A REVIEW ON ARTIFICIAL BLOOD

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ABSTRACT

Artificial blood is a product made to act as a substitute for red blood cells. While true blood serves many different functions, artificial blood is designed for the sole purpose of transporting oxygen and carbon dioxide throughout the body. Depending on the type of artificial blood, it can be produced in different ways using synthetic production, chemical isolation, or recombinant biochemical technology. Development of the first blood substitutes dates back to the early 1600s, and the search for the ideal blood substitute continues. Various manufacturers have products in clinical trials; however, no truly safe and effective artificial blood product is currently marketed. It is anticipated that when an artificial blood product is available.

KEYWORDS: Blood, Artificial blood, Per fluorocarbons.

INTRODUCTION

Artificial blood is a product made to act as a substitute for red blood cells. Blood substitutes are used to fill fluid volume and/or carry oxygen and other blood gases in the cardiovascular system. Human blood performs many important functions which blood substitutes may not. Red blood cells transport oxygen, white blood cells defend against disease, platelets promote clotting, and plasma proteins perform various functions. Donated blood has a relatively short shelf-life of 35 days, after which it must be thrown away. It also needs refrigeration, whereas the plastic blood will be storable for many more days and is stable at room temperature [1]. Artificial blood is a product made to act as a substitute for blood for the transportation of oxygen and carbon dioxide throughout the body. The most promising blood products under development as blood substitutes are perfluorocarbons and haemoglobin based oxygen carriers. PFCs are long chain compounds similar to Teflon having
oxygen carrying capacity [2]. It is very amazing that an artificial substance could replace something that is so central to human life. To understand the process, it helps to know a little about how real blood works. Blood has two main components plasma and formed elements. Nearly everything that blood carries, like nutrients hormones and waste, is dissolved in the plasma, which is mostly water. Formed elements, which are cells and parts of cells, also float in the plasma. Formed elements include white blood cells (WBCs), which are part of the immune system, and platelets, which help forming clots Red blood cells (RBCs) are responsible for one of the blood’s most important carrying oxygen and carbon dioxide. RBCs are numerous. They make up more than 90 percent of the formed elements in the blood. Virtually everything about them helps them carry oxygen more efficiently. A RBC is shaped like a disc that’s concave on both sides, so it has lots of surface area for oxygen absorption and release. Its membrane is very flexible and has no nucleus, so it can fit through tiny capillaries without rupturing.

ARTIFICIAL BLOOD CELLS

Artificial blood or blood surrogates are a substance used to mimic and fulfill some functions of biological blood, usually in the oxygen-carrying sense as shown in figure no.3. The main aim is to provide an alternative to blood transfusion, which is transferring blood or blood based products from one person into another [3], [4]. Artificial blood does not contain the plasma, red and white cells, or platelets of human blood, but functions to transport and deliver oxygen to the body’s tissues until the recipient’s bone marrow has regenerated the missing red blood cells [5]. Artificial blood can be produced in different ways using synthetic production, chemical isolation, or recombinant biochemical technology [6]. Current blood substitutes are either haemoglobin-based oxygen carriers (HBOCs) or per fluorocarbons (PFCs). While HBOCs utilize haemoglobin, an actual component of red blood cells, PFCs rely solely on synthetic chemical processes. Other novel products are in very early stages of development. None of the products perform all the functions of blood; neither do they persist in the circulation as long as human red blood cells. However, they all carry and transport oxygen to tissues and can support life temporarily until patients can either regenerate their own red cells or can be transfused with banked blood. In the short term,
the prospective benefits of a blood substitute overshadow the shortcomings. In addition to carrying oxygen, such compounds can be sterilized against infectious diseases and used in patients whose religious beliefs prevent them from accepting blood transfusions [7].

Fig 1. Artificial blood substitutes

**TYPES OF ARTIFICIAL BLOOD**

There are two main types of artificial blood

1. Perfluoro carbons (PFC) emulsions
2. Haemoglobin based oxygen carriers (HBOC’S).
HBOC HEMOGLOBIN BASED OXYGEN CARRIERS

Manufacturing Process

The production of artificial blood can be done in a variety of ways. For haemoglobin-based products, this involves isolation of haemoglobin, molecular modification then reconstitution in an artificial blood formula [8]. PFC products involve a polymerization reaction. A method for the production of a synthetic haemoglobin-based product.

ADVANTAGES OF HBOC

1. Available in much larger quantities.
2. Can be stored for long durations.
3. Can be administered rapidly without typing or cross-matching blood types.
4. Can be sterilized via pasteurization.
DISADVANTAGES OF HBOC
1. Reduced circulation half-life.
2. Disrupts certain physiological structures, especially the gastrointestinal tract and normal red blood cell hemoglobin.
3. The release of free radicals takes place into the body [9].

PERFLUOROCARBONS (PFC)
PFC’S are biologically inert materials that can dissolve about 50 times more oxygen than blood plasma. They are relatively inexpensive to produce and can be made devoid of any biological materials. This eliminates the real possibility of spreading an infectious disease via a blood transfusion. They are not soluble in water, which means to get them to work they must be combined with emulsifiers—fatty compounds called lipids that are able to suspend tiny particles of perfluorochemicals in the blood. They have the ability to carry much less oxygen than haemoglobin-based products. This means that significantly more PFC must be used. One product of this type has been approved for use by the Federal Drug Administration (FDA), but it has not been commercially successful because the amount needed to provide a benefit is too high. Improved PFC emulsions are being developed but have yet to reach the market [10].

