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A REVIEW ON ARTIFICIAL BLOOD

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ABSTRACT:

Blood is one of the most demanding sources in clinical and medical aspects due to its vital roles in man's day –to-day life. It is highly impossible to survive without it. But in 21st century due to increased population, population aging, generation of new infections and natural disasters increased the cost of storage and maintenance of collected blood. This has directed the world to find an alternate source i.e. artificial blood. Artificial blood is an innovative concept of transfusion of medicine where specifically designed compounds perform the task of transport and delivery of oxygen in the body to replace the functions of allogenic human blood transfusion. It is one of the evolutionary innovations which might lead the way to a new era in medicine. In this review, the importance of artificial blood is high-lighted and also the present status and improvement in the development of artificial blood substitutes mainly focusing on red blood cells substitutes are summarized. In addition, some of the promising benefits and disadvantages of this concept are also elaborated.

KEYWORDS: Artificial blood, oxygen carriers, hemoglobin, red blood cells

INTRODUCTION:

There has been a need for replacement of blood for as long as patients have been bleeding to death because of a serious injury. According to the medical folks, the ancient Incas were responsible for the first recorded blood transfusion[1]. No real progress was made in the development of the blood substitutes until 1616. When William Harvey described how the blood is circulated throughout the body it played a vital role later. In the years to follow, medical practitioners tried numerous substances such as beer, urine, milk, plant resins and sheep blood as a substitute to blood[2].later isolated hemoglobin and animal plasma are also tried as artificial blood substituent. In 1868, researchers found that solution containing hemoglobin isolated from RBC could be used as replacement for blood. In 1871, they also examined the use of animal plasma and blood as a human blood substitutes, but both of these approaches were stopped due to significant technological problems. First, scientists found it difficult to isolate a large volume of hemoglobin and next animal products contained many substances that are harmful to humans. Removing these toxins were challenging during the 19th century. But artificial blood was strongly highlighted after emergence of HIV in 1980 due to its risk of transmission through blood transfusion which imposes higher cost due to the necessary detection tests. In addition low blood supplies especially in developing countries, lower number of donors due to aging population, short storage period and consequently increased demand for blood products are other important reasons made development of suitable blood substitutes as an important aspect. In recent years, development of an agent which exactlymimics' the oxygen carrying capability of blood among its various functions have gained great interest[3]. Hence the products developed are also called as oxygen carriers. Based on this, Currently two different products are under development as blood substitutes and they are one is hemoglobin based product and the other is perflurocarbons(PFC).hemoglobin based products utilize components of red blood cells and PFC is totally a synthetic chemical process.

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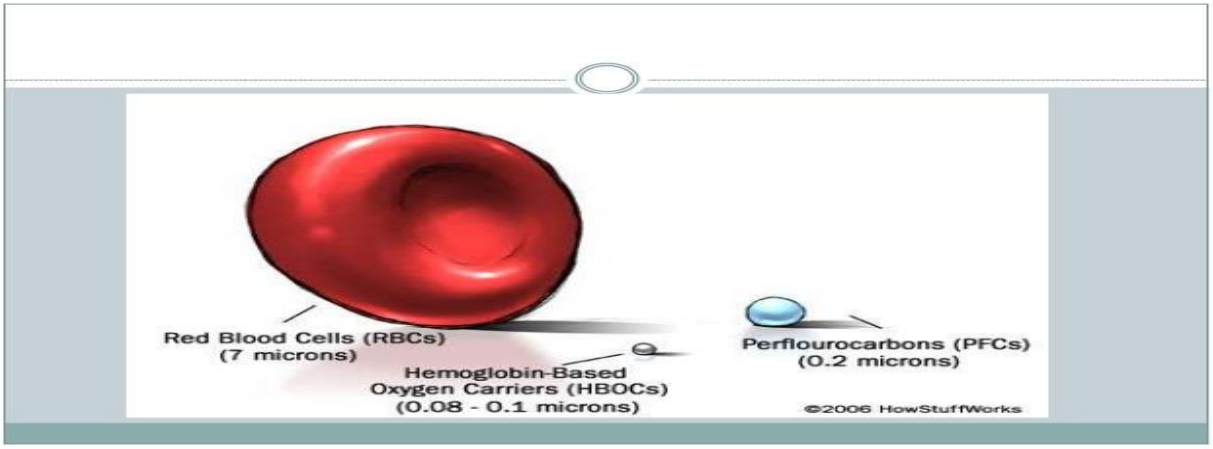

