FOUNTAIN JOURNAL OF NATURAL & APPLIED SCIENCES

A Publication of the College of Natural & Applied Sciences

Fountain University, Osogbo, Nigeria

Artificial oxygen carriers as an alternative to allogenic blood transfusion: success and challenges

Ibrahim, K. K.*, Bunza, B. U.

Department of Haematology, School of Medical Laboratory Sciences, College of Health Sciences, Usmanu Danfodiyo University (UDU), Sokoto, North-Western, 2346, Nigeria

**Correspondence:* Ibrahim.kwaifa@udusok.edu.ng

ABSTRACT

Artificial blood, also referred to as artificial oxygen carriers, is a blood substitute or an alternative to blood/blood products that can perform the most indispensable activities of blood, which are the transportation of oxygen and carbon dioxide. Artificial oxygen carriers could be a daily living support measure, particularly during serious blood loss in disasters; however, the products currently being developed can't provide the additional components of blood, such as immune support. The main indications for the clinical use of artificial oxygen carriers include cardiovascular surgery, elective surgery, trauma, perfusion of ischemic tissue, organ preservation, drug carriers, and oxygenation of solid tumours. Desirable qualities of artificial oxygen carriers included the absence of adverse effects and pathogens, in addition to oxygen transport; they can effectively deliver oxygen to tissues, have a long shelf life at room temperature, require no pre-requisite of cross-matching, blood grouping and Compatibility tests, and survive in circulation for a considerable time. The major types of artificial oxygen carriers include perfluorocarbons, fluorosol-DA, perftoan and dodecafluoropentane. Data were collected from PubMed, Google Scholar, Taylor & Francis, MDPI, Springer, Nature, BMC, and other related sources. In this review, the details of artificial oxygen carriers, and the successes and challenges of using them as an alternative to allogenic blood transfusion, were thoroughly analysed.

ARTICLE INFO

Article history:
Received April 2025
Revised September 2025
Accepted October 2025

Keywords:
Artificial oxygen carriers, perfluorocarbon, fluorosol-DA, perftoan and dodecafluoropentane

Introduction

The perpetual increase in knowledge and the expanding scope of newer generations' products, substitutes and materials in the fields of research, whilst many components are hand in areas, one of them is artificial oxygen carriers. Another one of the human creations is saline solutions that help to expand the volume of blood, which could help maintain blood pressure and aid RBCs to continue regenerating. A life-sustaining measure (artificial oxygen carriers) plays a crucial role in the treatment of severe blood loss [1]. With the exceptional expansion in the number of surgeries (both elective and emergency) and injury/trauma, the demand for human blood for transfusion has seen a mind-boggling rise. The quantity of units collected from blood donors is insufficient to meet the expanding demand for human blood, which current medical practices and surgeries require. Moreover, donated human blood is loaded with concerns identified with short storage life, probability of transmission of blood-borne contamination, unfavourable immune responses and increasing costs of collection, preparation, and cross-matching [2].

The significance of artificial oxygen carriers

The steady extension of the dissimilarity between the supply and demand of blood, and the challenges related to human blood, has led to the rise of artificial blood as a promising choice. Artificial oxygen carriers serve to provide a substitute for ordinary blood transfusion, where blood or blood products collected from an individual are transfused into another. The term artificial oxygen carriers is regularly utilised interchangeably with blood substitutes or surrogates,

DOI: https://doi.org/10.53704/fujnas.v14i1.627

and all of the terminologies are inaccurate as artificial blood does not have various fundamental properties of human blood like haemostatic cycles, grouping and immunologic defence of the body. In any case, it serves to do the significant function of delivering oxygen and carbon dioxide throughout the body (Fig. 2) [3]. Artificial oxygen carriers are not classified under any blood group system; therefore, they can be given to patients of any blood group. In this manner, the appropriate terms for these substances can be Red Blood Cell (RBC) substitutes or Artificial Oxygen Carriers [3].

