Development of a Field Stable IV Low-Volume Solution for Severe Hemorrhagic Shock Resuscitation.

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ABSTRACT

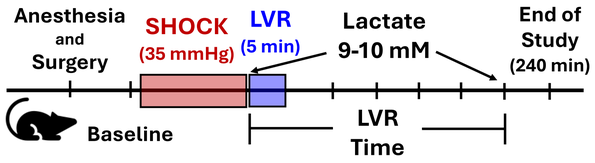
A new effective low volume resuscitation (LVR) IV solution was developed from customized cell impermeants. The best impermeants were polymers of **polyethylene glycol (PEG)**. The best polymer length of PEG was determined to be 20-35 kDa, because these sizes unequally distribute between the capillary and interstitial spaces (2:1 ratio). This unique biophysical property of the PEG IV solution rapidly moves water out of swollen ischemic cells and tissues back into the capillaries. In turn, this causes rapid oxygen transfer and repayment of oxygen debt after severe shock. Overall, PEG-20k IV solution restores blood pressure, drives down lactate, and significantly improves survival.

INTRODUCTION

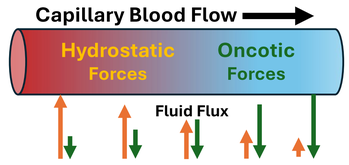
- Effective **field stable** artificial IV solutions are needed for pre-hospital hemorrhage and hemorrhagic shock (HS) resuscitation.
- Poor outcomes from acute shock are directly linked to **poor perfusion** and a dysfunctional micro-circulation (e.g. cell swelling, no reflow).
- **Impermeants** used in organ preservation solutions for transplant surgery improve tissue viability by targeting cell swelling.
- Since 2020, **Perfusion Medical, Inc**. has been developing a polyethylene glycol 20,000 Da ("**PEG-20k**") IV solution to treat hemorrhagic shock in civilians and military personnel.
- Now called "**PM-208**", this IV solution will enter Phase-I clinical trials in Q4-2025, and Phase-II trials in 2026. The specific polymer size and concentration in solution are key to its success.
- ***Goal**: To determine the optimal PEG size and concentration for treating hemorrhagic shock.*

METHODS

- **Hemorrhagic Shock (HS) Model:** Acute lethal controlled HS in adult male Sprague-Dawley rats.
  - *Anesthesia / Surgery*: 1-3% isoflurane with femoral venous and arterial catheters
  - *Shock*: intermittent arterial bleeding to MAP 35 mmHg until **lactate 9-10 mmol/L**
    - *Blood Loss: 50-60% total blood volume*
- **Low Volume Resuscitation (LVR):** IV solutions given over 5-10 min at 5-20% EBV (estimated blood volume). Survival ended when MAP < 30 mmHg or at the end of the acute study period (240 minutes).
- **Outcomes**: LVR time, survival, lactate, MAP, σ_d.



- **Oncotic Reflection Coefficient (σ_d)** = permeability of membrane to solute (*how effectively capillaries contain a substance, e.g. protein, impermeant)*
  - Colloid: $\sigma_d = 1$ (fully intravascular)
  - Crystalloid: $\sigma_d = 0$ (fully permeable)
- **Starling Equation:**
  - *Net fluid flux* = $K_f [(P_c - P_i) - \boldsymbol{\sigma_d} (\pi_p - \pi_g)]$



- **Rat Non-Shock Model: FITC-labeled PEG-20k** to measure the plasma to lymph ratio (n=6 rats).
  - Thoracic and Mesenteric duct cannulae
  - Induced lymph flow (0.25 ml/min) with saline
  - Measured FITC-PEG Ex-Em spectrofluorimetry

RESULTS

Figures: ***Effects of various crystalloid, impermeant, and colloid IV fluids on shock survival***

- Tx: ***GLU*** = 15% Gluconate, ***BSA*** *or* ***ALB*** = 10% Bovine Serum Albumin, ***HXT*** = 6% hetastarch, ***PEG*** = 10% PEG-20k
- Statistics: n=6-12 per group, *p<0.05 relative to other groups via One-Way ANOVA (Graph Pad Prism).

Fig 1: ***Crystalloid (Saline) vs. Impermeant (GLU, PEG) vs. Colloid (BSA)***

- IVFs given at 20% EBV, **PEG-20k + GLU** had superior LVR time, survival, & lactate.
- **PEG** (10% BV) vs. **PEG+GLU** (20% EBV). were indistinguishable, maxing out LVR time with return of lactate to baseline.
- **PEG** polymer was superior to **BSA** colloid.

