

Review Article

Investigation on artificial blood or substitute blood replace the natural blood

Keyhanian Sh PhD¹, Ebrahimifard M MSc^{2*}, Zandi M MSc³

1. Associate Professor of Oncologist, Islamic Azad University of Tonekabon, Tonekabon, Iran

2. Young Researchers and Elite Club, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

3. Department of Biology, College of Sciences, Damghan branch, Islamic Azad University, Damghan, Iran

Received: 5 November 2013

Accepted: 23 May 2014

Abstract

Blood is a liquid tissue in which dissolved with abundant chemical factors and millions of different cells. The reduction of unwanted side effects, especially diseases that emerge through blood such as HIV and hepatitis, has a significant role for modern medicine of transfusion and transplantation. The issues and costs of human blood collection and storage, direct this procedure towards the use of alternatives blood. Two important research fields of this area were oxygen carriers based on hemoglobin and perfluoro chemicals. While they do not have the same quality as the blood cell products, the oxygen carrier solutions have potential clinical and non-

clinical applications.

The result showed that these products can reach to the body tissues easier than normal red blood cells, and can control the oxygen directly. The final aim of transfusion is to establish a transfusion system with no side effects, and the fact that oxygen carrier artificial blood has this property. The article attempts to step towards solving some problems of blood transfusion through describing the properties of artificial blood alternatives.

Keywords

Hematology, Artificial Blood, Perfluoro, Hemoglobin, Blood Transfusion

Corresponding Author:

Ebrahimifard M MSc, Young Researchers and Elite Club, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran. Email: m_ebrahimifard_21@yahoo.com

Introduction

There was a retry to adequate blood replacement so they could be kept in one category for any time or place without considering the blood type. Injection of any material other than autologous blood is the transfusions to replace the blood. So the history of blood transfusion can be considered as an alternative blood history (1,2,3). Substances like milk, casein derivatives, starch and saline were the first material to inject from one human to other human. Since World War II, the study of blood proposes was taken seriously to overcome large-scale situations like civilian events. Blood composition and functions of each replacement is clear except for portability oxygen (4,5).

This is a significant approach in two main replacements, means Hemoglobin and Perfolocarbon solutions (PFC).

Suggestions for allogeneic RBC have been an attempt to timely action against the adverse effects of blood transfusion. The risks involved in blood transfusion include infection, delayed wound healing associated

with reactions transfusion, transfusion dependent chronic lung injury, and the potential recurrence of cancer of the immune system. Prevalence of HIV transmission by blood transfusion is about one in a million in 5.2 million units of blood and, hepatitis C risk is one in 100,000 to one in 350,000 units. Non-infectious complications are associated with allogeneic transfusion. Some examples or for example, hemolytic transfusion reactions, transfusion-related lung diseases, diseases of organ transplants, and anaphylactic reactions, and purpura after they are transferred (6,7,8). Special techniques to reduce the need for blood transfusions have been developed during surgery. These techniques included the use of erythropoietin, drug treatment, surgical techniques and the minimum acceptable level of hemoglobin and blood substitutes (3,9). Currently, studies about blood transfusion are emphasized on Hemoglobin and Perfolocarbon solutions. (10)

Fluorocarbon-based blood substitutes

To modify human or animal hemoglobin is one of the ways to create a blood substitute and thus help to solve the problem of lack of blood replacement the other way is to use materials better than hemoglobin. Thus, fluorocarbon chemicals were invented to replace the function of hemoglobin (11).

Fluorocarbon compounds

Liquid fluorocarbons are neutral chemical compounds in which hydrogen ions have been replaced by fluorine. They are sufficiently good solvents for oxygen and carbon dioxide to maintain the respiration of animal organisms (11,12,13).

Fluorocarbons are colorless, odorless, non-inflammable fluids of high density, stable in very high temperatures, entering poorly into chemical reactions, and poorly soluble. Their boiling point is low, as or because of their surface tension and viscosity. They differ in their molecular structure, boiling point, and oxygen solubility and the differences determine the variations in their biological action and in the time of their persistence in the organism. For blood replacement and for systemic and organ perfusion fluorocarbons are used in the form of emulsions: FX80, FC75, FC43, FC17 (perfluorotetrahydrofuran, perfluorotributylamine) and lately also perfluorodecaline and perfluoromethyl decaline.