On the other hand, blood is an important life-supporting fluid that delivers oxygen from the lungs to the heart and the rest of the body. Blood performs many functions, such as transporting nutrients from the digestive system, eliminating toxins and waste, and fighting germs. Blood is made up of a watery substance, considered plasma, just as three distinct types of cells or portions of cells that float in the plasma. The formed elements are platelets, White Blood Cells (WBCs) and Red Blood Cells (RBCs). White blood cells are important for the body's immune system that annihilates infections and microorganisms. Platelets form clots/clots to keep bleeding from cuts and injuries. RBCs represent over 90% of the formed elements in the blood. These bountiful cells transport oxygen and carbon dioxide through arteries and veins. RBCs contain a molecule i.e. Haemoglobin (Hb) that collects and delivers oxygen [4]. This review aimed to discuss deeply on the success and challenges of using artificial oxygen carriers as an alternative to allogenic blood transfusion.

Historical perspective

The quest for a suitable alternative for human blood dates back to the 17th century when Sir Christopher Wren suggested the use of ale, wine and opium as blood substitutes. Various other substances like urine, plant resins, sheep blood, milk (for treatment of Asiatic cholera) and salt solutions were also tried previously [5]. Following the path-breaking research of Landsteiner on the various blood groups, blood transfusion became a safer and established medical procedure. As the understanding of oxygen transport and delivery of RBCs gradually improved and the necessity of type-specific allogenic transfusion was recognised, the foundations of the development of artificial blood started being laid in the early 1900s. The first infusion of cell-free haemoglobin was reported in a patient with postpartum haemorrhage for resuscitation [5]. Animal experiments where free haemoglobin was collected by lysing the red blood cells and transfusing the unmodified products in animals resulted in renal failure, coagulopathy, complement activation, antigenicity, histamine release, iron deposition and vasoconstriction. The toxicity was later attributed to the presence of red cell stroma in the product. Also, the strong affinity of free haemoglobin for nitric oxide (a potent vasodilator) led to unopposed vasoconstriction and a pressure response due to its nitric oxide-scavenging effect [4].

Origin of blood substitutes

Focused innovative work in this field got a stimulus during the 1980s after the apprehensions brought about by the chance of HIV infected blood. Relationship of other irresistible sicknesses like Hepatitis B, Hepatitis C, West Nile infection encephalitis, COVID-19, human T cell leukaemia infection and bacterial contaminations with blood transfusions turned out to be progressively perceived [6]. Allogenic blood transfusions likewise brought about specific non-infectious complications like haemolytic transfusion response, transfusion-related intense lung injury, host rejection versus graft, hypersensitivity and post-transfusion purpura. The measure of donated blood was progressively being not able to adapt up with the expanding request and subsequently an insufficiency is projected in the years to come. The increasing use of collecting, storing and preparing blood and items is additionally rising progressively. Total impacts of these elements gave a significant lift to the Improvement of artificial blood in the couple of years. The principal reason for these substances is to offer transient help to the circulatory system till the bone marrow has recovered to produce adequate RBC's. They focus on one of the significant capacities of blood, which is oxygen transportation to the cells and tissues [1].

Manufacturing process for a synthetic haemoglobin-based product

A strain of bacteria (E. coli), a microscopic organism that can deliver human haemoglobin, is used to produce haemoglobin. In three days, the protein is collected, and the microorganisms are destroyed. To initiate the fermentation system, a sample of pure microorganisms (bacteria) culture is moved to a test tube that contains the required nutrient supplement. This underlying immunisation

