Haemoglobin Based Oxygen Carrier: Use in South Africa

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Until very recently, transfusion of red blood cells was the traditional method of restoring oxygen-carrying capacity in acutely anaemic patients. Blood transfusions are, however, associated with several intrinsic risks, such as blood-borne infections and allergic reactions. Upon storage, red blood cells become deficient in their ability to immediately offload oxygen and, therefore, may not be immediately effective in delivering oxygen to tissues.[1] Various pharmacological agents, including haemoglobin solutions, have been developed as replacements for red blood cells, as intravascular volume expanders and as oxygen therapeutics. The administration of these pharmacological agents, which can assist in the delivery of oxygen to the tissues, has unfortunately been historically associated with a high incidence of toxic events such as renal failure, pancreatitis, allergic reactions and vascular events.

HBOC-201 [haemoglobin glutamer-250 (bovine)] is a cell-free polymerised haemoglobin solution that not only carries oxygen in the plasma, but also enhances the ability of native red blood cells to take up and off-load oxygen. Studies in an artificial capillary model suggest that the free form in the plasma facilitates the diffusion of oxygen into the pulmonary capillary blood more rapidly and more efficiently than normal diffusion across the alveolar-capillary barrier and the red blood cell membrane.[2] It is manufactured from a plentiful and well-controlled source material, bovine haemoglobin. Only cattle from the United States are utilized as donors, and an extensive herd-management program ensures that only certified disease-free animals less than 30 months of age are used to provide the haemoglobin. The extensive extraction and purification process used in production has been validated for the removal of potential contaminants including plasma proteins, red blood cell stroma, endotoxin, bacteria, viruses and the agents that are thought to cause transmissible spongiform encephalopathies such as bovine spongiform encephalopathy (BSE) and variant Creutzfeld-Jakob disease (vCJD). This process produces a sterile, pyrogen-free balanced salt solution containing glutaraldehyde cross linked bovine haemoglobin polymers, which range in size from 130 to 500 kd and have an average molecular weight of 250 kd.[3,4]

The product's oxygen dissociation curve is right-shifted with a P_{50} of 38 mm Hg, compared to 27 mm Hg for human haemoglobin. In contrast to human haemoglobin whose oxygen affinity relies on adequate levels of 2,3-diphosphoglycerate, the affinity of bovine haemoglobin for oxygen is regulated by the concentration of chloride ions in the plasma. It has a dose dependent intravascular half-life of 16 to 20 hours.[5] When stored within a temperature range from 2° to 30° C, it is stable for at least two years, can be infused directly without reconstitution and does not require typing or cross matching.

In vitro studies utilizing an artificial capillary model and mathematical simulations demonstrate that HBOC-201 acts not only as an oxygen-carrying agent in the plasma but also facilitates the uptake and release of oxygen by the patient's own red blood cells.[2,6] Furthermore, in a canine model, it was shown to take up oxygen in the lungs and release oxygen for diffusion into body tissues at a higher rate than red blood cells. On a gram-for-gram basis, the HBOC-201 haemoglobin was approximately three times more potent than stored or fresh red blood cell haemoglobin at restoring baseline tissue oxygenation following severe acute anaemia.[7]

This product has been administered to more than 800 human subjects in 22 completed or ongoing clinical trials at doses up to 1080 g (36 units) of haemoglobin, including red blood cell controlled trials in elective surgical patients where the product was administered at doses up to

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300 g (10 units) of haemoglobin. This was done to eliminate or reduce the requirement for allogeneic blood transfusions. Results from two red blood cell controlled trials in general and orthopaedic surgery showed that >80% of patients who received the product avoided red blood cell transfusion on the day of surgery.[8] In addition, early results of the pivotal Phase III clinical trial in patients undergoing orthopaedic surgery demonstrated avoidance of red blood cell transfusion in 47% of the HBOC-201 treated patients at 42 days post surgery with an adverse event rate comparable to that of the red blood cell control group.[9]

Early clinical usage in South Africa as an alternative to allogeneic red blood cell transfusion suggests that administration of HBOC-201 to patients who are haemodynamically unstable as a result of acute anaemia results in rapid achievement of haemodynamic stability. Although the product is presently registered for the treatment of adult surgical patients who are acutely anaemic, the potential for future administration of an oxygen therapeutic that improves pulmonary diffusion capacity and improves tissue oxygenation holds great promise in the management of a diverse array of conditions such as medical anaemias, incipient respiratory distress, the trauma scenario and in the management of acutely ischaemic tissue in conditions such as acute cerebral and myocardial ischaemia. Further clinical trials in a broader spectrum of clinical scenarios are eagerly awaited.

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