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INVITED COMMENTARY

# We can Still Learn from a Negative Study

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## Introduction

There is a general lack of information regarding optimal methods to provide resuscitation in the setting of hemorrhagic shock and traumatic brain injury (TBI), especially as it relates to the cerebral response to contusion and decreased cerebral perfusion. Although there is some consensus regarding the concept of hypotensive resuscitation in hemorrhagic shock to prevent rebleeding from recently clotted vessels, the resuscitation fluid remains an area of active debate. Although some countries have ready access to colloids, such as blood, other countries, field hospitals in battle, or hospitals dealing with a mass casualty event may not always be fully resourced. This article aims to assess the strengths and weaknesses of this study [1] and how to evaluate a translational study and its applications to patient care. It is important for intensivists to be aware of the cerebral ramifications of resuscitation choice in patients with hemorrhagic shock and TBI.

## Summary

The hypothesis of this study is that terlipressin and low-dose crystalloid resuscitation is the optimal method to maintain cerebral perfusion pressure (CPP), cardiac index, and brain perfusion tissue oxygenation (PbtO2) in patients with hemorrhagic shock and TBI. Lactate and mixed veinous oxygenation were used as surrogates for effective end organ perfusion.

To test this hypothesis, the authors used a pig model of hemorrhagic shock and TBI. To simulate hemorrhagic shock, blood was withdrawn from the femoral artery at a rate of 50–70 ml/min to reach a mean arterial pressure of 40 mm Hg in 20 min, with the withdrawal being limited to 60% of the animal blood volume (8% of body weight). Correlating this to human shock, it is consistent with class IV shock, requiring immediate resuscitation due to end organ damage and hemodynamic instability. This class IV shock was maintained for 30 min.

Similarly, a severe TBI and an epidural "hemorrhage" were modeled via a fluid percussion piston, through a craniotomy, directly on to the dura at pressure of 4 atm. The epidural "hemorrhage" was approximated by inflating an epidural balloon with 5 ml of saline during the 20 min of hemorrhagic shock.

Importantly, both these models have been previously validated, so the rigor is established; however, this is the first time that these models have been performed simultaneously.

To test this hypothesis, the authors appropriately designed four experimental groups: a control group in which neither terlipressin nor saline was given, a saline-only group, a terlipressin-only group, and a terlipressin and saline group. In most animal studies, to assess whether the surgery itself is responsible for any component of the end points being studied, a sham group must also be done; that is, a group of pigs that receives a femoral cutdown with repair and craniotomy only. With large animal models, it is reasonable to assume that virtually none of the hemorrhagic shock is directly attributable to the femoral cutdown itself; and likewise, none of the TBI is due to the craniotomy alone. Large animals are expensive, and each of these animals was anesthetized in an operating room, intubated, ventilated, received vascular access, and underwent neurosurgery, which is very expensive and time-consuming. Having a sham group would have been better, but it is excusable.

With the hypothesis and aims to test the hypothesis decided, a power analysis must be completed to estimate the number of animals needed in each group. Sample size calculators exist, and in general using an $\alpha$ error of 0.025 is more conservative to allow for a negative difference between the tested groups. Here, it is reasonable

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that an $\alpha$ of 0.05 was used because one would generally expect the PbtO2 to be higher in the terlipressin group compared with the control group. A two-tailed $\alpha$ would have accounted for the PbtO2 being higher in the control group versus the terlipressin group and would have increased the sample size in each group. PbtO2 has been shown to be proportional to mean arterial pressure in most cases [2], and thus it is reasonable to use a one-tailed $\alpha$.

Next, the authors appropriately define their end points and the statistical methods used to determine significance. Here, using a generalized estimation equation is appropriate because all the independent variables change with time. Total anesthesia received and mean airway pressure should have been controlled for in the generalized estimation equation because these factors affect both cerebral and systemic hemodynamics. This is the biggest weakness in the study.

## Conclusions

The hypothesis, aims, and research strategy are well thought out and address a very complicated problem in a large animal model, more akin to human physiology. I applaud the authors for going to the lengths that they did to study resuscitation in a porcine model of hemorrhagic shock and TBI to evaluate permissive hypotension and what normotension does to cerebral hemodynamics. It is not surprising that CPP, and therefore PbtO2, cannot be recovered in the setting of active resuscitation for hemorrhagic shock due to increased intracranial pressure from severe TBI. Cerebral autoregulation is far from understood, especially in states of shock and TBI, but that should not stop us from trying to understand the process with studies such as this.

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