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VS-101, a Next-Generation PEGylated HBOC is a Superior Low-Volume Resuscitation Fluid Compared to Whole Blood in a Severe Swine Hemorrhagic Shock Model

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INTRODUCTION

Trauma

Severe blood loss and ischemia are leading complications from traumatic injury in civilian and military settings.

Hemorrhagic Shock

- Low blood volume limits effective perfusion of organs and tissues
- Low oxygenation leads to hypoxia, blood toxicity, multi-organ failure
- Rapid treatment is critical

Resuscitation

- Field Damage Control Resuscitation protocols call for **low-volume** resuscitation
- Evacuation delays may limit treatment to a **single unit** before reaching definitive care
- Ideal resuscitation fluid is **non-inferior** to whole blood or components

VS-101, Hemoglobin-Based Oxygen Carrier (HBOC)

Formulation

- Human acellular hemoglobin (oxygen transport)
- Low concentration of hemoglobin (6 g/dL)
- PEGylation moieties (steric hindrance, reduced vasoactivity)
- High oncotic pressure to increase and maintain circulatory volume (improve perfusion)

Advantages for Field Use

- Shelf-stable
- Universally compatible (no cross typing)
- Low volume resuscitation
- Manufacturing process eliminates risk of viral transmission

METHODS AND MATERIALS

Experimental Protocol:

- **Animals:** Anesthetized Sinclair Nanopigs (male, 10 kg)
- **Hemorrhage:** Two-step (pressure targeted) hemorrhage protocol
  - **60% Total Blood Volume** (T_{BV})
  - Rates: 3.5 mL/kg/min until MAP of 40 mmHg
  - Rates: 2.0 mL/kg/min until volume of 60% T_{BV}
- **Shock Period:** 15 min, unrelieved
- **Resuscitation:** 20% T_{BV}
- **Observation Period:** Up to 5 hours

Measurement Time Points:

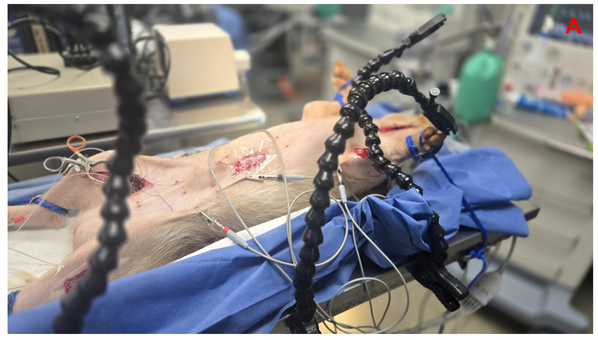
- Baseline (**BL**)
- End of Bleed (**EoB**)
- Prior to Resuscitation (**R**)
- Time point after resuscitation in minutes

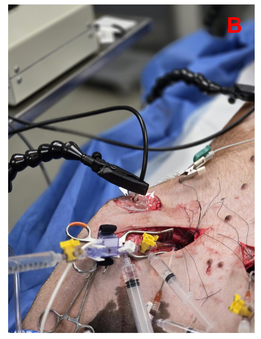
Study Groups:

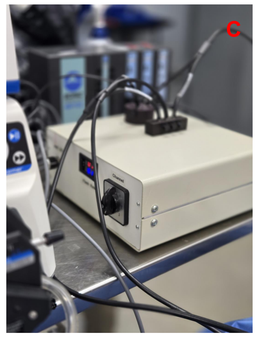
- VS-101 (Novel PEGylated HBOC); N = 7
- Blood (Fresh, autologous whole blood); N = 7

Catheters:

- Left femoral artery (hemorrhage)
- Left femoral vein (resuscitation)
- Right femoral artery
  - Blood sampling and continuous blood pressure / heart rate monitoring







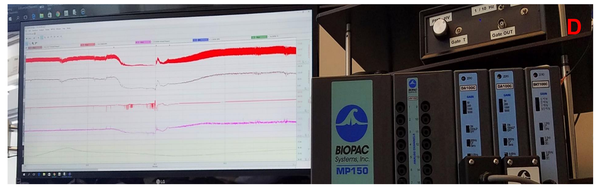


Figure 1: Measurements

- **A)** Anesthetized Sinclair Nanopig surgically instrumented
- **B)** Skeletal muscle window with dual lumen fiber optic for PQM
- **C)** Phosphorescence Quenching Multiplex setup containing fiber optic leads, photomultiplier tube, and data acquisition
- **D)** Continuous measurements of hemodynamics

SURVIVAL

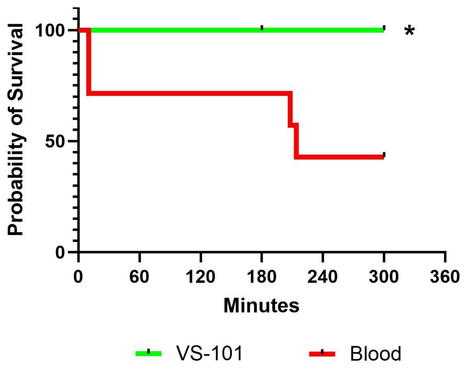


Figure 2: Survival

Survival duration was recorded from the end of resuscitation (0 min) until the earlier of demise or 300 min. VS-101 had a significantly higher survival rate than Blood (100 vs 43%). Two pilot VS-101 experiments (noted by a black dot) that followed the same protocol were ended at 180 min and included in the full study.

