Development of ShockDefender against Prehospital Hemorrhagic Shock

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Introduction

- Hemorrhagic shock causes >90% of survivable prehospital trauma deaths in U.S. military casualties.
- PARP activation drives inflammation, endothelial dysfunction, vascular failure, organ dysfunction, and mortality. PARP-deficient mice exhibit longer survival, improved cardiac function and blood pressure, reduced cardiovascular damage, and decreased gut permeability.
- Approved PARP inhibitors such as Olaparib are oral-only and therefore unusable at the point of injury. An injectable formulation is required for prehospital use.

Objectives

- To develop an injectable Olaparib formulation for rapid on-site administration at the point of injury, which can be reconstituted in aqueous buffer at sufficiently high drug solubility.
- Determine the preferred injection route under hemorrhagic conditions.
- Demonstrate proof-of-concept efficacy of the injectable formulation in a swine model of controlled hemorrhage (~50% blood loss)

Methods

- Optimized complexation of Olaparib with Captisol to achieve 5 mg/mL aqueous solubility and developed a lyophilized powder for rapid reconstitution and long-term storage.
- Compared IV versus IM pharmacokinetics and organ distribution in a swine model of controlled hemorrhage (~50% blood loss).
- Evaluated survival, cardiac PARP activity, and metabolic markers (lactate, base excess) after IV administration at the completion of hemorrhage.

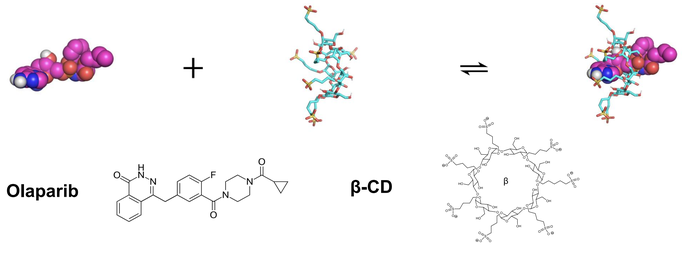


Fig. 1. The formation of inclusion complex between Olaparib and β-CD

Results and Discussion

1) Establishment of the Injectable Formulation

- Olaparib was complexed with β-CD to achieve 5 mg/mL solubility. The inclusion complex was lyophilized as a free-flowing powder that reconstitutes rapidly in aqueous buffer.
- Accelerated stability testing of the lyophilized powder showed only~2% loss after two months, supporting projected long-term stability of >3 years at ambient conditions (Fig. 2).

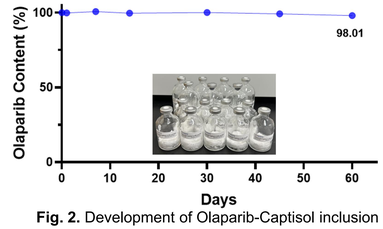


Fig. 2. Development of Olaparib-Captisol inclusion complex stored as powder.

2) Evaluation of PK and Biodistribution

- Under hemorrhagic conditions (~50% blood loss), IV administration produced plasma exposure comparable to normovolemic conditions, whereas IM absorption was markedly reduced (Fig. 3A, B)
- Heart concentrations peaked within 20 minutes and remained >100 ng/g at 2 hours (Fig. 3C). High levels were also reached in other organs within 30 minutes. These results support IV as the preferred emergency route.

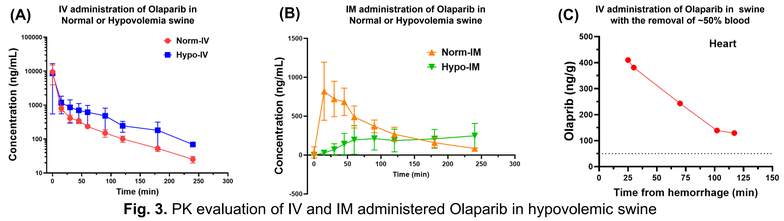


Fig. 3. PK evaluation of IV and IM administered Olaparib in hypovolemic swine

3) Demonstration of Enhanced Survival by PARP Inhibition

- Significant PARP inhibition in the heart was achieved by 10 minutes after IV dosing and was sustained for at least 120 minutes (Fig. 4),consistent with the observed tissue distribution.

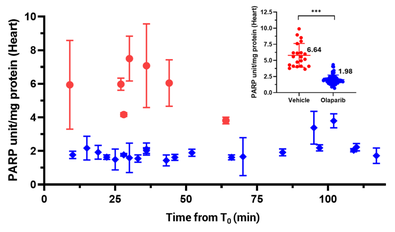


Fig. 4. PARP activity in the hearts of swine with controlled hemorrhage.

- IV Olaparib administered at the end of hemorrhage (T_0) significantly prolonged mean survival **from 34 minutes** (vehicle) **to 57 minutes** (Fig.5).
- Survival improvement was mainly observed in swine with plasma lactate <7.5 mmol/L at T_0 (Fig. 6A).

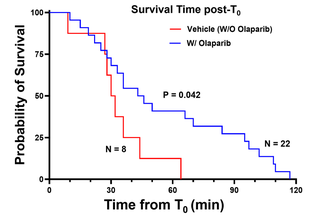
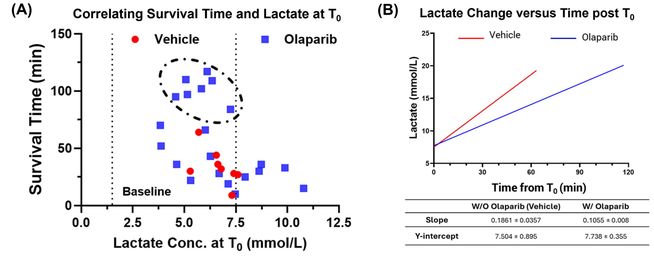


Fig. 5. Olaparib treatment extended the survival in swine with controlled hemorrhage.

- The rise in plasma lactate was attenuated by Olaparib (1.8-fold smaller lactate versus vehicle; Fig. 6 (B). A similar trend was observed for base excess.



	W/O Olaparib (Vehicle)	W/ Olaparib
Slope	0.1861 ± 0.0357	0.1055 ± 0.008
Y-intercept	7.504 ± 0.895	7.738 ± 0.355

Fig. 6. Olaparib treatment reduced the lactate level in swine with controlled hemorrhage.

Conclusions

- The injectable formulation of Olaparib (ShockDefender) is a promising candidate to extend the prehospital survival window for casualties with hemorrhagic shock.

Future Studies

- Combinational use with approved hemostasis agents to maximize benefit from improved cardiac function.
- Explore dual-use potential in acute cardioprotection and stroke.

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