Reformulation and Dosing Options of the Anti-Shock IV Solution PM-208 for Optimal Field Portability.

†**Perfusion Medical, Inc**, Reston, VA and §**Virginia Commonwealth University**, Richmond, VA

Loren K. ***Liebrecht****, MD*§*, Derek* ***Lust****, BS*§*, Jade* ***Montano****, BS*§*, Michelle* ***Yoon****, BS*§*, Nancy* ***Lee***§*, Ihita* ***Bolisetty***§*, Iman* ***Abdous***§*, David* ***Park****, BS*§*, Lais* ***Morandini****, PhD*§*, Gerard* ***Eldering****, MBA*†*, Martin J.* ***Mangino****, PhD*§†

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ABSTRACT

Strategies to reduce (by 50%) the carry weight and volume of IV fluid (IVF) bags containing **PM-208** were tested. Reducing the volume of standard formulation PM-208 caused a dose dependent degradation of survival paired with terminal MAP and lactate. Increasing PEG polymer mass concentration ("C") in reduced volume doses improved survival, MAP, and lactate. The most effective strategy was to give two sequential standard formulation PM-208 doses at 50% volume up to 2 hours apart. This dosing scheme could be effective in military settings with use of a "buddy system".

INTRODUCTION

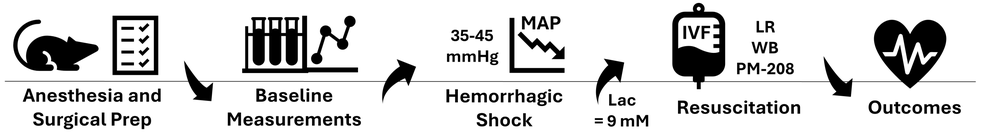
- Effective **field stable** artificial IV fluids are needed for pre-hospital hemorrhage and shock resuscitation.
- "**PM-208**" containing 10% PEG-20k (polyethylene glycol 20,000) is highly effective in preclinical swine survival studies as a bridge to whole blood and could serve as a force multiplier.
  - *Standard PM-208* = PM-100% (1X), given at 6.8 ml/kg single IV dose is ~500 ml volume for 73 kg person.
- ***Hypothesis****: Strategies to reduce IVF weight and volume while maintaining effectiveness will improve field utility.*

METHODS

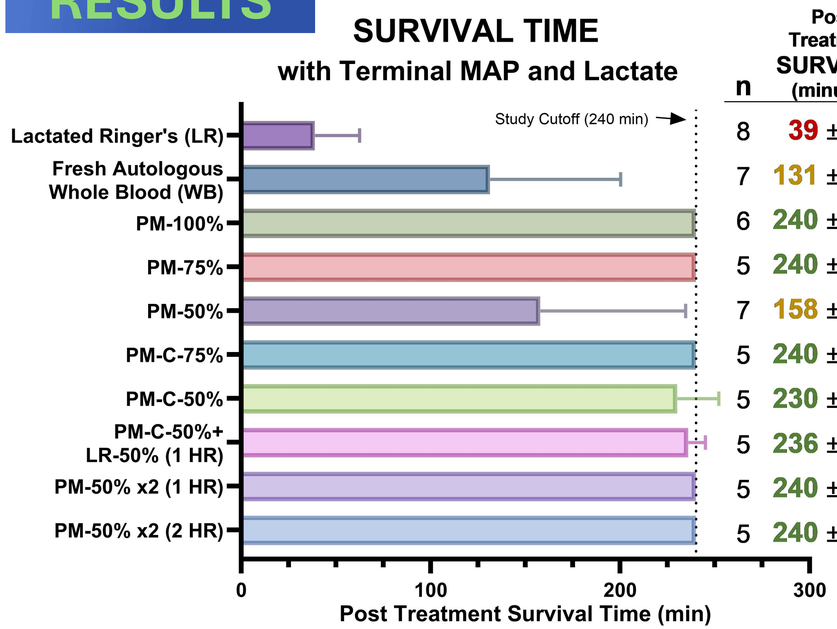
- Lethal acute controlled hemorrhagic shock studies were carried out in **adult male Sprague Dawley rats** (n = 5-8 / group).
- After anesthesia and surgery, **arterial** bleeding was continued until reaching **lactate 8.5-10.5 mM** (MAP 32-45 mmHg).
- Resuscitation with **3.4-6.8 ml/kg IVF** was completed over 5 min (one time dose) or 2.5 min (two split doses given 1-2 hrs apart).
- Survival ended when MAP (mean arterial pressure) was sustained at ≤ 30 mmHg.
- **Outcomes**: survival time (to 240 minutes), terminal lactate, terminal MAP.