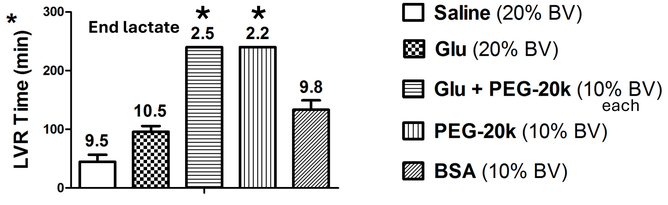
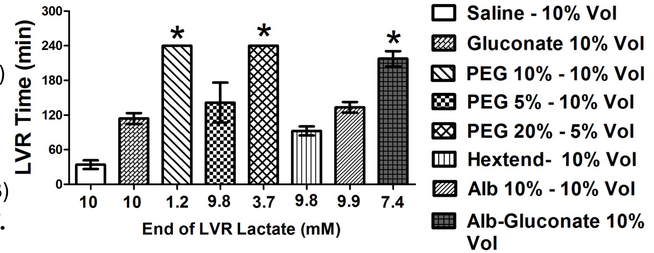


Fig 2: ***PEG-20k Dose Optimization vs. Crystalloid, Impermeant, and Colloids (ALB, HXT)***

- **10% PEG-20k** (at 10% EBV) was superior to all other groups with end lactate of 1.2
  - ***Became basis of lead IVF = "PM-208"***
- Doubling polymer concentration (20% PEG-20k) but giving half the volume (5% EBV) was next best, but terminal lactate was 3x higher (3.7).
- Half the polymer concentration (5% PEG-20k) was no different than colloid controls (HTX, ALB)
  - ***A critical volume and mass is required.***
- **ALB+GLU** did not reproduce 10% PEG-20k.



RESULTS

Fig 3: ***Osmotic Reflection Coefficient (σ_d)***

- **σ_d = ~0.5**, indicating a 2:1 distribution of **10% PEG at 10% EBV** (6.8 ml/kg) between the capillary and interstitial spaces.

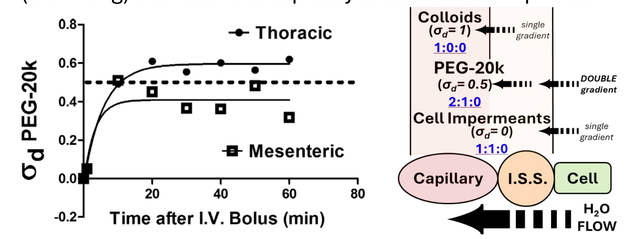
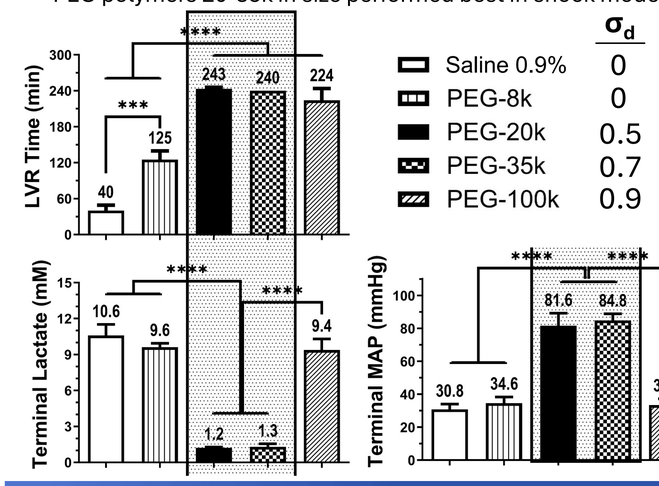


Fig 4: ***PEG Polymer Size Optimization***

- PEG polymers 20-35k in size performed best in shock model.



CONCLUSIONS

- **PEG polymers** between **20-35 kDa** performed best in this shock model at *10% concentration* and when given at *10% blood volume (6.8 ml/kg)*.
- The **mechanism of action (MOA)** is due to a unique reflection coefficient *(i.e. σ_d between 0 and 1)* that effectively pulls water from swollen ischemic tissues back into capillaries to directly increase blood flow, oxygen transfer, and tissue perfusion.

Acknowledgements

This study was funded by DOD MRMC grants W81XWH-12-1-0599 and W81XWH-16-2-0040 to Dr. Mangino. The VCU IACUC approved this study.