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EDITORIAL:

IS THERE A NEED FOR BLOOD SUBSTITUTES IN THE NEW MILLENNIUM AND WHAT SHOULD WE EXPECT IN THE WAY OF SAFETY AND EFFICACY?

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Sensitive screening tests for H.I.V., hepatitis viruses and other potential infective organisms have now resulted in much safer donor blood. This being the case, is there any need for blood substitutes in the new millennium? This question sounds somewhat similar to the comments made some 40 years ago regarding the first reports of “modern” approaches to blood substitutes (1-6). The result is that little or no effort was made to develop these blood substitutes. Thus, there was nothing to replace donor blood during the H.I.V. crisis in the 1980’s and patients had to take their chances until many years later when sensitive screening tests become available. This was then followed by hepatitis C etc. Many groups started to catch-up on blood substitute research and development. Unfortunately, given such a complicated product as blood substitutes, it has been more than 10 years of intensive efforts and we still have nothing ready for routine clinical use. Had serious efforts been made to
develop the modern concepts of blood substitutes 40 years ago, it would be likely that blood substitutes could have been ready for the H.I.V. crisis in the 1980’s. In the new millennium is anyone willing to say that we no longer need blood substitutes and take the responsibility if something similar to H.I.V. or hepatitis C should unexpectedly come up? In addition, there is also the continuing need in emergency situations, peri-operative needs and also in less accessible regions.

Any blood substitutes must be safe and efficacious before they can be used clinically (7). However, safety and efficacy can have many interpretations. Should we demand that blood substitutes have to be equivalent to blood before they can be considered useful clinically? To answer this question, we only have to look at the most commonly used volume replacement solution in the form of Ringer-Lactate solution. It is nothing more than a solution with electrolytes and glucose in concentrations similar to that in the plasma. There is no plasma protein and no blood cell in the solution. It is not even equivalent to plasma. Yet it has been a well-established and effective solution for volume replacement in less severe blood loss and volume depletion. No one ever expects or asks for equivalency tests with blood or even with plasma. The present first generation blood substitute is nothing more than Ringer-Lactate solution with modified hemoglobin or fluorochemicals added as oxygen carrier and also for colloid osmotic pressure. They do not have clotting factors, antioxidant enzymes, white blood cells nor platelets. This being the case, can we expect this simple solution to have the same equivalency as blood or even as red blood cells? Any equivalency tests should only be done in those clinical
conditions that require only volume replacement and oxygen carrier. In this regard, first generation blood substitutes like polyhemoglobin in Phase III clinical trials (8-11) and perfluorochemicals (12) are being tested in clinical trials for peri-operative surgery for hemodilution, in surgery with large volumes of blood loss and in other conditions requiring only oxygen carrier and volume replacement. In these clinical trials up to 20 to 23 units of glutaraldehyde crosslinked polyhemoglobin (8-10) have been infused (13).

What happens if one tries to test the safety and efficacy of first generation blood substitutes in conditions requiring more than volume replacement and oxygen carrier? For instance, in conditions with potentials for ischemia-reperfusion injuries including sustained ischemia in stroke, sustained severe hemorrhagic shock with intestinal ischemia, sustained cerebral ischemia and transplantation of donor organs. Unlike red blood cells, first generation blood substitutes contain no red blood cell antioxidant enzymes like catalase and superoxide dismutase. In the absence of these antioxidant enzymes, hemoglobin in the blood substitutes can break down more easily to release heme and iron in the presence of oxidants in ischemia-reperfusion and intensify injuries (14,15). In a 1998 editorial (16) I have emphasized that in these conditions, not only is first generation blood substitutes not efficacious, they are not safe to use. For these conditions, in addition to volume replacement and oxygen carrier, we need the addition of antioxidant enzymes to the blood substitutes. Thus, second generation blood substitutes that contain antioxidants as in the case of polyhemoglobin-catalase-superoxide dismutase (14) are being developed.
First generation blood substitutes have a circulation half-time of only up to 24 hours and any equivalency test should only be within this time frame. Conditions requiring more than this time frame would require repeated infusion with blood substitutes or later replacement with donor blood. Studies are being actively carried out to increase the circulation time of blood substitutes. For example, lipid membrane encapsulated hemoglobin is being developed (17,18). The circulation half-time has been increased to more than 50 hours (17) and further increase are being studied. Nanotechnology and biodegradable polymer have been combined to form biodegradable hemoglobin nanocapsules and to increase their circulation time and to include multienzyme systems (19).

The beginning of this new millennium will be an exciting period for blood substitutes. First generation blood substitutes suitable as oxygen carrier and volume replacement are in the final stages of clinical trials. These first generation blood substitutes would have important potentials especially for peri-operative uses as in hemodilution and in surgery with extensive blood loss. For other conditions that require more than just oxygen carrier and volume replacement, new generations of blood substitutes are being actively developed (14-22). It is hoped that we have learned from the last millennium that we cannot wait for an emergency situation before starting to do catch-up research and development on available ideas of blood substitutes (23). They need to be actively developed before it is too late. After all, no one can be sure that there will not be another crisis similar to the H.I.V. crisis of the last millennium.


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