DOI: https://doi.org/10.53704/fujnas.v14i1.627

makes the microscopic organisms duplicate. After gaining the necessary number of bacteria, they are moved to a seed tank [7,8]. A seed tank is a huge tempered steel kettle that gives an optimal climate to developing microscopic organisms. It is loaded with warm water, food, and ammonia source which are completely needed for the developing haemoglobin. Other development factors like nutrients, amino acids, and minor supplements are also added. The bacterial arrangement inside the seed tank is continually washed with compressed air and blended to keep it moving [9]. At the point when enough time has elapsed, the substance of the seed tank is transferred to the fermentation tank. The fermentation tank is a larger version of the seed tank. It is additionally loaded with a growth medium required for the microorganisms to develop and produce haemoglobin. Since pH control is fundamental for ideal development, ammonia water is added to the tank as vital. Once enough haemoglobin has been delivered, the tank is exhausted, allowing isolation to begin with a diffusive separator that removes a significant portion of the haemoglobin. It tends to be additionally isolated and filtered utilising fractional distillation. This standard column separation method relies on the principle of boiling liquids to isolate at least the required components and utilises vertical constructions called fractionating columns [10].

From this column, the haemoglobin is moved to a final processing tank. Here, it is mixed with water and other electrolytes to produce artificial blood, then pasteurised, and finally packaged appropriately. The quality of compounds is checked at each step of the process (checking bacterial culture). Various physical and chemical properties of the final product are checked, such as melting point, pH, and moisture content (Fig. 1). This method of production has the capacity to produce batches as large as 2,640 gal (10,000 L) [11].

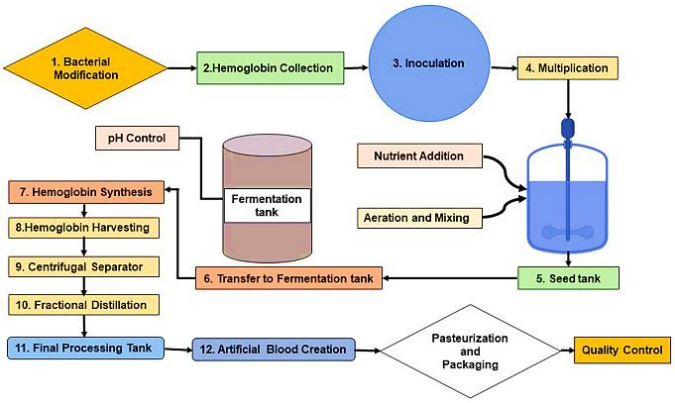

Figure 1: The Mechanism Involved in the Manufacturing Process for Synthetic-Based Haemoglobin Product, Modified from [7, 11).

Development of blood substitutes

Focused research and development in this field received an impetus in the mid 1980's following the apprehensions caused by the possibility of HIV infected blood [12]. Association of other infectious diseases like Hepatitis B, Hepatitis C, West Nile virus encephalitis, coronavirus, human T cell leukaemia virus and bacterial infections with blood transfusions became increasingly recognised. Allogenic blood transfusions also resulted in certain non-infectious reaction, transfusion-related acute lung injury, graft versus host rejection, anaphylaxis and post-transfusion purpura. The amount of donated stored blood was gradually becoming unable to cope with the ever-increasing demand, and with a deficiency projected in the years to come, coupled with the increase in the cost of collecting, storing and processing blood and blood products [1]. The cumulative effects of these factors have provided a major boost to the development of artificial blood over the past few decades. The main purpose of these substances is to provide temporary support to the circulatory system till the time when the body's bone marrow has regenerated sufficient RBC's. They concentrate on one of the important functions of the blood, which is oxygen transportation to the cells and tissues [13]. The main clinical indications of administration of artificial blood include:

- trauma: For volume replacement and stabilisation.
- elective Surgery: Preoperative blood conservation in the form of acute normovolemic haemodilution and preoperative volume replacement following massive blood loss:
    - Cardiovascular Surgery: For pump priming, deep hypothermia and intraoperative replacement.
    - perfusion of Ischemic Tissues: In sickle cell disease, strokes, peripheral vascular diseases.
    - oxygenation of Solid Tumours: For increasing susceptibility to radiotherapy and chemotherapy.
    - preservation of Organs: During transport for transplantation or as cardioplegia.

