2010 MSG Abstract

SAFETY AND FEASIBILITY OF TRANSVENOUS LIMB PERFUSION WITH SALINE IN HUMAN MUSCULAR DYSTROPHY

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INTRODUCTION: High-pressure retrograde transvenous limb perfusion has been successfully used to deliver plasmid DNA and AAV-minidystrophin transgenes into skeletal muscle in experimental animals. Translating this promising technique to humans with muscular dystrophy requires addressing multiple safety and logistical aspects including analgesia, vascular access and substantially larger infusion volumes.

OBJECTIVES: To determine the safety profile of a dose escalation study of transvenous single limb perfusion with 0.9% saline in adults with Becker and Limb-Girdle muscular dystrophies.

METHODS: An 18 or 20 g intravenous catheter was inserted into the distal lesser saphenous vein. A Zimmer ATS 2000 single cuff tourniquet was placed just above the knee. Infusion of normal saline was carried out with a Belmont FMS 2000 Rapid Infuser. Infusion volume was escalated from 5% to 20% limb volume in sequential patients. Cardiac function was continuously monitored by echocardiography while observing for any intracardiac microcavitations indicative of saline leakage during the infusion. Anesthesia was provided with a combination of fentanyl, midazolam and propofol. The following parameters were monitored to determine safety: (1) systemic cardiovascular function (2) limb tissue compartmental pressures (3) limb tissue oximetry (4) Doppler ultrasonography for local venous and arterial damage (5) electrodiagnostic studies for local nerve damage (6) local muscle function (7) serum and urine muscle enzymes and (8) renal function.

RESULTS: To date, five subjects have been studied with written informed consent. Limb volume was determined by water immersion. No subject complained of any post procedure pain other than due to needle punctures. Safety warning boundaries were transiently exceeded only for tissue compartment pressures and limb tissue oximetry.

There was no evidence of nerve, muscle or vascular damage associated with the transient elevation of compartment pressures.

CONCLUSION: We have demonstrated that high-pressure retrograde transvenous limb perfusion with saline up to 20% of limb volume at these infusion parameters is safe and feasible. We will document the effectiveness of these infusion parameters to produce entry of fluid into muscle by T2 MRI. These studies will serve as a basis for future gene therapy clinical trials.

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