44491 - HRC 101 IMPROVES SURVIVAL DURING HYPOXIA IN SAD MICE

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INTRODUCTION: Red cell transfusion decreases morbidity in sickle cell disease (SCD), but is not without risk. Utilization of a hemoglobin-based oxygen carrier (HBOC) could offer the benefits of red cell transfusion while reducing transfusion-related complications. We studied the effect of a novel HBOC, HRC 101, on survival during acute hypoxia in a murine model of SCD, the transgenic mouse expressing hemoglobin SAD.

METHODS: After approval from the Animal Care Committee, 66 pathogen-free wild-type (n = 30) and transgenic SAD mice (n = 36) aged 6 - 13 weeks and weighing 17 - 31g were assigned at random to receive 0.02 ml/g body weight HRC 101 or an equal volume of 5% albumin administered via a 26-G catheter over 2 min into a tail vein. Following fluid administration, the animals were placed in a custom built Plexiglas chamber and observed for 20 min while breathing room air. Anesthesia was induced with halothane in 30% oxygen using a calibrated vaporizer and a continuous fresh gas flow rate of 5 l/min. Lead II of the electrocardiogram was monitored using needle electrodes and data acquisition software (AcqKnowledge version 3, MP100 Work Station, Harvard Apparatus). During halothane anesthesia (0.5% inspired concentration) and spontaneous ventilation, either 30% or 6% oxygen was administered. Heart rate, inspired concentrations of oxygen and halothane, and rectal temperature were recorded every 5 min. Time to cessation of cardiac electrical activity was recorded. At the time of death (cessation of cardiac electrical activity) or at the end of 1 h, blood was sampled via cardiac puncture for determination of blood gases and lactate concentration. Kaplan-Meier analysis with the log-rank test was used to compare survival rates. Two-way repeated measures or one-way ANOVA and the Student-Newman-Keuls post hoc test were used for statistical comparisons as appropriate. $P < 0.05$ was considered significant.

RESULTS: In control groups, all mice survived the 60-min study period, whether breathing 30% or 6% oxygen. In contrast, all SAD mice administered albumin and 6% oxygen died, with a median survival time of 9.0 min (interquartile range, 6.9 - 11.6 min) ($P < 0.0001$).

Administration of HRC 101 significantly increased median survival time in SAD mice breathing 6% oxygen (figure). Of twelve SAD mice administered HRC 101 and 6% oxygen, four survived the entire study period and eight died, with a median survival time of 48 min (19 - 60 min) ($P < 0.0001$ vs. albumin).

DISCUSSION: Administration of the HRC 101 significantly increased survival during acute hypoxia in murine SCD. HRC 101's unique colloidal and other physical properties, including large molecular size, high p50, high oxygen carrying capacity, and near-blood viscosity could have contributed to the improved outcome of SAD animals. These data suggest that HRC 100 may be useful as a therapeutic modality in SCD.