The Future of Clinical Trials Evaluating Blood Substitutes

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Despite an adequate and safe blood supply in North America and Europe, the pursuit of an artificial blood substitute remains noble if 3 conditions are met: it is safe, effective, and universally available. In this issue of *JAMA*, the findings of Natanson and colleagues[1] of a clinically important increase in risk of mortality and risk of myocardial infarction across hemoglobin-based oxygen carrier (HBOC) trials cast serious doubt on the first and second conditions, thereby making the third irrelevant. Specifically, based on their analysis of available data, the authors found a 30% increase in the risk of death and nearly a 3-fold increase in risk of myocardial infarction when all HBOC trials were pooled. More troubling, trials continue to be planned and conducted in the presence of accumulating knowledge as demonstrated by the cumulative meta-analyses.

Natanson et al conducted a systematic review that sought to identify all published and unpublished clinical trials of HBOCs. The general consistency of harm across all HBOC products regardless of technology (cross-linked, polymerized, and conjugated hemoglobin) and important subgroups suggests that the findings are robust. Although the adverse outcomes assessed were not significant within any of the trials except one, individual trials were generally not powered to detect important differences in harm. The value of a meta-analysis is to synthesize evidence across trials regardless of size to better understand benefits and harms. Identifying all eligible trials can be a limitation of systematic reviews, but Natanson et al went to great lengths to identify all potential trials. Even though non–peer-reviewed studies were included, the overall findings were not affected by the unpublished studies.

The flurry of activity in the 1980s and 1990s to develop a viable and universal HBOC was largely predicated on concerns about the adequacy of the blood supply and real or perceived deleterious effects of transfusions of red blood cells (RBCs). In many developed countries, refined donor selection criteria to increase transfusion safety have limited the blood donor pool, although there are no readily identifiable, published, methodologically sound research reports documenting the effect of blood shortages, such as the number of cancelled surgeries or transfusion-dependent patients denied therapy. As for the harmful effects of RBC transfusion, such as transmission of viral and bacterial organisms, the blood supply in many developed countries has never been safer.[2] More importantly, the adverse effects of RBC administration need to be compared and contrasted with pharmacologic, behavioral, or mechanical technologies aimed at reducing or eliminating use of RBC transfusions. For blood substitutes administered in the hospital setting, the risks of HBOCs need to be at least comparable with the risks associated with RBCs. For patients who require out-of-hospital treatment or who are in a remote location where RBCs are not immediately available, the risks of HBOCs need to be compared against the risks of resuscitation fluids used in those settings.

Given the observed findings, it is important to consider how trials were planned and

conducted in the face of known and accumulating evidence of harm. Were there clues from preclinical and clinical studies indicating the deleterious effects of HBOCs? Investigators, sponsors, regulatory agencies, and research ethics boards have a number of important responsibilities in assessing the evidence base and incorporating this knowledge in the design, review, and approval of clinical studies. These stakeholders also have a responsibility to ensure that patient safety is properly accounted for in the study design and during the conduct of the study. To this end, investigators must conduct systematic reviews of animal and clinical evidence, assessing both potential benefits and harms of the study interventions; define, measure, monitor, and adjudicate potential serious adverse events in all patients; and report all serious adverse events in a timely manner. From the published reports, it appears that many of the trials evaluating HBOCs did not fulfill some or all of these important steps.