Fluorocarbon alone injected intravenously causes death of the animal since it does not mix with blood and produces pulmonary embolism, right ventricular failure, and asphyxia. Sloviter et al showed that the pulmonary changes result from the production of platelet and not fluorocarbon emboli (11, 14).

Fluorocarbon emulsion is usually well tolerated, although at the beginning of perfusion. They often cause a fall in arterial blood pressure. The emulsifiers used including bovine albumin, lipids, and polyols for example, Pluronic F68, a mixture of polyoxypropylene and polyoxyethylene. The emulsions are produced by the use of mechanical energy or ultrasound, and selection of the right degree of dispersions of great importance for ensuring easy flow through the capillary vascular system and for obtaining the viscosity, gas diffusion capacity, and time of retention of the fluorocarbon in the circulation (14).

Why fluorocarbon can be considered as an oxygen carrier?

PFC is able to carry and release high volume oxygen to tissue, which is even more volume of physically dissolved gas relies on the solubility coefficient for that gas of the PFCs utilized, and is proportional to the gas' partial pressure. This situation leads to several-fold increase of the oxygen concentration in

PFCs emulsion by increasing oxygen concentration in the air inspired by the patient (15).

Because of the weak interaction between oxygen molecules and PFCs, the release of O₂ to tissues is greatly enhanced, and extraction rates and ratios are a lot higher with PFCs, which is able to reach 90% oxygen of its carrying, compared to only 25-30% for hemoglobin (15,16,17).

PFCs are non-reactive, and very stable for chemical properties.

Hemoglobin-based oxygen carrier (HBOC)

Hemoglobin is an obvious candidate for blood substitute that has a number of desirable features. The carrier has the ability to carry oxygen, and is countless of non-antigen complexes of RBC membrane (9,18,19). According to molecular stability improvements techniques, there are 4 groups of Hemoglobin cells. Surface modified hemoglobin - the molecule linked hemoglobin - polymerized hemoglobin - the hemoglobin liposomal capsule. HBOCs has half-life of 18 to 24 hours, which are sufficient for use in acute care. And they can be maintained for a period of 1-2 years in room of 4°C (21,24,25). The oxygen affinity of HBOCs is less than human's major blood (26).

Traditionally it is recommended that for less than 600ml of blood, plasma expanders should be used. For 600-1200ml, red blood cells products are essential, and blood plasma derivatives or products such as low platelets or whole blood transfusion is critical. Blood substitutes should be used as a suggestion and / or complementary transfer of autologous or homologous or should be used in combination with Rito Protein (6, 27).

Human recombinant hemoglobin

Hoffman and his colleagues described this human hemoglobin in E.coli in 1990. Luker and his colleagues in 1992 modulated the same hemoglobin as an artificial oxygen carrier, and generated rHb1.1. A2β2 titrimetric hemoglobin is stabilized by the fusion of two α chain reducing renal toxicity associated with a titrimetric structure. The second generation of rHb2.0 hemoglobin has less NO than rHb1.1. But its production, despite favorable environmental effects as a side effect profile similar to DCLHb, were investigated by Boxer in 2003 in a significant level (6,20,21,28,29,30)

Raffimer hemoglobin

Hemoglobin-based oxygen carrier hemoglobin Raffimer, Hemolicoxidase from raffinose related to human blood were obtained by Mary Bridges. This hemoglobin covers only the remaining 40% tetrameric with only partial polymerization and has a half-life of one year. During the test phase 1 Hemolic From Kormicheal and his colleagues showed benefit,

but the inductor vasoconstriction, especially in people. In phase 2, 60 patients were studied, but there was a side effect of stress. In phase 3 transmission rate in the 299 patients with cardiac bypass surgery dropped 56% compared with 76% in the control group to indicate decreases. However, in a Phase 3 registration was suspended because it was increases in cardiac diseases. So Hemolic production ended in 2003 (31,32,33,34,35).

Modified hemoglobin - activated polyethylene glycol - maleimide (MP4)

MP4 was produced by the Winslow & Sangret company. Hemoglobin molecules have been activated by surface interaction with polyethylene glycol maleimide. MP4 with high oxygen affinity of hemoglobin concentration was less 4/2g/dL of p50 was 2/5cp 60mmHg and high viscosity. (36,37,38).

