EDITORIAL

Hemoglobin-Based Oxygen Carrying Solutions: Will They Replace Red Blood Cells?

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It would be very useful to have an immediately available resuscitation fluid that carries similar qualities of oxygen as blood carries. Producing such an oxygen-carrying fluid from a hemoglobin (Hb) solution is appealing for two reasons. First, as Hb has no "blood type" the resultant Hb-based oxygen carrier (HBOC) would be a universal donor. Second, free Hb molecules may be stored for long periods of time. Unfortunately, when Hb is removed from the red cell the tetrameric structure breaks down into two α-β dimers, resulting in a small molecule that is quickly diuresed (1). In addition the 2,3-DPG molecule that maintains the p50 of Hb in the 27 mm Hg range dissociates from the Hb leaving the resultant p50 at approximately 12 mm Hg. With this high oxygen affinity, the free Hb avidly binds oxygen and is diuresed (oxygen attached), making this resuscitation fluid effectively "red mannitol." More than 50 years of research has been directed toward producing a HBOC with a larger molecular weight (so that it would not be diuresed) and a higher p50 (1–3).

A variety of HBOC products have been developed using different approaches to resolve the above-mentioned problems (1–3). The solutions can be divided into those products that use outdated human blood as their Hb source and those that use bovine Hb. Hb has also been produced using recombinant technology. The benefit of using bovine Hb is not only that it is in plentiful supply but also that it does not have 2,3-DPG and its p50 remains in the range of 30 mm Hg whether it is in the red cell or free in solution. Unfortunately, a bovine product does have the disadvantage that it is a protein from another species and that it raises concerns regarding viral contamination (4). The products using outdated human Hb require chemical modifications to increase the p50 (3).

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The size of the Hb dimer molecules can be increased by either conjugation with a larger molecule, cross-linking, or polymerization. Polymerizing and cross-linking the Hb dimers have the advantage of not only increasing the molecular size but also increasing the Hb concentration while at the same time decreasing oncotic pressure. Once cross-linking or polymerization is complete the resulting solution may comprise a distribution of molecular weights, i.e., tetramers to octamers. To produce a more homogenous weight distribution, some of the products are further fractionated to eliminate the smaller Hb molecules (5). Because each of the HBOC products is chemically distinct, they must be tested individually for effectiveness and side effects (3). This spectrum of side effects is a similar issue that is seen with any other new class of drugs.

There are limitations common to all HBOCs. First, although the size is large enough that they are not readily diuresed, they are still identified as foreign proteins in the vascular space and are rapidly cleared by the reticuloendothelia system with a plasma half-life of 12 to 20 hours. Given this short half-life, the anticipated clinical applications of these oxygen-carrying colloids would be for acute resuscitation where blood might not be available or as a temporary oxygenating supplement, which may reduce the amount of bank blood used (6,7).

Another universal finding in animal and clinical studies was an interesting hemodynamic response: pulmonary and systemic hypertension. The etiology of this hypertensive response remained a mystery until the elucidation of nitric oxide's (NO) role in vasomotor control of pulmonary and peripheral resistance. It then became evident that free Hb is a NO scavenger, as is red-cell-encapsulated Hb. Because free Hb is in closer proximity to the production of NO in the endothelial cells, it appears to be more effective in scavenging NO, thereby producing a vasoconstrictive response leading to hypertension. It has been suggested that as the size of the Hb polymer increases, this effect is diminished (3,7). Despite these limitations it still would appear beneficial to have a readily available oxygen carrying colloid in situations of life threatening anemia where blood is not available.

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Given the small particle size of HBOCs relative to red blood cells, there is also a potential for these fluids to oxygenate ischemic tissue where disease may impair normal red cell flow. In addition, if the p50 of the Hb solution is higher than that of red blood cells, off-loading of oxygen into the tissues may be enhanced (8,9). In this issue of *Anesthesia & Analgesia* Torres-Filho et al. (10) present an interesting study assessing the hemodynamic and metabolic response to hemodilution in rats which have been transfused with HBOC, fresh blood, or 10-day old blood. The authors sought to determine if the critical oxygen delivery (DO_2) (defined as the DO_2 at which oxygen consumption decreases) differed among these three groups of rats during progressive hemodilution. They found some differences, but the primary result was that all solutions had a similar critical DO_2. One may have predicted that the fresh blood would have had an improved response relative to 10-day-old blood, and one may have hoped that the HBOC-treated rats would have had an improved critical DO_2. This study adds to the accumulating evidence that HBOCs can maintain oxygen transport for acute resuscitation but are not superior to blood (2,3).

Clinical studies have tried to demonstrate the benefit of HBOC treatment by reducing the overall use of red blood cells. This assumes the risks of HBOCs are less than those of blood transfusions or that the cost would be less. At this time, the cost of HBOCs has not been determined and not enough patients have been treated to compare the overall risks. The comparison is further complicated by the fact that there still remains a substantial controversy over when to transfuse the blood itself. The largest HBOC clinical study to date (181 patients) compared a HBOC product to banked blood in a randomized prospective fashion in elective surgery (6). In this multicentered study, there was no specific transfusion trigger based on Hb, just the reliance on clinical judgment considering Hb, coexisting disease, and the likelihood of future blood loss, as well as the availability of salvaged red cells and current hemodynamics. The HBOC product in this study was a diasperin cross-linked Hb that has subsequently been withdrawn from the market as a result of side effects, including an increased incidence of pancreatitis in the treated patients. Other clinical studies using other HBOC products have demonstrated some effectiveness in reducing the short-term need for red blood cells immediately after surgical procedures or acute resuscitation from trauma (3). Again, because of the short intravascular half-life, most of this reduced need for banked blood in the HBOC-treated patients was diminished during the hospital stay. Because the number of patients who have received these products is still relatively small, it will take time to determine how this moderate savings of banked blood and its associated risks will compare with the side effects of repeat HBOC treatment. Studies such as Torres-Filho et al.'s provide interesting comparisons but, unfortunately, do not demonstrate the definitive advantage we hope to see.

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