Intravenous Infusion of Keratose-based Fluid Produces NO-induced Arteriolar Vasodilation in Cremaster Muscle of Rats

Nunez, F; Trach, S; Van Dyke, M; Callahan, M; Smith, T

Wake Forest University Baptist Medical Center, Winston Salem, NC, Heidelberg University, Heidelberg, Germany, Wake Forest Institute of Regenerative Medicine, Winston Salem, NC

INTRODUCTION:
Many materials have been investigated as plasma expanders for the treatment of Hypovolemic Shock. Both synthetic (1, 2) and polymeric biologic materials (3, 4) have been considered, studied and brought to use in human subjects. None have proven to be more beneficial than another or as effective as whole blood in re-instating normal tissue oxygenation. Alpha-Keratose has recently been proposed as a possible substitute (see A. Widra U.S. patent # 6,746,836). Keratose can be formulated as a hyperviscous compound. High viscosity plasma potentiates the release of strong vasodilators through sheer stress on vascular walls (5). Keratose also possesses high osmotic pressure, which induces a net transport of water from the extravascular space into the vascular stream thus increasing circulating volume. The net effects are: peripheral vasodilation and increased cardiac contractility without causing tachycardia due to better venous return. All this translates into lower cardiac work and better tissue perfusion. Based on these theories we decided to test the null hypothesis that a Keratose-based fluid would not induce more arteriolar vasodilation than Hetastarch in saline solution.

METHODS:
A topload model was employed using a defined volume of resuscitation fluid (2.25ml/100g body weight) added to a euvoletic rat. Eleven rats received KRF; eleven rats received Hetastarch 6% in 0.9% sodium chloride solution; a control group of seven rats received the vehicle for KRF: phosphate buffered saline (PBS); and five rats received KRF after topical application of L-Nitro-Arginine Methyl Ether (L-NAME)(30mg/ml) in order to inhibit Nitric Oxide Synthase activity. A cremaster muscle microvascular preparation was used to measure the changes in diameter of arterioles 20µm to 65µm in size (Figure 1). Measurements were performed prior to infusion of the various fluids and at five-minute intervals up to thirty minutes after infusions were initiated.

RESULTS:
Two-way analysis of variance showed significant differences between the three treatment groups. Bonferroni’s multiple comparison tests performed post-hoc showed that KRF induced greater vasodilation than PBS, Hetastarch or the L-NAME primed group. Hetastarch did not show vasodilatatory effects greater than those obtained with PBS at any time-point (Figure 2).

DISCUSSION:
Toploaded KRF produces NO-induced vasodilation in the cremaster microvasculature. This effect is significantly higher when compared to equivalent infused volumes of Hetastarch or PBS. The use of KRF in a hemorrhage model could reduce cardiac work and improve contractility by decreasing peripheral vascular resistance and increasing venous return respectively. In addition, functional capillary density (FCD) is improved. FCD is considered a reliable index of tissue perfusion that has been highly correlated with survival in studies of severe hemorrhagic shock (6). Further studies utilizing simulated hemorrhage by volume depletion including measures of hemodynamic parameters are necessary.

REFERENCES: