PEGylated Carboxyhemoglobin (SANGUINATE®) Restores Blood Flow and Tissue Oxygenation in a Novel Rat Model of Acute Vaso-Occlusive Crisis

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OVERVIEW

Vaso-occlusive Crisis (VOC) is a complication of Sickle Cell Disease (SCD) that manifests as red blood cells sickle in response to low oxygen tension, acidosis, or dehydration and obstruct normal capillary flow. The immediate consequences of this reduced microvascular perfusion are hypoxia and ischemic injury with further organ-specific pathologies. Treatments include red blood cell transfusions, analgesic pain management, and breathing techniques to maximize oxygen delivery without inducing respiratory acidosis. PEGylated carboxyhemoglobin bovine (PEG-COHb; SANGUINATE®) has been previously shown to reverse sickling of SCD RBC in vitro by directed gas transfer to hypoxic RBC. A rat model was used to evaluate the capability of SANGUINATE® to restore cardiovascular rheology and tissue oxygenation (P$_\text{O}_2$) at sites distal to acute vaso-occlusions (VOC).

METHODS

Figure 1: (A) Microscopy setup. (B) 3-D printed thermostabilized platform. (C) Spinotrapezius muscle mounted to thermostable pedestal ready for intravitral microscopy. Palladium porphyrin (RO) oxygen probe typically applied and distributed into interstitium. (D) Phosphorescence quenching and intravitral microscopy. (E) Phosphorescence decay curve captured and fit to standard curve for translation to P$_\text{O}_2$. (F) Radiometer ABL90 FLEX for blood gas and chemistry analysis. (G) Systemic parameters collected via BIOPAC MP150 (real-time analysis). (H) Microvascular images (SX magnification) of VOC development. (H1), Baseline (H2) Post-ET.

RESULTS

Figure 3: Post-Treatment Survival

SANGUINATE® treated animals survived significantly longer than LRS or Sham (p<0.001 and 0.0003 respectively). LRS and Sham were not different from each other (p=0.7462).

Figure 4: Mean Arterial Pressure (MAP)

Continuous data were averaged every 60 s and plotted discretely for ease of visualization. Treatment with SANGUINATE® restored MAP to BL immediately; whereas LRS did not return to BL until 60 post infusion.

Figure 5: Peripheral Tissue Oxygenation

Skeletal muscle oxygenation dropped following ET in all groups and remained severely hypoxic until intervention.

Figure 6: Systemic Lactate

Lactate was assessed at BL, after exchange transfusion, and at the end of the experiment, which was after 4 hours of observation, or before death. Two-way ANOVA showed lower lactate levels for SANGUINATE-treated animals by the end of the experiment.

CONCLUSIONS

• A rat model of SCD VOC was successfully implemented using an exchange transfusion protocol with human donor HBSS red blood cells
• SANGUINATE® significantly increased survival times versus LRS and Sham groups
• SANGUINATE® improved microvascular perfusion as indicated by both visual inspection and measurements of tissue oxygenation
• Systemic consequences of VOC - lactate and hypotension - were also improved by treatment with SANGUINATE®

AKNOWLEDGMENTS

This study was funded by Prolong Pharmaceuticals, LLC. Prolong Pharmaceuticals, LLC, also provided SANGUINATE® while all other reagents were commercially sourced.

We are thankful for other logistical and technical support that Prolong graciously provided.