DOI: https://doi.org/10.53704/fujnas.v14i1.627

- drug Carrier: In the form of drug conjugated haemoglobin and perfluorocarbons.
- Miscellaneous: Anaerobic infections, gas embolism, CO poisoning.
- Contrast Agent: Perfluorooctyl bromide is used as a contrast agent with oxygen carrying capacity in ultrasound, CT scan, MRI, angiography, liver, spleen and tumour imaging [11].

Apart from being able to transport oxygen, the desirable qualities in artificial blood are:

- No prerequisite of blood grouping, cross-matching and compatibility tests.
- Long shelf life (preferably at room temperatures).
- Survival in circulation for a substantial period (the intravascular "dwell" time before being cleared from the kidneys.
- Absence of pathogens and their adverse effects. Able to effectively deliver oxygen to tissue in addition to transportation. Current strategies to produce artificial blood include synthetic production, chemical isolation and recombinant biochemical technologies. Conventional blood substitutes belong to either of the two classes: Haemoglobin-Based Oxygen Carriers (HBOCs) or Perfluoro Carbons [11].

cComposition of artificial blood/oxygen carriers perfluorocarbons (PFCs)

These are synthetic artificial blood products which are derived from fluorine-and carbon-containing synthetic compounds. They are artificially inactive, however, more viable than water or blood plasma in dissolving and retaining oxygen in the lungs and transporting oxygen throughout the body. PFCs remain in the circulatory system for around 48 hours [14]. In light of their oxygen-dissolving capacity, PFCs were the principal artificial blood products considered by researchers. They are the original blood substitutes. Unlike red coloured HBOCs, PFCs are typically white. PFCs are such acceptable oxygen transporters that scientists are currently attempting to discover if they can lessen enlarged cerebrum tissue in serious brain injury. PFC particles may cause influenza-like side effects in certain patients when they breathe out these mixtures. These particles are equipped for dissolving many gases including oxygen. PFCs can convey more oxygen than red cells do. PFCs are hydrophobic (water-repellent), so they are first emulsified in other substance before intravenous infusion [15]. The emulsified drops segregate inside the vein, and the PFC circulates in the blood by releasing oxygen. The PFC is ultimately delivered through the lungs as the individual exhales, similar to how carbon dioxide is processed out of the lungs, and the liver and kidneys eliminate the emulsifiers. Examples of PFC blood substitutes include: oxygent, perftoran, fluosol-DA-20, PHERO2, oxycyte [16, 17].

Perfluorocarbons

Perfluorocarbons are chemically inert, odourless compounds that have been used in the past for various medical applications, such as nanoinaging, due to their properties. They can dissolve huge amounts of gases and can be potent oxygen carriers [14].

Various types of PFCs:

Perfluorocarbons are used as artificial oxygen carriers in synthetic blood to act as RBCs. Within the literature, the types of PFCs used to form the artificial blood are:

Fluosol-DA: This was the first oxygen carrier developed, Fluosol-DA (20%), after the experiment on the survival of mammals breathing organic liquid was conducted, which led to the revolution in the field of finding a suitable substitute for human blood. In comparison, the mice that were breathing the liquid fluorocarbon for 1 hour, with those breathing the silicone oils, survived for several weeks after removal from the fluid. The diffusion of oxygen through the fluorocarbon is four times as fast as through saline [18]. Experimental studies proved that Fluosol-DA has sufficient oxygen-carrying capacity to maintain cardiac function during perfusion in larger animals. But to ensure safety and to avoid the risk to the myocardium, the carrier solution for the Fluosol-DA must be adjusted to an appropriate electrolyte content [14]. The storage requirements for Fluosol-DA led to its market withdrawal, as the product had to be kept at very low temperatures, then thawed and mixed with additives before use [19].

