The Ideal Blood Substitute

A. Gerson Greenburg, MD, PhD[a,b]

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• Blood • Blood substitute • Hemoglobin
• Homeostasis • Transfusion

In writing this article, I take the prerogative of a senior investigator in the field of blood substitutes to express my opinions and views of what constitutes an ideal blood substitute. My perspective, based on a 35-year involvement with wide-ranging contributions from chemical modification of hemoglobin (Hb) to improve its characteristics as a ''blood substitute'' through the design and evaluation of Phase III clinical trials is perhaps unique in that regard. I have no doubt that there is a need for a blood substitute now and in the near future. In this article, I address some of the key elements to consider, offer some guidelines, and place a context on my suggestions in light of known physiology.

BLOOD

Blood is indisputably essential for life, and specifying the attributes of a solution to replace the life force of blood is a daunting task. An appreciation of the composition and structure of blood in the context of its many functions is an essential prerequisite for listing design specifications of an ideal blood substitute (IBS). Only by understanding the functions of blood is it possible to define the characteristics needed for an IBS.

The chief functions of blood are the provision of tissue perfusion with oxygen carried by the red cells' Hb and maintenance of vascular volume. Loss of vascular volume, as in trauma or operative surgery with loss of red cell mass, has widely known undesirable clinical consequences. In addition, blood provides cellular and molecular elements of the coagulation and immune systems and, by providing the vascular volume, serves as a communication pathway for hormonal and cytokine signaling and the delivery of nutrients and removal of metabolic waste products. Within each of these broader categories there are subsets of elements and components with complex interactions and functions that serve to maintain life and homeostasis, and participate in the protective responses to injury and the restorative processes required. Within each functional component there is an optimal operating level and

[a] Biopure Corporation, 11 Hurley Street, Cambridge, MA 02141, USA
[b] Brown University, Providence, RI, USA
E-mail address: aggreenburgmdphd@gmail.com

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reserve capacity to respond to acute needs. An IBS would, de facto, have to replace all of these functions.

Given the prominence of the need to perfuse tissue with oxygen, the role of Hb and intravascular volume replacement has consumed and attracted great attention in the pursuit of an IBS. Replacing the lost oxygen-carrying capacity of blood, whether from hemorrhage or disease, has been an objective of much research. Failing to replace lost oxygen-carrying capacity, Hb perpetrates impaired tissue perfusion with consequent critical organ ischemic injury, initiating a downward spiral of organ failure, multi-system organ failure, and death. The need to avoid this sequence of events has driven the development of blood substitutes for over a century.

In the past 25 years, concerns about the safety of the blood supply and the inventory of available red cells as well as issues with storage, the quality of stored red blood cells and their impact on function and immune consequences and the potential for transmission of infectious disease have encouraged further development. Currently, an alternative to red blood cells as treatment does not exist. In the event of a major disaster or epidemic there is no available replacement. Stockpiles of red blood cells beyond the normal storage cycle of days do not exist. The availability of an option, even one that addresses only some of blood's functions while relying on the reserve capacity of the system for some of the other functions, is certainly a desirable goal. Indeed, faced with the nonavailability of blood for whatever reasons, restoring the oxygen-carrying capacity to the cardiovascular system until red cells are available is a reasonable bridge to definitive treatment.

An oxygen-carrying IBS to treat hemorrhagic shock or symptomatic acute blood loss as observed from time to time in surgical settings across all surgical specialties is preferable to standard asanguinous fluid therapy. The treatment of anemia and its consequences of ischemic insult for patients with primary hematologic malignancy or the side effect of chemotherapy could be enhanced, thus permitting patients to receive treatment otherwise denied, particularly if they object to blood transfusion. When blood is not available or otherwise not an option, the therapeutic armamentarium would be significantly enhanced with the inclusion of an IBS.

FORMULATION

Is there really an ideal blood substitute, a multipurpose formulation that would mimic the full functionality of blood or, as might be reasoned from the potential range of applications, could be formulated into separate solutions for separate applications? Should the properties be maximized for directed application or optimized for general use? The decision taken at this point has significant implications for the eventual formulation, for it will define the characteristics of the proposed solution. Matching form to function is a critical design element.

In the case of new therapeutic products, one needs an appreciation of the underlying mechanisms of disease and the influence they might have on the safety and effectiveness of any new approach. Understanding the pathophysiology to be treated is essential for the design and formulation of an IBS for that disease. It also permits differentiation of disease effects from treatment-associated effects during the critical safety analysis.

In my opinion, the ''ideal blood substitute'' is fresh whole blood, an autologous donation achieved by intraoperative hemodilution. With all the cellular and molecular components and functionality necessary and none of the safety issues associated with passage through the blood bank, it meets all the needs all the time. Unfortunately,