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Evaluating the Effects of Aprotinin and Activated Protein C on Trauma-Induced Endotheliopathy (EoT) in a Rat Model of Polytrauma-Hemorrhage

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Introduction

Aprotinin (a serine protease inhibitor) and activated protein C (APC) both have effects that improve hemostasis, mitigate inflammation and provide cellular protection, however the results from the previous clinical trials are controversial.

This study reevaluated the effect of acute administration of aprotinin or APC during pre-hospital time frame on EoT using a rat model of polytrauma and hemorrhage (PTH).

Objective/Hypothesis

The objective of this study is to evaluate the outcome of acute administration of aprotinin or activated protein C (APC) in the rat model of polytrauma with hemorrhagic shock.

We hypothesize that acute administration of aprotinin or APC will mitigate the endotheliopathy of trauma (EoT).

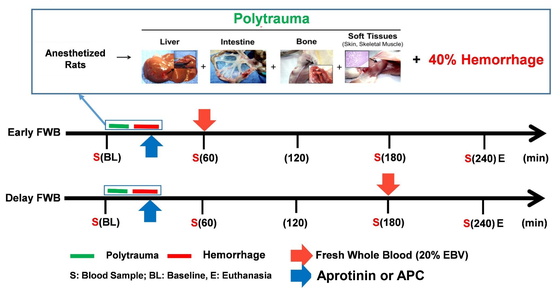
Methods

Isoflurane-anesthetized Sprague-Dawley rats were subjected to polytrauma, including multi-organ crush injuries and femur fracture, followed by a 40% hemorrhage.

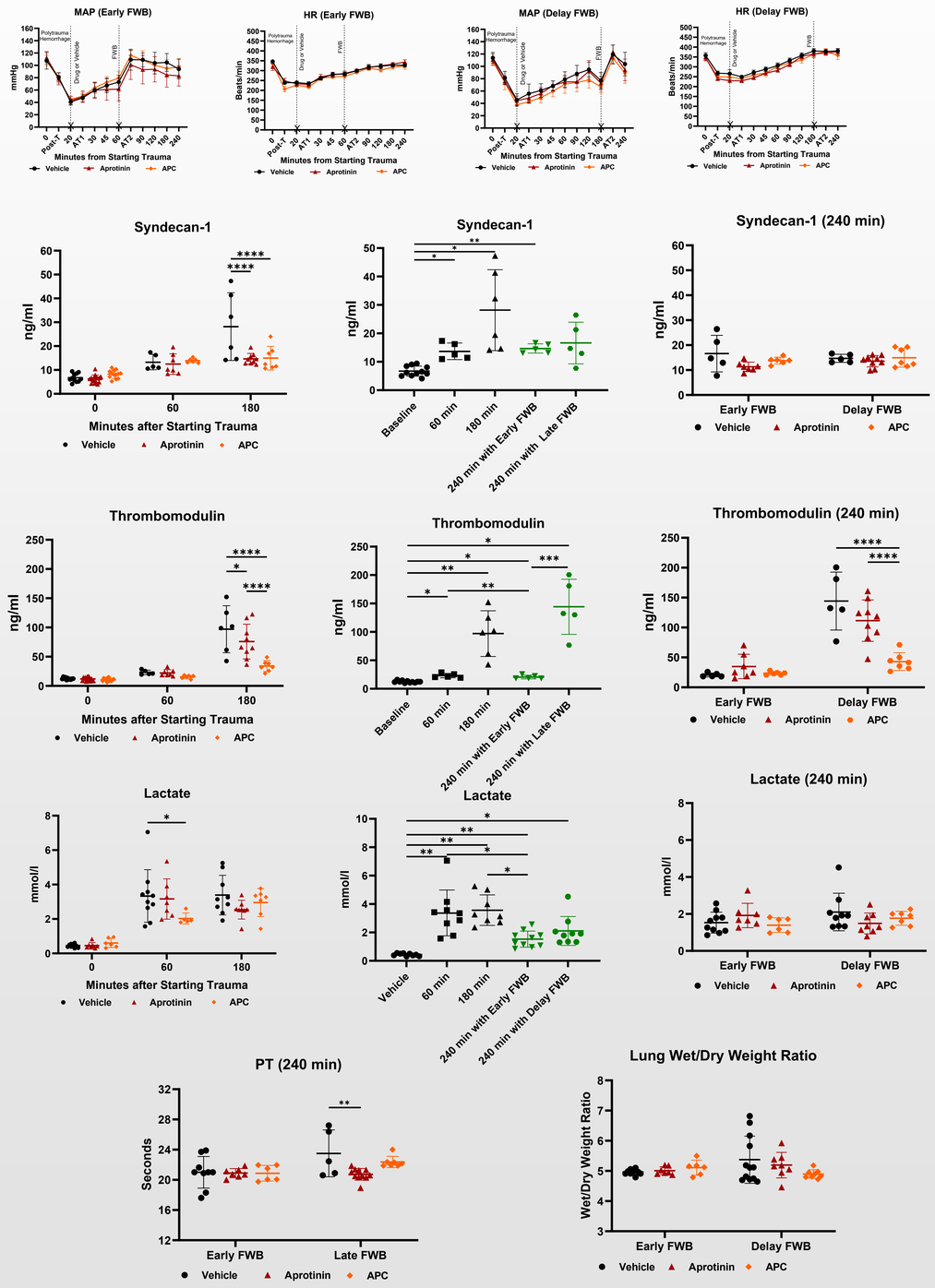
Twenty minutes after PTH, rats intravenously received either a vehicle (Veh), 5 mg/kg aprotinin, or 20 mg/kg human recombinant APC, followed by a limited volume of fresh whole blood resuscitation (FWB) at 1 or 3 hr postinjury.

Key EoT biomarkers, Syndecan-1 (SDC1) and thrombomodulin (TM), were measured by ELISA at baseline and 1, 3, or 4 hr after trauma. Primary outcomes also included lactate levels, hemodynamics, prothrombin time (PT), and lung wet/dry weight ratio (LWDR) to assess tissue edema.

Study Scheme



Results



Summary

Acute administration of either aprotinin or APC significantly attenuated the rise in EoT biomarkers at 3 h post-injury compared to the Veh group.

Notably, TM levels in the APC group were significantly lower than those in the aprotinin group. Although limited volume of FWB resuscitation at either 1 or 3 h post-injury stabilized SDC1 levels, TM levels continued to rise at 4 h in the Veh group with delay FWB. Both aprotinin and APC treatments significantly lowered TM levels at 4 h in these delayed resuscitation groups.

Furthermore, only APC treatment, not aprotinin, significantly reduced lactate at 1 hr compared to the Veh group.

At 4 h post-injury, PT was significantly shorter in the delay FWB resuscitation cohort of the aprotinin group compared to the Veh group, suggesting a superior hemostatic outcome associated with aprotinin treatment in this model.

Finally, there were no significant differences in hemodynamic changes, or lung wet-to-dry weight ratios among the various treatment groups.

Conclusion

The acute administration of either aprotinin or APC mitigates EoT in a rat model of polytrauma and hemorrhage, as indicated by a reduction in the shedding of key glycocalyx components.

Although this mitigation did not directly lead to a significant improvement in hemodynamics or a reduction in tissue edema following resuscitation, these findings suggest that both aprotinin and APC may be valuable adjunct therapies to attenuate EoT while maintaining a stable coagulation status. Future studies are warranted to optimize the dose and timing of treatment.

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Disclaimer: Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AALAC International.

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