Animal evidence and early clinical trials demonstrated that HBOCs were associated with risks such as renal dysfunction and systemic vasoconstriction.[3-9] Even though there are different HBOC technologies and there is lack of clarity on precise mechanisms of action, these toxicities must be defined before justifying further clinical trials regardless of whether the HBOCs are cross-linked, polymerized, or conjugated. To substantiate the need for a clinical trial, systematic reviews need to be conducted and reported.[10] Examination of the introduction sections of the 13 published studies of HBOCs identified by Natanson et al reveals that no studies (0 of 13) reported whether a systematic review of either animal or clinical evidence was conducted. Although some studies did cite animal or clinical studies, it is essential to guard against selective reporting of only studies that support the trial rationale.[11]

In terms of presenting potential harms, only 3 trials (23%) included in the analysis by Natanson et al mentioned the potential increase in mortality with HBOC products, and none of the articles specifically mentioned the issue of myocardial infarction in their introduction sections. The importance of synthesizing available animal evidence is best demonstrated by the decision by US Army scientists to abandon its cross-linked hemoglobin product ($\alpha\alpha$-Hb) in 1993 because animal studies consistently showed that the deleterious vasoconstrictive properties precluded any clinical benefit.[5, 12] Yet trials of $\alpha\alpha$-Hb in stroke and trauma populations continued to be designed and conducted by the manufacturer of these products.[13-14] These trials in humans confirmed the very risk identified by the US Army animal studies conducted years earlier. Aside from the preclinical evidence, a systematic review and synthesis of accumulating clinical trials should have detected early signs of deleterious effects as demonstrated by Natanson et al.

In light of the animal and clinical evidence suggesting deleterious effects of HBOCs, investigators had a responsibility to collect and monitor clinically important harms such as those related to vasoconstriction and nephrotoxicity in all study patients regardless of trial sample size and primary objectives. Although collecting and monitoring these data are resource intensive, the established toxicities mandated active examination and not passive reporting. It is unclear whether this duty was fulfilled, but Natanson et al found that 38% of trials did not report the number of myocardial infarctions. In the 13 studies in the report by Natanson et al that were published as full journal articles, only 1 reported a priori definitions of myocardial infarction or other potentially important adverse effects related to HBOCs such as renal failure or stroke. Moreover, only 1 of the 13 publications reported whether

patients were actively assessed for the presence or absence of clinically important harms and no study reported that the outcomes were adjudicated. As such, there may be an underreporting of harm.

The timely reporting of all evidence independent of positive or negative findings is not only essential but ethical. Natanson et al provide evidence that study results were made public well after the trials had stopped enrollment. Thus, it was not possible for ethics boards to properly review proposed studies because they did not have all available information. Additionally, patients or proxy decision makers were not in a position to make well-informed decisions at the time of providing informed consent. Regardless of whether studies are conducted under the auspices of commercial or academic entities, studies need to be centrally registered and their findings duly reported.[15-16] Not doing so places patients at unnecessary risk. Yet as Natanson et al point out, trial registries alone will not prevent the nonpublication or nondisclosure of all trial results. Measures are needed to ensure that the results of all registered clinical trials are reported.

Based on the findings of Natanson et al and the consistency of these results with preclinical evidence of potential toxicity, further phase 3 trials of HBOCs should not be conducted. There has been a tremendous amount of resources expended and knowledge gained from the pursuit of HBOCs. This vast body of knowledge should be reviewed critically and systematically, including theoretical constructs, animal studies, mechanistic studies, and early-phase clinical trials before further phase 3 trials are undertaken. As Stowell[17] suggests, the unpredictable clinical response to HBOC therapy seen in animals and humans "highlights the somewhat embarrassing fact that we do not fully understand oxygen delivery and utilization." Until the mechanisms and potential toxicities of HBOC products are better understood, patients cannot be placed at unacceptable risk. If and when phase 1 through 3 studies can be justified, initial studies should involve patient populations who would benefit the most—namely, trauma patients who require out-of-hospital resuscitation, where blood is not accessible or available.

Given the safety of the blood supply, availability of blood products, and technologies to minimize transfusion, it does not seem prudent to study use of HBOCs in elective surgical populations. Finally, although it is difficult to argue that transfusion avoidance supersedes mortality and myocardial infarction as an end point, the onus is on investigators and sponsors to demonstrate that HBOCs are at least as effective in reducing mortality or serious morbidity as the current standards of care.

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