Perftoran: Perftoran was developed in Russia as an oxygen-carrier for patients facing acute blood loss due to anaemia. It was approved in Russia in 1996 and used extensively for acute haemorrhagic anaemia. It was tested on 964 people with different conditions like haemorrhagic anaemia, trauma, sepsis, limb ischemia, cardiac surgery, and organ transplantation.

DOI: https://doi.org/10.53704/fujnas.v14i1.627

The results show improved oxygenation and also reduced need for allogenic blood. It was administered to 30,000 people, and all these results showed the useful effects with mild and manageable side effects. Perftoran infusions were accompanied by acceleration of platelet aggregation and disaggregation, diminution of acidosis, and inhibition of peroxidative waste production in the blood by 1.5-2.0 times, resulting in improvements in recovery and possibly reduction in mortality and morbidity [20].

Dodecafluoropentane (DDFPe): The utilisation of Dodecafluoropentane emulsion (DDFPe) as a technique for oxygen delivery has shown promise in addressing severe medical conditions such as haemorrhagic shock and traumatic brain injury [21]. This innovative approach has the potential to save lives in battlefield scenarios and traumatic injuries by enabling its application in prehospital settings. By facilitating the early reversal of hypoxic conditions, DDFPe can reduce the severity of injuries and provide additional time for the successful transportation of injured patients. The emulsion, stabilized at a concentration of 2% weight/volume, contains DDFPe particles with a mean size of less than 260 nm. Once introduced into the bloodstream, DDFPe travels to the lungs to pick up oxygen and subsequently delivers it passively to hypoxic tissues. Dodecafluoropentane distinguishes itself from previously developed perfluorocarbons through its significantly lower boiling point, molecular weight, and enhanced oxygen-carrying capacity [22]. It is worth noting that the particle size of PFCs tends to increase over time and may be affected by deviations from standard temperature conditions. The shelf life of DDFPe is approximately 2 years at 4 °C and 1 year at room temperature. However, the shelf life decreases when exposed to higher temperatures. Despite several advantages over other PFCs, DDFPe failed to effectively treat decompression sickness in a rat model due to microbubble expansion [23].

Limitations of PFC:

Original PFCs were liable for supplement activation. Particularly, those which were lecithin-based demonstrated cytotoxicity of phagocytic cells like granulocytes and monocytes. PFC is known to make influenza-like manifestations, which happen due to opsonisation and phagocytosis of PFC emulsion by the individual's immune system capacity. Openings to high oxygen focus during PFC implantation can lead to oxygen toxicity. PFC is additionally involved in a transient decrease in platelet counts, which starts 3-4 days after administration and standardises by 7 to 10 days. Additionally, PFC products can't be utilised by the human body and should be eliminated; this cycle requires nearly 18-24 months. They can overburden the reticulo-endothelial system and reduce its capacity [12].

Haemoglobin-based oxygen carriers (HBOCs)

HBOCs are made from sterilised haemoglobin and look fairly like real blood. These dim red or burgundy shaded blood substitutes are regularly produced using RBCs of expired human blood, cow blood, haemoglobin-delivering genetically adjusted microbes, or human placentas. The components of artificial haemoglobin are adjusted to make a strong framework to work without the protective cover of RBCs [24]. Through a compound interaction called polymerization, at least two to three atoms bond together to shape a large HBOC particle. HBOCs are more modest than regular RBCs. While normal RBCs remain active in the circulatory system for around 120 days, HBOCs circulate in human blood for just a day. Results of HBOCs might incorporate raised circulatory strain, abdominal distress, and a transient reddish tinge of the eyes or skin. Haemoglobin is the regular oxygen transporter, and substitute blood products made with haemoglobin open a significant area of research to explore [8]. Haemoglobin without the cell membrane (stroma-free haemoglobin) breaks down rapidly and can cause coagulation issues, hypertension and kidney damage. Analysts developing this type of experimental blood substitute should purify and change the haemoglobin to make it steadier [8]. Examples include Hemopure, engineered haemoglobin, polyheme, MPO4X, and Hemotech. Techniques used to stabilise haemoglobin include: recombinant haemoglobin, polymerised haemoglobin, haemoglobin wrapped in a fatty capsule, haemoglobin cross-linked with enzymes, conjugated haemoglobin, etc.