Fig.no-1. Comparison size of normal RBC to that of artificial blood substituent

1.1 perflurocarbons based oxygen carriers:

Perflurocarbons (PFCs) are colorless, inert, and apparently nontoxic liquids with low boiling point temperatures and are insoluble in water and alcohol. The capacity of PFCs in carrying oxygen was demonstrated for the first time by Clark in 1966 by using mice. Surprisingly, the mice was found to survive even after being immersed in PFC and the animals lived for a few hours and recovered completely after their blood was replaced .So PFCs can be considered as biologically inert materials and they can also dissolve about 50 times more oxygen than blood plasma. Their production is cost effective and can be made without any biological materials and this eliminates the possibility of spreading an infectious disease through blood transfusion.

Table no-1: Composition of perflurocarbons based oxygen carriers:

Name of the compound	**percentage**
Distilled water	57.8%
DSPE-50H	0.12%
Perfluoro-octyl bromide	28%
Fo-9982	12%
Yolk lecithin	2.4%

Table no-2: Advantages and disadvantages of PFCs:

Advantages	**Disadvantages**
1. Does not react with oxygen.	1. Causes flu like syndrome when administered.
2. Allows easy transportation of oxygen to the body.	2. It is not soluble in water and hence it should be formulated as emulsion for patient's use.
3. PFCs allow more solubility of oxygen in plasma.	3. May lead to mild thrombocytopenia (reduced platelet count).
4. Their small size enables them to enter into vessels which are occluded in some diseased conditions.	4. PFCs absorb oxygen passively hence the patient need to breath in linear way to ensure oxygenation of tissues.
5. Minimizes the effect of pH and temperature on blood circulation	5. As the products of PFCs are harmful for human use they need to be discarded and this takes more than 18 months.

1.2 Hemoglobin based oxygen carriers:

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Hemoglobin carries oxygen from the lungs to the other tissues in the body. Artificial blood based on hemoglobin takes advantage of this natural function[4].The key mechanism of hemoglobin based oxygen carriers is oxygen covalently bonding to hemoglobin. These hemoglobin products are different when compared to normal blood so they are not contained in a membrane and hence theproblem of blood typing is eliminated. Human hemoglobin derived from expired RBC bags is the main source of hemoglobin for the production of hemoglobin-based RBC substitutes[5]. Other sources for this purpose include cord blood RBCs and animal (bovine) and recombinant Hemoglobin. The hemoglobin-based oxygen carriers (HbOCs) are divided into two groups: AcellularHbOCs and Cellular HbOCs.

1.2.1 AcellularHbOCs:

Acellular HBOCs have been developed to increase Hb performance and decrease its side effects (These are now in various phases of clinical trials and belong to three categories including cross-linked HBOC, polymerized HBOC, and conjugated HBOC). However, among different modifications of Hb, only nanotechnology-based polyhemoglobin (PolyHb) and conjugated Hb are effective. However, due to their short blood half-lives and side effects, a majority of these products did not achieve required criteria in clinical trials[6]. One of the main problems limiting the application of these products is their inability to convert Fe^{3+} to Fe^{2+}, which is an important function of RBCs. As a result, Met-Hb with low oxygen-carrying capacity was produced, showing that such complications can be avoided by attaching reducing agents to Hb surface in this product series.