Bridge enzyme-linked hemoglobin

Dismutase is an enzyme-linked hemoglobin product like this Catalase superoxide. They had advantages when used as oxygen carrier for the treatment of organ ischemic. Reperfusion in a mouse model confirmed a decreased production of oxygen free Radikal, but studies on animals or even humans do not (9,20,39,40).

Stem cell hemoglobin

Giaratana and colleagues generated human RB adult stem cells developed hemoglobin. They contain the equivalent of hemoglobin and red blood cells in normal life. Stem cells are high per unit cost to produce the complexes (41).

Future uses of perfluorocarbon emulsions

Optimal use of perfluorocarbon emulsions in the future may consist of a combination of ANH preoperatively with application of an artificial oxygen

carriers such as a perfluorocarbon emulsion during the operation, a procedure termed. Augmented ANH is a concept in which patients undergo ANH to relatively low hemoglobin levels preoperatively. During the operation, when the hemoglobin concentration decreases further due to surgical blood loss and concomitant colloid or crystalloid replacement, perfluorocarbon emulsions in conjunction with 100% oxygen ventilation is administered to enhance oxygen delivery and improve tissue oxygenation. As a consequence, lower levels of hemoglobin concentration can be safely tolerated (12,25,42,43,44)

Results

With the advance in bio-technology, there will be more blood substitutes available, which could permanently replace the natural blood. The substitute holds this kind of promise is artificial blood powder. The ultimate goal of the transmission is the transmission system without any side effects and effective for the treatment. Although the current system of homologous blood has lack of issues, but it is much less expensive with fewer side effects, and is more acceptable. However, new technologies need to produce increasingly effective alternative for blood transfusion medicine. At present, the use of artificial blood due to short half-life and potential toxicity and costs, access to raw materials and the FDA is difficult. This caused temporary change to replace the red blood cells and the use of homologous blood transaction. Although the use of blood substitutes has higher safety incidence of viral infections like HIV, certainly in the near future, blood substitutes such as oxygen carrying will bring a new dimension in transfusion medicine.

Table I: Potential clinical applications of oxygen carrying solutions

<p>1- Treatment</p> <ul style="list-style-type: none"> • Blood substitutes : hemorrhagic shock; hemorrhage (war, surgery); anaemia. • Whole-body rinse out : acute drug intoxication; acute hepatic failure. • Local ischemia: acute MI; evolving MI; cardiac failure; brain infarction; acute arterial thrombosis and embolism; PTCA of coronary artery. • General ischemia: gas embolism; CO intoxication; HAPO; HACO. • Aid for organ recovery : acute renal failure; acute hepatic failure; acute pancreatitis. • Infectious disease : anaerobic and aerobic diseases;
<p>2- Perfusional protection of organs during surgery – cardiopulmonary bypass, deep hypothermia, circulatory arrest, cardioplegia.</p>
<p>3- Preservation of donor organ.</p>
<p>4- Drug carrier - drug-conjugated haemoglobin and perfluorochemicals.</p>
<p>5- Contrast agent - (Perfluoro-octylbromide)</p>

