**Blood Substitutes**

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**Introduction**

Blood Substitute is a substance used to fulfill few functions of biological blood. They aim to provide an alternative to transfusion. Because of the increased demand and shortage of blood, the need of blood substitutes is increased which has propelled its biotechnology. Developing artificial blood for the mankind has been a major issue; artificial blood would relieve shortages and prevent transmission of deadly diseases caused by transfusion of contaminated blood. Blood substitutes also serve as a bridge between the need and the supply of blood and its components. At present the healthcare industry is pursuing the development of blood substitutes.

Today artificial blood is designed to only complete the task of carrying oxygen and carbon dioxide. No substitutes have yet been invented that can replace the other vital functions of blood.

 An effective blood substitute must have the properties of blood. Blood substitutes can be stored for much longer than transfusable blood, and can be kept at room temperature. Blood substitutes allow for immediate full capacity oxygen transport, as opposed to transfused blood which can require about 24 hours to reach full oxygen transport capacity due to 2, 3[-diphosphoglycerate](http://en.wikipedia.org/wiki/2%2C3-diphosphoglycerate) depletion. Also, in comparison, natural replenishment of lost red blood cells usually takes months, so an oxygen-carrying blood substitute can perform this function until blood is naturally replenished

The blood substitutes can be of great help in the following conditions:

* Severe hemorrhagic shock.
* Most Important benefit could be derived from the rapid treatment of patients in trauma situations. Because these blood substitutes do not contain any of the antigens that determine blood type, they can be used across all types without immunologic reactions
* Supplying devascularized organs with oxygen prior to transplantation.
* Heart attack.
* Sustained intestinal ischemia.
* Sustained intestinal ischemia during stroke or head injuries.
* During disasters or natural calamities.
* In battlefield scenarios, medical care in the armed services would benefit from a safe, easy way to manage blood supply
* For individuals where the religious belief does not allow them to use donor blood or product prepared from donor blood.
* Liquid ventilation.
* As a radio contrast material

Several researches are done in this field of Transfusion Medicine, but still the biggest hurdle is the toxicity at various steps, which has complicated their development and final outcome. Till date, various types of blood substitutes developed are as follows:

**Hemoglobin Based Solutions (HBOs)** which are also called *artificial hemoglobin*, is an artificially made blood substitute whose main function is to carry oxygen, as does natural hemoglobin. They are derived from humans, animals, or artificially via recombinant technology. They are often called Oxygen therapeutics. HBOs can be sterilized, hence the risk of bacterial contamination is nil. There onset of action is immediate

There is considerable increase in bilirubin, amylase and some degree of lipase level when hemoglobin-based solutions are metabolized. The consequences of metabolism of hemoglobin-based oxygen carriers may be similar to those of multiple transfusions, namely haemosiderosis and chronic iron overload.

They are readily available and provide excellent resuscitation tool. HBOS are universally compatible.

They can be stored at room temperature, no need of refrigeration required as compared to blood.

Their shelf life is 36 months as compared to 42 days of Transfused red cells.

 The lack of iso-agglutinating antigens due to the absence of a red cell membrane eliminates blood typing, screening and cross-matching related morbidity and mortality of allergenic and autologous transfusions.

Hemoglobin-based oxygen carriers have some advantages over allogeneic red blood cell transfusions. The lack of iso-agglutinating antigens, due to the absence of a red cell membrane, obviates blood typing and screening and eliminates the most common morbidity and mortality of allogeneic and autologous transfusions, mismatching of blood units and the transfusion recipient. The lack of cross-matching requirements also allows immediate availability of an oxygen carrier in critical periods of trauma or hemorrhage.

There is no interference with the coagulation system. The hemoglobin solutions have minimal direct effect on coagulation. They do not significantly alter the prothrombin time, partial thromboplastin time, factor X, fibrinogen, antithrombin III, antiplasmin or plasminogen function.