HBOCs are prepared to fulfil the following activities:

- In order to increase tissue unloading, the inherent decrease in oxygen capacity,
- Decrease in colloidal osmotic activity,
- Prolong intravascular retention,
- Source in the absence of renal toxicity [25].

Limitations of HBOC:

DOI: https://doi.org/10.53704/fujnas.v14i1.627

HBOC's circulation half-life is limited compared to normal RBCs. A larger part of HBOC stays available for use for around 20-30 hours, while the entire blood transfusion lasts 34 days. They discharge free revolutionaries inside the body from free haemoglobin and the breakdown products like haem and iron. Methemoglobin concentrations likewise increase because of the oxidative properties of HBOCs. The best option for obtaining haemoglobin is obsolete human blood, which is in limited supply. Subsequently, bovine blood should be used for the acquisition of haemoglobin [26].

Success and other significances of artificial oxygen carriers over RBCS

Faster and better oxygen distribution: These molecules allow full-capacity oxygen transport immediately after transfusion, unlike stored blood, which requires 24 hours to attain full oxygen-carrying capacity due to depletion of 2,3-diphosphoglycerate. Higher extraction rates and ratios of PFC's allows for reaching 90% of the oxygen carrying capacity compared to only 25-30% for haemoglobin. Low affinity for oxygen allows for rapid unloading of oxygen to the tissues. They can ensure adequate oxygen delivery at haemoglobin levels of 2 gm/dl without adverse effects[27]. The real processes are illustrated in Fig. 2 [28].

Longer shelf life: They can be stored at room temperature for prolonged periods (1-3 years) and are ready to be used, as compared to stored blood, which can be stored for around 35-42 days. There is no need to refrigerate these products.

Universal compatibility: Since all the protein components are removed, the human immune system does not recognise it as a foreign entity. Hence, the necessity of compatibility testing based on blood groups is avoided. The possibility of clerical errors, which might result in mismatched transfusions, is also evaded [29].

Prevention of transmission of infectious/anaphylactic agents: Products are sterilised, and hence, chances of viral or disease transmission are alleviated.

Reduction in ischemic: Inflammatory and reperfusion injury.

Jehovah's witness: This religious group's belief prohibits the acceptance or donation of blood or blood products. Due to the chemical nature of PFC, it can be an acceptable and practical alternative for this group to fulfil the need for blood transfusions [30].