References

1. Ajit W, Anna B, Roger SH. (2006). "Autologous Blood Transfusion". Continuing Education In Anaesthesia, Critical Care & Pain, Volume 6 Number 2005; 192-196.
2. Magnus J. "Autologous Blood Transfusion", Presented At Astra Tech Symposium - My Own Blood. Gothenburg, Sweden. 2002.
3. Donat RS. "Blood Substitutes Artificial Oxygen Carriers: Perfluorocarbon Emulsions". Crit Care. 1999;3(5):R93-7.
4. Barbosa FT, Jucá MJ, Castro AA, Duarte JL, Barbosa LT. "Artificial Oxygen Carriers As A Possible Alternative To Red Cells In Clinical Practice". Sao Paulo Med J. 2009;127(2):97-100.
5. Powanda D & Chang TMS Artificial Cells, Blood Substitutes & Immobilization Biotechnology, an international journal 30:25-42.
6. Goorha YK, Prabal D, Chatterjee T, Dhot PS, Prasad RS. "Artificial Blood". MJAFI 2003; 59 : 45-50
- Moore EE, Cheng AM, Moore HB, Masuno T, Johnson JL. Hemoglobin-Based Oxygen Carriers In Trauma Care: Scientific Rationale For The US Multicenter Prehospital Trial. World J Surg. 2006;30(7):1247-57.
7. Alayash AI. Hemoglobin-based blood substitutes: oxygen carriers, pressor agents, or oxidants? Nat Biotechnol. 1999;17(6):545-9.
8. Alayash AI. Setbacks in blood substitutes research and development: a biochemical perspective. Clin Lab Med. 2010;30(2):381-9
9. Lígia G. "PERFLUOROCARBONS COMPOUNDS USED AS OXYGEN CARRIERS: FROM LIQUID VENTILATION TO BLOOD SUBSTITUTES". Edições Universidade Fernando Pessoa.
10. Alayash AI. Setbacks in blood substitutes research and development: a biochemical perspective. Clin Lab Med. 2010;30(2):381-9.
11. Riess JG. Overview of progress in the fluorocarbon approach to in vivo oxygen delivery. Biomater Artif Cells Immobilization Biotechnol. 1992;20(2-4):183-202.
12. Keipert PE1, Faithfull NS, Bradley JD, Hazard DY, Hogan J, Levisetti MS, et al: Oxygen delivery augmentation by low-dose perfluorochemical emulsion during profound normovolemic hemodilution. Adv Exp Med Biol. 1994;345:197-204.
13. Olsen G.W., Church T.R., Miller J.P., Burris J.M.,

- Hansen K.J., Lundberg J.K., et al. Perfluorooctanesulfonate and other fluorochemicals in the serum of American Red Cross adult blood donors. *Environ. Health Perspect.* 2003; 111(16), 1892–1901.
14. Squires JE. “Artificial blood” .*Science.* 2002;295(5557):1002-5
15. T.M.S Chang Blood substitutes: Principles, Methods, Products and Clinical Trials 1997 Vol. 2 P106.
16. Riess JG, Keipert PE. Update on perfluorocarbon-based oxygen delivery systems. In: *Blood Substitutes: Present and Future Perspectives.* Edited by Tsuchida E. Lausanne: Elsevier Science SA, 1998:91–102.
17. Henkel-Honke T and Oleck M. Artificial oxygen carriers: a current review. *AANA J.* 2007;75(3):205-11
18. Jahr JS, Mackenzie C, Pearce LB, Pitman A, Greenburg AG. HBOC-201 as an alternative to blood transfusion: efficacy and safety evaluation in a multicenter phase III trial in elective orthopedic surgery. *J Trauma* 2008;64(6):1484–97.
19. Khan AK1, Jahr JS, Nesargi S, Rothenberg SJ, Tang Z, Cheung A, et al. Does lead interfere with hemoglobin-based oxygen carrier (HBOC) function? A pilot study of lead concentrations in three approved or tested HBOCs and oxyhemoglobin dissociation with HBOCs and/or bovine blood with varying lead concentrations. *Anesth Analg.* 2003;96(6):1813-20.
20. Looker DI, Abbott-Brown D, Cozart P, Durfee S, Hoffman S, Mathews AJ, et al. A human recombinant hemoglobin designed for use as a blood substitute. *Nature.* 1992;356(6366):258-60.
21. Malhotra AK, Kelly ME, Miller PR, Hartman JC, Fabian TC, Proctor KG. Resuscitation with a novel hemoglobin-based oxygen carrier in a Swine model of uncontrolled perioperative hemorrhage. *J Trauma.* 2003;54(5):915-24.
22. Chang TM. Blood replacement with nanobiotechnologically engineered hemoglobin and hemoglobin nanocapsules. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2010;2(4):418-30
23. Day TK (2003) Current development and use of hemoglobin-based oxygen-carrying (HBOC) solutions. *J Vet Emerg Crit Care* 13(2):77–93.
24. Dube GP, Vranckx P, Greenburg AG. HBOC-201: The multi-purpose oxygen therapeutic. *EuroIntervention.* 2008;4(1):161-5.
25. Chang TM. Hemoglobin-based red blood cell substitutes. *Artif Organs.* 2004;28(9):789-94
26. Isbell TS, Gladwin MT, Patel RP. Hemoglobin oxygen fractional saturation regulates nitrite-dependent vasodilation of aortic ring bioassays. *Am J Physiol Heart Circ Physiol.* 2007;293(4):2565-72
27. Provan D. Better blood transfusion: we must use donated blood better and consider alternatives. *BMJ* 1999; 318(7196): 1435–6.
28. Doyle MP, Armstrong AM, Brucker EA, Fattor TJ, and Lemon DD. Design of second generation recombinant hemoglobin: minimizing nitric oxide scavenging and vasoactivity while maintaining efficacy. *Artif Cells Blood Sub Immobil Biotech* 29: 100, 2001.
29. Graves PE, Henderson DP, Horstman MJ, Solomon BJ, Olson JS. Enhancing stability and expression of recombinant human hemoglobin in *E. coli*: progress in the development of a recombinant HBOC source. *Biochim Biophys Acta.* 2008;1784(10):1471-9.
30. Kumar R. Recombinant hemoglobins as blood substitutes: a biotechnology perspective. *Proc Soc Exp Biol Med.* 1995;208(2):150-8.
31. Carmichael FJ1, Ali AC, Campbell JA, Langlois SF, Biro GP, Willan AR, et al. A phase I study of oxidized raffinose cross-linked human hemoglobin. *Crit Care Med* 2000;28:2283-92.
32. Cheng DC1, Mazer CD, Martineau R, Ralph-Edwards A, Karski J, Robblee J, et al. A phase II dose-response study of hemoglobin raffimer (Hemolink) in elective coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* 2004;127(1):79-86.
33. Greenburg AG1, Kim HW; Hemolink Study Group. Use of an oxygen therapeutic as an adjunct to intraoperative autologous donation to reduce transfusion requirements in patients undergoing coronary artery bypass graft surgery. *J Am Coll Surg.* 2004;198(3):373-83
34. Scatena R, Giardina B. O-Raffinose-polymerised haemoglobin. A biochemical and pharmacological profile of an oxygen carrier. *Expert Opin Biol Ther* 2001;1(1):121-7.
35. Chatterjee R, Welty EV, Walder RY, Pruitt SL, Rogers PH, Arnone A, et al. Isolation and characterization of a new hemoglobin derivative cross-linked between the alpha chains (lysine 99 alpha 1—lysine 99 alpha 2). *J Biol Chem.* 1986;261(21):9929-37
36. Rao SV1, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA.* 2004;292(13):1555-62
37. Vandergriff KD, Malavalli A, Wooldridge J, Lohman J, Winslow RM. MP4, a new nonvasoactive PEG-IIb conjugate. *Transfusion* 2003;43:509-16.
38. Liu ZC, Chang TMS. Effects of PEG-PLA-nano artificial cells containing hemoglobin on kidney function and renal histology in rats. *Artificial Cells,*