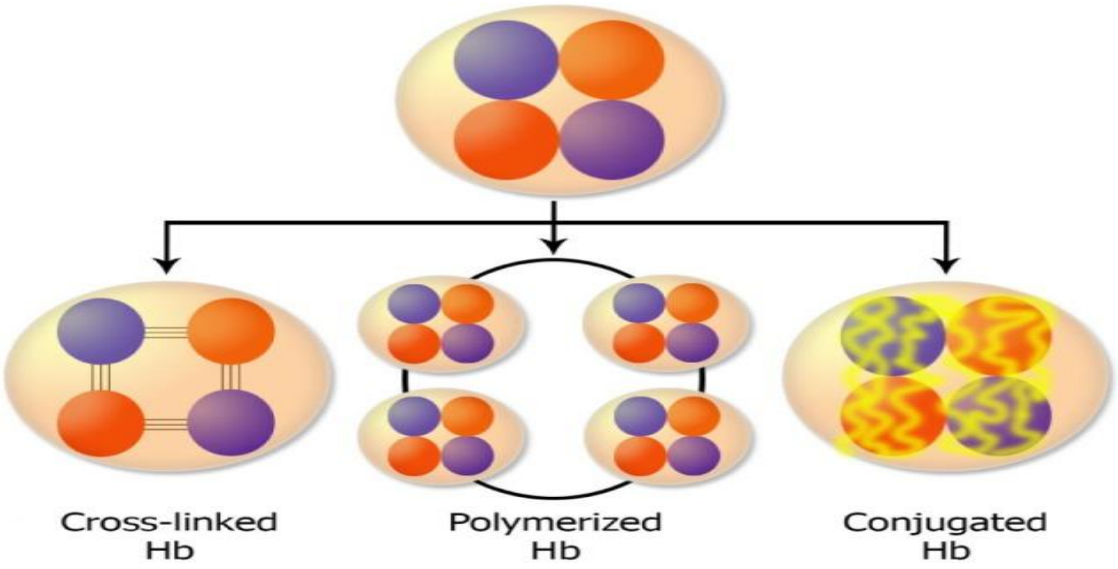

Fig.no-2 different types of acellularHbOCs:

1.2.2 Cellular HbOCs:

Other types of Hb-based products as artificial blood are cellular HBOCs, in which Hb is encapsulated in a cell-like structure[7]. In this way, some products with highest similarity to RBCs were produced, which do not cause vasoactivation due to scavenging of nitric oxide. Encapsulation of Hb by a phospholipids layer prolonged its half-life and shelf-life comparing to acellular products. LEH particles are much smaller than RBCs (1:30). This small size enables their entry into areas of body that are not accessible for RBCs. Hence they can pass through clots and blockages even during stroke conditions which enable more oxygenation. Though it seems to have many promising benefits it also has its own demerits. Among them the major drawback of this product is that it has a short circulation half-life.but this can be solved by a number of approaches for example by PEGylation of the particles' surface. In a study, liposome-encapsulated Hbs known as neo red cells were developed, and their efficiency as artificial RBCs was demonstrated in total cardiopulmonary bypass in an animal study, which showed even higher oxygen delivery capacity than RBC[8]. Modifying the surface of this liposome, including PEGylation, can result in

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products with higher half-life, stability, and solubility, as well as lower antigenicity and immunogenicity. Hb vesicle is a PEGylated product with increased serum half-life and decreased recognition by the immune system.