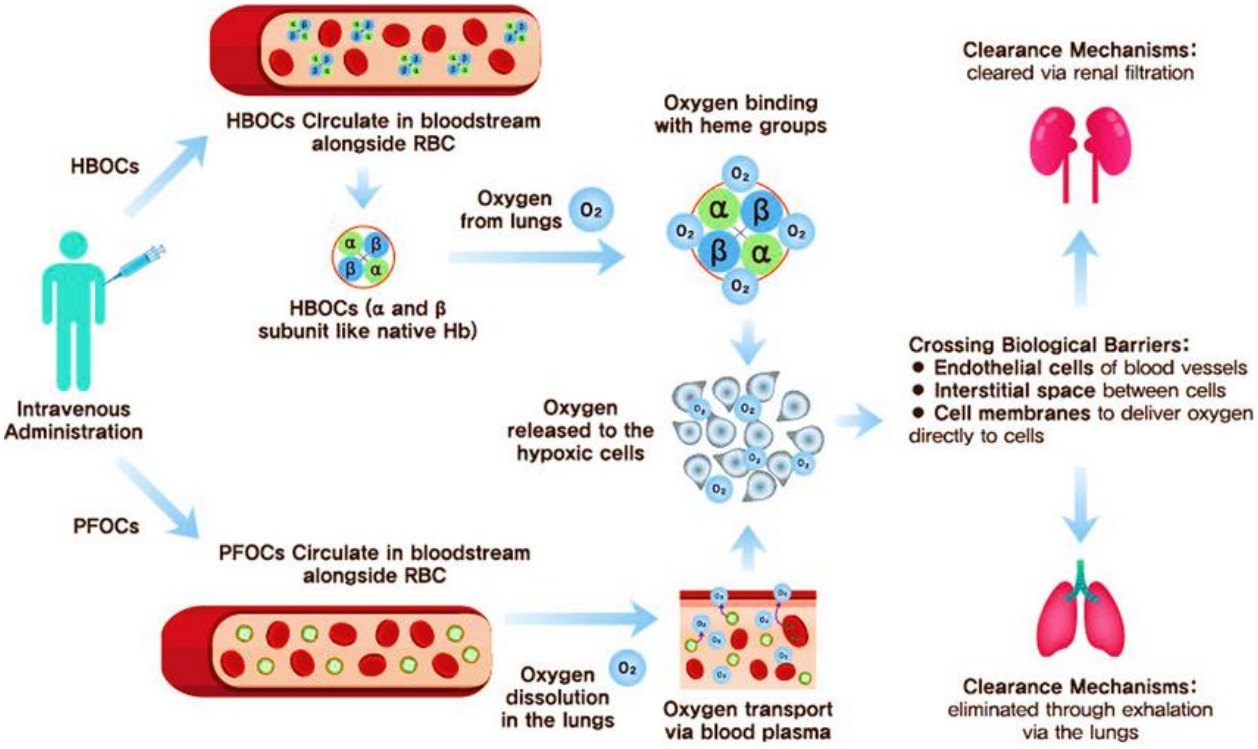

Figure 2: Schematic Presentation of Oxygen Delivery Mechanism of Artificial Oxygen Carriers. Adapted from [28].

Challenges associated with the use of artificial oxygen carriers and PFCs:

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Although artificial oxygen carriers recorded a huge success to the present day, a lot of challenges have also been attributed to their use, including safety concerns, lack of other natural constituents that are in the blood, e.g., clotting factors, cost implications, limited oxygen carrying capacity, and limited immune-motivated activities. Others include:

- First-generation PFC were responsible for complement activation, especially those which were lecithin-based, demonstrated cytotoxicity of phagocytic cells like monocytes and granulocytes.
- PFC is known to cause flu-like symptoms, which occur due to opsonisation and phagocytosis of PFC emulsion by the recipient organism's immune system.
- Exposures to high oxygen concentration during PFC infusion can result in oxygen toxicity.
- PFC is also implicated in a transient reduction in platelet counts, which begins 3-4 days after administration and normalises by 7 to 10 days [31].

Also, PFC products cannot be used by the human body and need to be removed, and this process requires around 18-24 months.

- They can overload the reticuloendothelial system and suppress its function. As it can be retained in organs, histological effects like appearances and enlargement of vacuolated histiocytes are seen in liver biopsies. Higher rates of neurological complications have been found in human cardiac surgery cases [32].

Conclusion

Artificial blood offers several advantages over stored blood, including faster and more efficient oxygen distribution. Unlike stored blood, which requires 24 hours to achieve full oxygen-carrying capacity, artificial blood provides immediate oxygen transport. It also has a significantly longer shelf life, ranging from 1 to 3 years at room temperature, compared to 35–42 days for stored blood. Being sterilised, artificial blood eliminates the risk of viral or disease transmission often associated with allogenic blood transfusions. Furthermore, it bypasses the dependency on blood donors, addressing the persistent scarcity of non-remunerated blood donors.

Acknowledgement: I extend my heartfelt gratitude to all the authors who generously contributed financially towards the publication of this manuscript. I am especially thankful to the authors for their unwavering support, guidance, and encouragement throughout the process.

Conflict of interest: The authors declare no competing interests.

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