Blood Substitutes & Biotechnology, An International Journal. 2008; 36 in press.

39.Spahn DR1, KocianR.Artificial O2 Carriers: Status in 2005. Curr Pharm Des. 2005;11(31):4099-114.

40.Vandegriff KD. Haemoglobin-based oxygen carriers. Expert OpinInvestig Drugs 2000;9(9):1967-84.

41.Creteur J, Vincent JL. Haemoglobinsolutions : an “all-inone” therapeutic strategy in sepsis? Crit Care Med 2000;28(3):894-6.

42.Keipert PE: Perfluorochemical emulsions: future alternatives to transfusion. Blood SubstPrinc Meth Prod Clin Trials 1998; 2:127–156.

43.Monk TG, Winston RS, Wahr JA, et al, Perflubron Emulsion Study Group: Safety and coagulation profile following administration of

perflubron emulsion in patients undergoing moderate blood loss surgery [Abstract]. Anesthesiology 1998; 89 (suppl):A397.

44.Paxian M. Synthetic oxygen carriers as an alternative to foreign blood transfusion. Anaesthesist 2001;50Suppl 1:43-9.

45.Keyhaniash, Ghavamzade A, Bahar B, Alimoghaddam K, Shamshiri AR, Gholibeikian S : Non –Myeloablative stem cell transplantation in hematologic malignancies : an experience from the hematology – oncology and BMT research center.International journal of hematology-oncology & bone marrow transplantation .vol.1,No.2,May 2004.

46.Keyhaniash, Gholizade Z, Nazemi A : The frequency of ordering and consuming blood products in EmamSajad hospital in Ramsar.Journal of modern studies of blood.vol.2,No.2, winter 2010.