Hemoglobin Solutions Come of Age

IN this issue of ANESTHESIOLOGY, Lamy et al.¹ present their findings regarding the use of a commercially produced hemoglobin-based oxygen-carrying (HBOC) solution as an alternative to traditional allogeneic blood transfusions in patients who have undergone cardiac surgery. The study included a large number of patients (N = 209) and involved the use of a commercially produced HBOC solution (Baxter, Deerfield, IL) in cardiac surgery patients after cardiopulmonary bypass. Although the study presents certain problems in study design, it is important because it illustrates the potential future importance of such HBOC materials, which are currently in clinical trials.

The concept of using purified, chemically modified hemoglobin extracted from erythrocytes is not new and dates to the mid-19th century. In the approximately 100 yr that followed, numerous attempts have been made to develop HBOC solutions, largely in university- or hospital-based laboratories. In 1978, the promising clinical trial with such a material² ended with significant systemic toxicity, leading workers in the field to conclude that hemoglobin itself is fundamentally toxic when outside of the erythrocyte. With the appearance of the human immunodeficiency virus infection in the early 1980s, allogeneic blood transfusions received increased scrutiny, and there appeared renewed interest in techniques to save allogeneic blood exposure. At that time, industry became involved in the development of HBOC solutions, and modern techniques of purification and process engineering were applied to this endeavor. The result was that by the late 1980s, hemoglobin solutions could be purified to the same degree and to the same standard that is applied to other high-volume parenteral solutions; the previously reported toxicities no longer occurred. Furthermore, advances in vascular biology and the opportunity to study these materials in numerous experimental systems has led to further understanding of their fundamental biologic properties. HBOC solutions have demonstrated potential for vascular reactivity, hypothesized to be the result of nitric oxide binding. Their ability to be transported in the plasma phase has important implications for their physiology in the microcirculation, and their degradation during elimination may liberate heme iron that may benefit postoperative hematopoiesis.³

With resolution of the previously observed toxicity problems, HBOC solutions have moved through phase I and phase II clinical trials and are entering final phase III clinical study for potential regulatory approval. As these materials have been put into clinical use, new issues have been identified and must be kept in mind. The present study by Lamy et al.¹ further illustrates this point.

With respect to study design, it is well recognized, particularly in cardia surgery, that transfusion decision-making is a complex process that integrates measured physiologic parameters and a patient’s total hemoglobin level, as well as their age and cardiovascular reserve. In this particular clinical specialty, there is not a predetermined set of transfusion criteria; patient transfusion decisions are made by the bedside “integration” of the aforementioned parameters. Accordingly, designing clinical trials to assess the blood-conservation efficacy of HBOC solutions in cardiac surgery remains a challenge.

Particularly because of this nature of transfusion criteria, the single-blind trial design in the study by Lamy et al. remains an important flaw that the authors have acknowledged. Nonetheless, this study did show blood-conservation efficacy when an HBOC solution was used in the immediate postoperative period after cardiac surgery. The amount of blood conservation was modest; however, the study used relatively low doses of HBOC solution.

Further complicating the efficacy issue is the relatively short circulating half-life of these materials, complicated

Key words: Blood substitute; blood transfusion; HBOC; hematocrit; methemoglobin.

Dr. Vlahakes was an investigator in an industrially sponsored clinical trial of a related material (Hemopure; Biopure Corporation, Cambridge, Massachusetts). He does not personally have any financial holdings in this Editorial View accompanies the following article: Lamy ML, Daily EK, Brichant JF, Larbuisson RP, Demeyere RH, Vandermeersch EA, Lehot JJ, Parsloe MR, Berridge JC, Sinclair CJ, Baron JF, Przybelski RJ, for the DCLHb Cardiac Surgery Trial Collaborative Group: Randomized trial of diaspirin cross-linked hemoglobin solution as an alternative to blood transfusion after cardiac surgery. ANESTHESIOLOGY 2000; 92:646–56.

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Lamy et al.¹ present their findings regarding the use of a commercially produced hemoglobin-based oxygen-carrying (HBOC) solution as an alternative to traditional allogeneic blood transfusions in patients who have undergone cardiac surgery. The study included a large number of patients (N = 209) and involved the use of a commercially produced HBOC solution (Baxter, Deerfield, IL) in cardiac surgery patients after cardiopulmonary bypass. Although the study presents certain problems in study design, it is important because it illustrates the potential future importance of such HBOC materials, which are currently in clinical trials.

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by the fact that some of the circulating HBOC hemoglobin can undergo auto-oxidation in the plasma phase. Because methemoglobin reductase activity is not present to any appreciable degree in the plasma phase, the result is that oxidation potentially may further decrement the efficacy of HBOC solutions. One study suggested that low-molecular-weight moieties may be somewhat more susceptible to oxidation. Accordingly, study design (and hence, eventual clinical use) must take into account the relatively short effective half-life of these materials as compared with either native or transfused erythrocytes.

Cardiac surgery is a particular clinical specialty in which a short-lived oxygen-carrying solution may have a special application. In cardiac surgical patients, during rewarming in the first postoperative hours, fluid repletion is needed, resulting in hemodilution in most patients. Transfusion decisions, particularly in the intensive care unit, are usually made around the nadir of hematocrit that occurs during the first 12 postoperative h. In the few days that follow, diuresis and mobilization of fluid results in some hemoconcentration and often a substantial increase in hematocrit. This has even led to the notion by some investigators that cardiac surgical patients are often overtransfused. HBOC solutions may fill this particular niche in clinical transfusion practice by providing a temporary oxygen carrier during the relatively short period of time (up to 3 days), during which time a patient’s hematocrit is increasing. In this setting, the short effective half-life of some HBOC solutions is less of an issue.

The study by Lamy et al. illustrates the ability of some HBOC solutions to increase blood pressure, again thought to be the result of nitric oxide binding. Early work in the field suggested that this might be a deleterious effect; however, in the context of cardiac surgical patients, it actually may be of benefit. Cardiac surgical patients, when relatively anemic after surgery, can sometimes be hypotensive because of low systemic vascular resistance; systemic vascular resistance in this setting may also be decreased because of preoperative vasodilator medication. Thus, early after surgery, these patients often require use of agents such as norepinephrine to increase systemic vascular resistance and, hence, blood pressure. Thus, in this particular clinical setting, some degree of vasoconstrictor activity may be of benefit. In preclinical and clinical trial studies conducted to date, the vasoconstrictor effect of an HBOC solution has not been demonstrated to cause ischemia of a vascular territory, suggesting that this physiologic side effect may not be deleterious.

This study also has interesting implications for future HBOC solution design and formulation, as well as clinical trial design. The short half-life may be extended further by polymerization or encapsulation, and clinical trials must be designed to permit repeated or continuous administrations. If the hypothesis is true that HBOC solutions increase vascular resistance by nitric oxide binding in the interstitial space, then polymerization or encapsulation also may reduce the diffusion of HBOC hemoglobin into this space, thus diminishing the observed vascular effects.

Lamy et al. are to be congratulated for organizing and conducting this study on a new class of materials that, hopefully, will be introduced into eventual clinical use. As with any new agent, methods and principles for its clinical use must be elucidated during early clinical experience. Furthermore, industry is to be congratulated for entering this field in the 1980s and for solving the previously observed toxicity issues.

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References