Experimental Design: IVF and PM-208 Formulations

Treatment Group	Resuscitation Formulation	Volume (%)	Dose (ml / kg)	PEG Mass (µmol / kg)
LR: Lactated Ringer's	Negative Control and IVF Vehicle Control	100	6.8	0
WB: Whole Blood, Fresh	Positive Control and Gold Standard	100	6.8	0
PM-208:	***Experimental Dose / Concentration Variations:***	-	-	-
PM-100%	Standard PM-208 (**1X**) at **100%** dose	100	6.8	34
PM-75%	Standard PM-208 (**1X**) at **75%** dose	75	5.1	25.5
PM-50%	Standard PM-208 (**1X**) at **50%** dose	50	3.4	17
PM-C-75%	Concentrated PM-208 (**1.33X**) at **75%** dose	75	5.1	34
PM-C-50%	Concentrated PM-208 (**2X**) at **50%** dose	50	3.4	34
PM-C-50% + LR-50% (1-HR)	Concentrated PM-208 (**2X**) at **50%** dose + **50%** LR	50 / 50	3.4 / 3.4	34 / 0
PM-50% x2 (1-HR)	Std. PM-208 at **50%** dose x2, ONE hour apart	50 / 50	3.4 / 3.4	17 / 17
PM-50% x2 (2-HR)	Std. PM-208 at **50%** dose x2, TWO hours apart	50 / 50	3.4 / 3.4	17 / 17



RESULTS



	n	Post-Treatment SURVIVAL (minutes)	Terminal MAP (mmHg)	Terminal LACTATE (mM)
Lactated Ringer's (LR)	8	39 ± 24	30 ± 1	11.1 ± 3.2
Fresh Autologous Whole Blood (WB)	7	131 ± 69	36 ± 5	12.8 ± 3.5
PM-100%	6	240 ± 0 *†	86 ± 11 *†	3.5 ± 1.4 *†
PM-75%	5	240 ± 0 *†	72 ± 18 *†	4.7 ± 1.3 *†
PM-50%	7	158 ± 77	41 ± 19	10.3 ± 5.5
PM-C-75%	5	240 ± 0 *†	79 ± 15 *†	3.9 ± 1.5 *†
PM-C-50%	5	230 ± 22 *	61 ± 24 *†	5.0 ± 3.3 *†
PM-C-50%+ LR-50% (1 HR)	5	236 ± 9 *	68 ± 23 *†	4.9 ± 3.8 *†
PM-50% x2 (1 HR)	5	240 ± 0 *†	86 ± 9 *†	3.1 ± 1.2 *†
PM-50% x2 (2 HR)	5	240 ± 0 *†	88 ± 8 *†	1.8 ± 0.6 *†

*$p<0.05$ from LR, †$p<0.05$ from WB
(Survival = Kruskall-Wallis with Dunn's)
(MAP/Lactate = One-Way ANOVA with Holm-Sidak)

CONCLUSIONS

- **Volume dose reduction** of standard (1X) PM-208 100% to 75%, but not 50% volume, produced little degradation of resuscitation effectiveness in this severe shock model (48-52% average blood loss across groups).
- **Maintaining PEG-20k mass constant** (1X → 1.3X → 2X) while decreasing PM-208 dose volume (100% → 75% → 50%) improved performance of both concentrated PM-C groups compared to the unconcentrated counterparts, but did not surpass effectiveness of standard PM-208.
- Giving a 50% dose of LR (3.4 ml/kg) an hour after a 50% dose of 2X concentrated PM-208 does not improve performance relative to single PM-C-50% dose alone.
- **Administration of two standard PM-208 half-doses** (3.4 ml/kg) up to two hours apart does not result in any degradation of resuscitation outcomes compared to the PM-208 full dose (6.8 ml/kg) given once. This regimen could be considered for a field stable military "buddy system" to decrease IV bag carrying volumes to 250ml.

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