Data are mean ± SEM.
* P < 0.05 between groups

PERFUSION

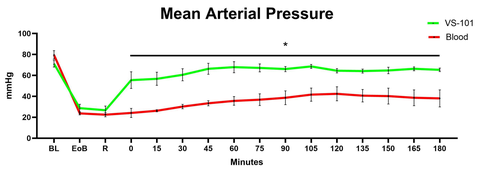


Figure 3: Mean Arterial Pressure

Hypovolemic resuscitation produced a stark and sustained contrast between groups. VS-101 rapidly returned and maintained MAP at baseline. Blood had a significantly lower effect, which was likely a critical factor in overall outcomes.

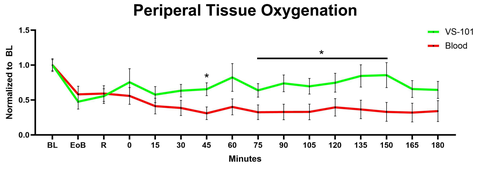
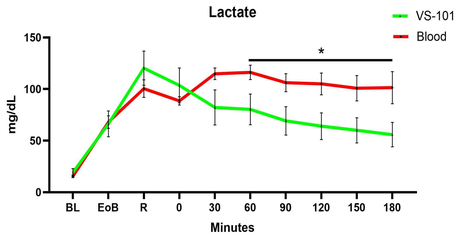


Figure 4: Peripheral Tissue Oxygenation

Three peripheral skeletal muscle sites (fore and hindlimb extensors and external oblique) were assessed for interstitial oxygen tension. Hemorrhage produced a consistent and sustained hypoxia in the peripheral capillary beds. Resuscitation resulted in a slow separation of groups with VS-101 showing positivity by 45 min. Overall, VS-101 showed greater peripheral oxygen delivery than Blood, however Blood still maintained a vital level of oxygen delivery as compared with historical results from administration of crystalloids.

METABOLIC



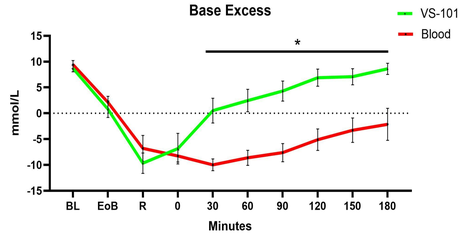


Figure 5: Metabolic Parameters

After resuscitation, lactate progressively decreased in VS-101 treated animals but not Blood-treated animals. Unit conversion between mg/dL to mmol/L or nM is 0.111 or 111,000, respectively. Base Excess indicates the degree of acid-base imbalance. A value below -2 mmol/L indicates metabolic acidosis, which is consistent with severe blood loss. Base excess returned to baseline in VS-101-treated animals, while Blood-treated animals remained acidotic.

IMMUNOLOGICAL

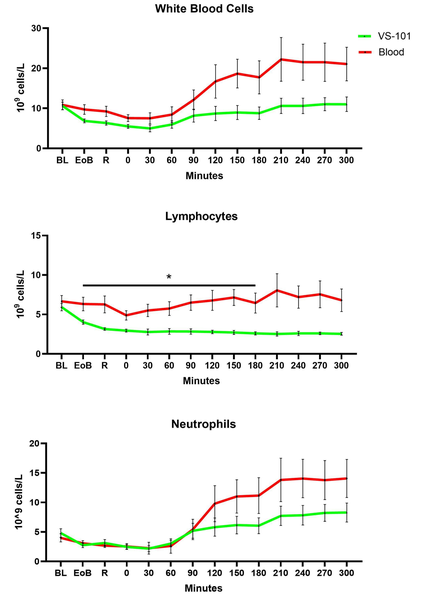


Figure 6: Immune Cells

The three-part CBC differential showed a reduction in overall immune cells for VS-101. Some of that may be dilutional since Blood was complete, but the neutrophil response, which is involved in ischemia/reperfusion injury, showed a latent rather than immediate separation between groups.

CONCLUSIONS

VS-101 vs Fresh Autologous Whole Blood

1. Improved survival
2. Improved peripheral tissue oxygenation
3. Restored blood pressure, no hypertension
4. Improved systemic aerobic respiration
5. No rise in inflammatory cells

Transient hemorrhagic shock model in Sinclair Nanopigs offers robust testing platform for Damage Control Resuscitation protocols.

Results encourage safety and toxicological testing to advance VS-101 into clinical phases.

Study results should be interpreted in the context of low volume resuscitation protocols only.

INSTITUTIONS

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