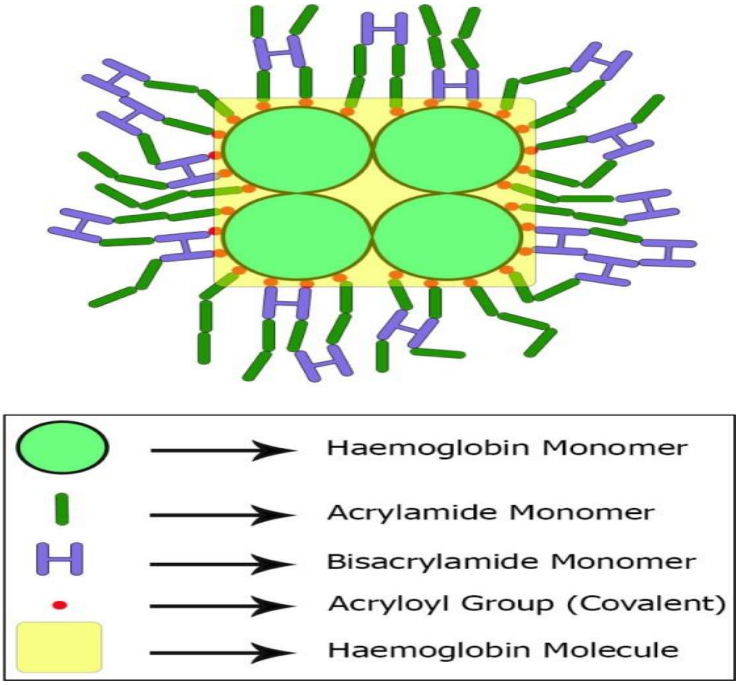

Fig no-3: typical structure of a cellular HbOCs

1.3 Red blood cells differentiated from stem cells:

The real RBCs are RBCs which are differentiated from stem cells. These cells can be used as an ideal product for injecting to the patients requiring blood transfusion in emergency conditions as well as for patients with rare blood groups. Stem cells derived from various sources including bone morrow, cord blood, embryonic stem cells, and induced pluripotent stem cells (iPSCs) have been used for this purpose. RBCs were derived from iPSCs from fetal and adult human fibroblasts for the first time by Lapillonne et al[6]. This suggests that iPSCs could pave a way for an unlimited supply for the production of RBCs for clinical application. Mass production of RBCs in laboratory for their application in transfusion have been performed by adjusting various production conditions such as providing optimal culture conditions for cord blood-derived hematopoietic stem cells and subsequent coculture of erythroid progenitors with human fetal liver stromal cells[9]. This resulted in improved terminal erythroid maturation process and plenty of cells were obtained, which were comparable with natural RBCs in many properties. Immortalized erythrocyte progenitor cells are obtained through the introduction of C-MYC and BCL-XL into multipotent hematopoietic progenitor cells derived from pluripotent stem cells. Over expression of these proteins led to erythroblasts which have high self-replication capacity. Elimination of over expression of these genes induced the differentiation of these erythroblasts to mature erythrocytes. Exposing $CD34^{+}$ cells to a short pulse of cytokines is required for erythroid differentiation before their expansion. Although it was found to be highly beneficial its mass production and high production costs for clinical applications are the most important problems in this field. But this could be possibly overturned in the coming future.