Their main **disadvantages** are:

* Reactions similar to the administration of a foreign protein, like allergy, fever, chill headache, blood pressure changes and gastrointestinal symptoms.
* Vasoconstriction-The hemoglobin solutions can produce vasoconstrictive effect which can result in systemic and pulmonary hypertension, coronary vasoconstriction, cardiovascular complications and decreased organ blood flow, aggravating microcirculatory failure.
* Renal dysfunction-Free hemoglobin molecules are known to produce acute tubular necrosis and renal failure.
* Free hemoglobin binds nitric oxide. Although binding of nitric oxide has been implicated as the cause of hypertension commonly seen with hemoglobin infusion.
* Metabolism of plasma free hemoglobin-based oxygen carriers is identical to native hemoglobin released as a red blood cell is destroyed. Bilirubin levels will rise as hemoglobin is metabolized resulting in increase of Amylase and lipase levels.
* The results of metabolism of hemoglobin-based oxygen carriers may be similar to those of multiple transfusions, like hemosiderosis and chronic iron overload.

**Perflurocarbons (PFCs)** are synthetic fluorinated hydrocarbons that are capable of dissolving oxygen and delivering it to tissues without binding the oxygen molecule. They can be solid, gas & liquid for use in blood substitute preparation, PFCs that are liquid are preferred. The particles are not metabolized in the body and are eliminated unchanged from the circulation by the reticuloendothelial system. The half-life is only 2-4 hours. PFCs are cleared usually in 4 to 12 hours from the circulation.

They are synthetic materials and so can be produced in large amounts and can be stored in emergency vehicles and emergency departments.

There are no changes in liver, lung or renal function after their use and can be used as a contrast agent in ultrasound, CT scan, angiography, MRI and liver, spleen and tumor imaging.

Due to the small size (<0.2mm in diameter) per fluorocarbon emulsion particles perfuse even in the tiniest (4-5mm in diameter) or blocked capillary beds. So they are used in situations like MI or cerebral ischemia.

These agents are useful for perfusional protection or organs during transplant surgery.

Their main **disadvantages** are:

* Anaphylaxis due to the emulsifying agent.
* Facial flushing, backache, fever and flu-like symptoms within 1 to 4 hours of the infusion.
* Transient thrombocytopenia may occur in 3-4 days after administration which returns to normal in 7-10 days.
* Perfluorocarbons are inert biologically. The molecules are sequestered in the reticuloendothelial system, particularly in the Kupffer cells of the liver and macrophages, and subsequently released back into the plasma as a dissolved gas. The perfluorocarbon gas is then exhaled unchanged and non-metabolized via the lungs.
* So there is retention in the Lung, liver and spleen.
* Decrease in platelet count due to opsonization of platelets by the perfluorocarbon and subsequent sequestration and elimination by the reticuloendothelial system.

**Respirocyte** also known as Erythrocytes are intended to duplicate all of the important functions of the red blood cell; carrying oxygen and carbon dioxide molecules. This could serve as a universal blood substitute to preserve living tissues, to treat anemia and respiratory problems.

**Platelet Substitute** also known as Synthocytes. They are microcapsules to which fibrinogen is linked. It acts as a replacement for human blood platelets in the prevention of bleeding. The product is believed to offer certain key advantages over blood-derived platelets which have the potential to transmit viral infections and suffer from instability during storage and cause immune reactions. They can be:

* Frozen Platelets – Which can be cryopreserved in 6% DMSO (dimethyl sulfoxide) for up to 10 years when stored at -80°C. But they are expensive to produce than fresh platelets & morphological defects can be present due to freezing processes
* Cold Liquid – Stored Platelets – As the name suggests these are platelets stored in cold liquid & therefore freezing induced changes in platelet shape is inhibited and also freezing induced activation processes.

### Summary

Current blood substitutes have been demonstrated to be safe when administered in small quantities. Both perfluorocarbon and haemoglobin based oxygen carriers have undergone clinical trials designed to determine the safety of these compounds. The short plasma half-life of these compounds limits the usefulness of blood substitutes to short periods of time. Ultimately, the blood substitute will be sequestered or metabolized, and decreased oxygen carrying capacity will reappear as the plasma oxygen carrying capacity diminishes. In order to effectively use these compounds, special techniques should be considered.

 Different classes of Blood Substitutes are being developed, each capable of transporting and delivering oxygen to peripheral tissues. However, safe blood substitutes will not replace allogeneic blood transfusions as a means of treating many types of anaemia.

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