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EDITORIAL

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The clinical trials of diaspirin cross-linked hemoglobin (DCLHb) in severe traumatic hemorrhagic shock: the tale of two continents

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Drs. Kerner, Ahlers, Riou, Saunders and Pison are to be commended for their hemorrhagic shock work with the hemoglobin solution DCLHb, which is published in this volume of *Intensive Care Medicine* [1].

Severe traumatic hemorrhagic shock is known to be a cause of significant morbidity and mortality, despite optimal resuscitation efforts with crystalloids, colloids and blood [2]. Based on promising pre-clinical and early clinical data, DCLHb, a hemoglobin solution derived from human red blood cells, was tested in two companion hemorrhagic shock studies in the US and EU [3, 4, 5, 6, 7, 8]. These human efficacy studies were conducted in order to assess the effectiveness of DCLHb in improving outcome when used in addition to the standard resuscitation therapies that are provided in the pre-hospital (EU) and emergency department (US) settings.

In the US DCLHb hemorrhagic shock study, patients who were resuscitated with DCLHb had a higher mortality than did those who received standard therapy, leading to early study termination after only 98 (14%) of 850 planned patients had been enrolled [8]. Despite the absence of a clear adverse DCLHb effect in the EU study, enrollment was also halted prematurely after the enrollment of only 121 patients. This EU study showed that the median volume of cumulative blood product use was 57% lower after 24 h and 30% lower by 14 days in patients treated with DCLHb. However, like with the US DCLHb study, this study provided no evidence of a DCLHb benefit as measured by 5 and 28 day organ failure rates or mortality rates at 5 and 14 days.

Since the time of the publication of the US study results, several additional observations have been made regarding the conduct of these clinical trials. It is noteworthy that the US study was the first to be conducted using the new regulations allowing for an exception to informed consent in instances when it is not feasible to obtain prospective consent (FDA 21 CFR 50.24). The US consent strategy was similar to the approach taken in this EU study, in which consent to study participation was sought once the patient was enrolled in the study. In the US study, a consent exception was necessary for 94% of patients, and consent to continue was granted by 98% of patients or their families [9]. The occurrence of a negative result in the randomized US efficacy study confirmed that clinical equipoise did exist, a situation that was viewed as essential because a consent exception was used.

It was noted in the US study that although injury severity, as measured by ISS, was normally distributed, the mortality risk distribution was at the extremes of risk, such that there were fewer patients than expected who might have benefited most from this "add-on" therapy (those with a 40–60% mortality risk) [10]. A bimodal mortality risk distribution was also noted in this EU study and separately by Riou, who examined mortality risk using a European trauma patient database [11].

When considering inclusion criteria in these DCLHb studies, vital sign criteria, including a systolic blood pressure (SBP) below 90 mmHg, were deemed useful by most US investigators. The EU clinicians who participated in this study, however, repeatedly expressed the concern that vital signs were less useful clinical indicators in EU prehospital patients, since ambulance response times were extremely short, and most patients had not had a chance to develop a class III–IV hemorrhage and unstable vital

signs. Although this concern was addressed jointly by members of both investigator groups, hypotension continued to be used as an inclusion criterion because it was felt reliably to identify a uniform group of hemorrhagic shock patients. In retrospect, perhaps the use of hypotension was more relevant in the US study, where there was a 40% greater enrollment of patients who sustained penetrating trauma, a setting in which the occurrence of hypotension may be more consistently observed due to accelerated hemorrhage from a presumed vascular injury.

Although the interim results of the EU study would not necessarily have led to early termination of patient enrollment, the lack of efficacy in EU patients, combined with the unexpected untoward outcome in US patients, required that the use of DCLHb in trauma patients be reassessed. A post hoc mortality review demonstrated that 72% of US patients who died had either prior traumatic arrest, a Glasgow Coma Scale (GCS) score of 3, or a base deficit above 15 mEq/l [12]. Despite the observation that 94% of the deaths were clinically justified, DCLHb-treated patients predicted to survive using the TRISS and PTOS models more often died than did control patients. Given this finding, and the absence of a sub-group from either the EU or US studies for whom DCLHb imparted an improved outcome, it seems reasonable to have terminated clinical study of this drug in the setting of traumatic hemorrhagic shock.

In response to a *Journal of Trauma* letter suggesting that free iron was responsible for the observed mortality imbalance, it was noted that there was no evidence of an adverse effect related to reactive oxygen species or iron-induced infection/sepsis [13]. It also was stated in this reply that DCLHb has been given to critically ill patients in other clinical settings, including an EU cardiac surgery study, without causing an adverse mortality imbalance [14, 15].

Even though the US DCLHb showed an adverse treatment effect, in this EU hemorrhagic shock study it was noted that mortality was not significantly higher in DCLHb-treated patients. Dr. Kerner and his co-authors address many of the possible explanations for the lack of an adverse treatment effect in the EU study, including the lower penetrating trauma rate in the EU study population and the fact that the DCLHb was infused "on-scene" in the EU, as opposed to in the Emergency Department, as was the case in the US study. Another protocol difference that may have altered the results in the EU study was the requirement that no enrolled patients received more than 1000 cc of a resuscitation fluid prior to study randomization. Because this requirement did not exist in the US study, some patients could have received large crystalloid volumes prior to being randomized, an occurrence which might have differentially affected outcome in the US DCLHb-treated patients. The absence of a positive DCLHb effect in both studies may, in fact, have been related to the small infused DCLHb volume, which may have been inadequate to improve long-term morbidity and mortality substantially, despite its apparent ability to transiently increase SBP.

The research findings produced by these two companion studies were both novel and rewarding. All of the EU clinicians with whom we worked were motivated, skilled and engaging as we investigated how to improve the care of patients in severe hemorrhagic shock. It makes sense to conduct companion studies like these, with "on-scene" care being provided by EU physicians and Emergency Department care being provided by US clinicians. This approach may best allow the effects of clinical variables such as the volume and type of resuscitation fluids, the timing of the resuscitation and the differences in patient populations to be studied optimally.

As hemoglobin and other oxygen-carrying solutions are developed, emergency care providers in the US look forward to studying with EU clinicians ways to enhance the care of patients in hemorrhagic shock. In doing so, we might be able to improve the outcomes of trauma patients from both of our continents.

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