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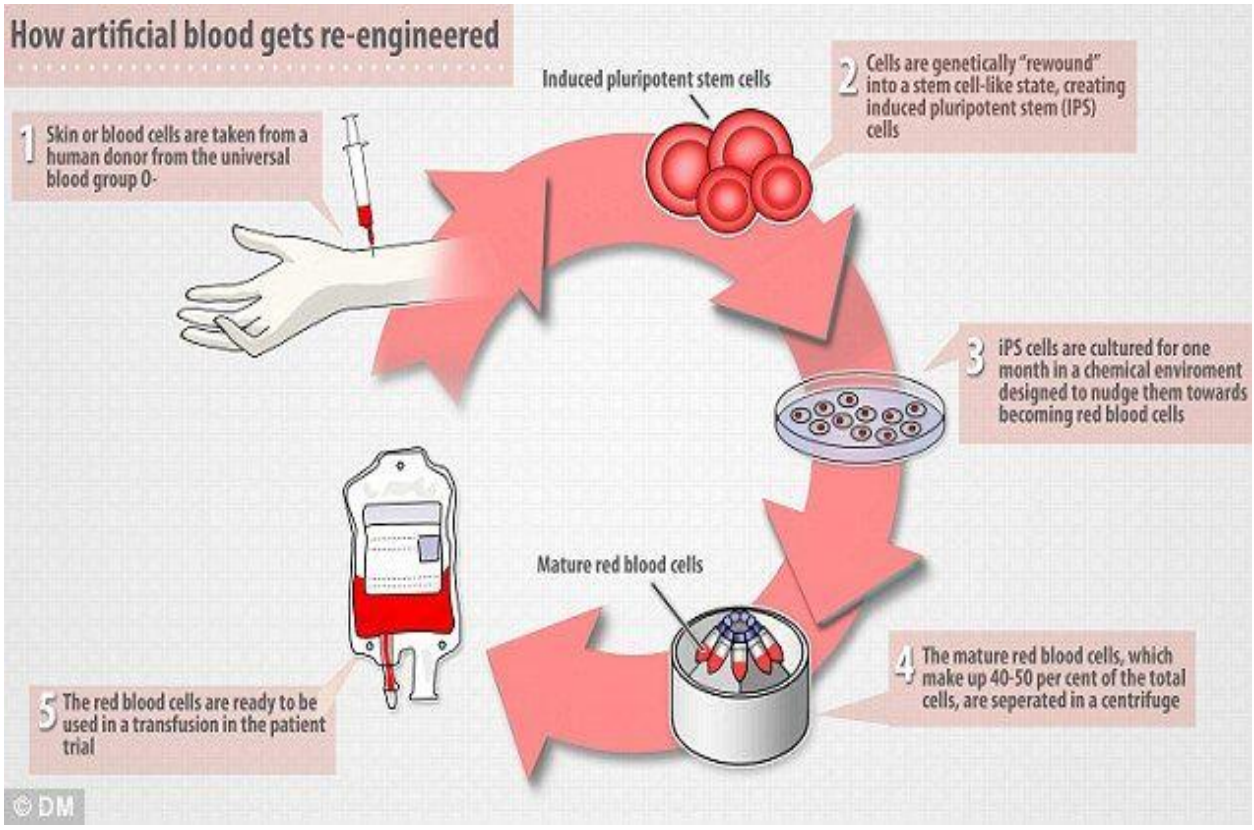

Fig.no-4: method to differentiate RBCs from stem cells

SUMMARY:

Table.no-3: Summary of key blood substitutes that are approved, in clinical trials, or withdrawn.

Name of the blood substitute	Blood Substitute Class	Information on Clinical Trials	Approval status
Fluosol-DA-20	Perflurocarbons	Clinical-Trials completed in 1980s: Discontinued due to side effects	It was approved in 1989 but withdrawn in 1994
Oxygent	Perflurocarbons	Phase Clinical III trials: Increased risk of stroke	Not Approved; Phase III trials stopped
Perftoran	Perflurocarbons	Completed (Russia)	Approved in Russia and Mexico
Oxycyte	Perflurocarbons	Phase II Clinical Trials (traumatic brain injury)	Not Approval; Further research is needed

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		underway in Switzerland and Israel	
PHER-O2	Perflurocarbons	Pre-clinical-Trials underway	Not Approved; Further research is needed
Oxyglobin	Hemoglobin based oxygen carriers	Trials completed by late 1990s: Canine anemia	Approved for Veterinary Medicine
Hemopure	Hemoglobin based oxygen carriers	Completed (South Africa)	Approved (South Africa); May be withdrawn
PolyHeme	Hemoglobin based oxygen carriers	Phase III Trial (U.S.A): Increased side effects in treatment group; no difference in 30 day survival rate	Not Approved; Further research is needed
MP4OX (Hemospan)	Hemoglobin based oxygen carriers	Phase II Trials (U.S.A): Raised oxygen levelswithout fatal side effects	Not Approved; Further research is needed

CONCLUSION:

Based on the literatures retrieved, artificial blood development is still in experimental stage. None of The product has been approved by FDA for clinical use in US except for Fluosol-DA. There were sufficient evidences on the harmful effect of oxygen therapeutics products more research is needed to develop a safe product for human use. But the efforts made so far assures that a blood substituent with diverse features and safe for human use can developed in coming years.

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