bisbenzimide staining [EB/BB]), and inflammatory response (adherent and rolling leukocytes in venules) within the extensor digitorum longus muscle (EDL) were assessed using intravital video microscopy (IVVM) at 24, 48, and 72 hours following injection. Data were analysed using 2-way analysis of variance.

Results: Elevation of ICP resulted in significant microvascular perfusion deficits at 24, 48, and 72 hours post-CS (39 ± 5%, 44 ± 10%, 35 ± 4% continuously perfused capillaries, respectively, vs 79 ± 9% in sham; 35 ± 5%, 29 ± 7%, 35 ± 4% non-perfused capillaries, respectively, vs 11 ± 3% in sham, P <0.001), increased tissue injury (EB/BB of 0.31 ± 0.08, 0.41 ± 0.08, 0.40 ± 0.10 ,respectively, vs 0.03±0.01 in sham, P <0.001), and adherent leukocytes (6 ± 1, 8 ± 2, 7 ± 1 respectively, vs 1 ± 0 in sham, P <0.001). CORM-3 restored the number of continuously perfused capillaries at all time points (24, 48, and 72 hours) post-CS (57 ± 3%, 61 ± 2%, 52 ± 7%, respectively, P <0.01), reduced tissue injury (EB/BB of 0.15 ± 0.04, 0.17 ± 0.04, 0.20 ± 0.04, respectively, P <0.001), and diminished leukocyte adhesion (2 ± 1, 1 ± 0, 3 ± 1, respectively, P <0.001).

Conclusion: Systemic application of CORM-3 without fasciotomy demonstrated improvement in microvascular perfusion, reduced tissue injury, and diminished leukocyte activation at different time points, indicating its potential in prolonging the surgical window and its use as a nonsurgical pharmacologic treatment for CS.