ADVANTAGES OF PFC
1. PFCs do not react with oxygen.
2. PFCs allow easy transportation of the oxygen to the body.
3. They allow increased solubility of oxygen in plasma.
4. PFCs minimize the effects of factors like pH and temperature in blood circulation.

DISADVANTAGES OF PFC
1. Often causes flu-like symptoms, this is often caused by phagocytosis of the perfluorocarbon emulsion by the recipient organism’s immune system.
2. Unable to remain mixed as aqueous solutions thus, they must be prepared as emulsions for use in patients.
3. A decrease in blood platelet count.
4. PFC products cannot be used by the human body, and must be discarded this takes approximately 18-24 months.

5. Because PFCs absorb oxygen passively, patients must breathe at a linear rate to ensure oxygenation of tissues [11].

**WHY ARE ARTIFICIAL BLOOD VESSELS NEEDED?**

Cardiovascular diseases (CVDs) are still the number one cause of death or invalidity in the western world today. Cardiovascular diseases alone account for approximately 30% of all global deaths, and in 2005 an estimated 17.5 million people died from CVDs. The World Health Organisation (WHO) estimates, that if current trends are allowed to continue, by 2015 20 million people will die [12], [13]. The CVDs are a group of disorders that affect the heart and blood vessels including coronary heart disease, cerebrovascular disease and peripheral arterial disease, deep vein thrombosis and pulmonary embolism. The main cause of these acute life- threatening conditions is atherosclerosis. Atherosclerotic plaques and restenosis can result in severe occlusions of peripheral and coronary arteries [14]. Treatment depends on the severity of the disease and includes drug therapy, coronary artery angioplasty and bypass surgery. Generally, antilogous saphenous veins or mammary arteries are used as replacement grafts and are the first choices as vascular graft materials. However, if the patient does not have vessels with sufficient quality, as a result of previous operations or other diseases, artificial grafts may be used. Today, biomaterials such as polytetrafluorethylene (ePTFE) and polyethylene terephthalate fibre (Dacron®) are in use in the clinic as prosthetic grafts for reconstructive vascular surgery. In small diameter vessels (>6mm) like coronary arteries their performance is dismal, resulting in early thrombosis and intimal hyperplasia. They only function satisfactorily in large- diameter, high flow vessels. Approximately 10% of patients with coronary artery disease are therefore left untreated [15]. Tissue engineered blood vessels could be a solution to this problem.

**The native blood vessel**

Human blood vessels consist of three different layers from the luminal side outwards: tunica intima, tunica media and tunica adventitia. The composition and structure of these layers depend greatly on the position of the vessel in the vascular tree, e.g. size and type of
vessels. Since arteries transport blood under high pressure in contrast to veins, the walls of arteries are thicker and more elastic and muscular than those of veins. The capillaries, the smallest vessels, are an exception from the general structure. Their function is to supply the surrounding tissue with oxygen. To permit oxygen diffusion, the capillary walls are only one cell thick. The intima is the innermost layer of arteries and veins and consists of a monolayer of endothelial cells, called the endothelium, with a thin underlying basal lamina of connective tissue, the lamina propria intimae. In large elastic arteries such as the aorta, the intima has a third component called the sub-endothelial layer, which contains smooth muscle cells, collagen, elastic fibrils and a few fibroblasts. Endothelial cells in the intimae are inter-connected with tight occluding junctions (zonulae occludentes) that regulate the transport of molecules across the endothelial monolayer as well as with in-plane communication junctions (gap junctions; maculae communicantes), which allow cell-to-cell-communication via the transport of ions and metabolites. Other structures involved in transendothelial transport are the pinocytic vesicle, or Weibel-Palade bodies, that are mainly connected to the luminal, the basal cell membranes. In arteries, the endothelial cells are flat, elongated and oriented in the direction of the blood flow. Endothelial cells communicate with underlying smooth muscle cells directly through processes that extend through the basal lamina and into the media. The main function of the basal lamina is to provide an adherent network, which consists of an extracellular matrix (ECM) of type IV collagen, lamina, fibronectin and proteoglycans on which endothelial cells can grow. It also provides structural support to the arterial wall [16], [17], [18].

**Blood Compatibility**

Thrombogenicity is defined by Williams as the ability of material to induce or promote the formation of thromboemboli [19]. Non-thrombogenic materials should have a low thrombin production rate constant, low platelet consumption and low degree of platelet activation, perhaps some platelet spreading and low complement and leukocyte activation [20]. Since the blood-biomaterial interactions are complex and not yet fully understood, it is not surprising that many studies are contradictory concerning what non-thrombogenic material really is and why no non-thrombogenic material has yet been found.
Homeostasis
The maintenance of a normal and healthy circulatory system requires several mechanisms that can uphold normal functions and respond to a wide range of physiological conditions such as tissue damage, healing of wounds, alteration of blood composition, and inflammatory responses. The coagulation cascade of homeostasis is often divided into two phases; primary homeostasis where platelets form an initial clot at the site of injury and secondary homeostasis where fibrin is generated through a complex pathway of plasma proteins, the coagulation factors, that strengthen the initial clot. These coagulation factors interact with each other in a Y-shaped pathway that join into a common pathway that ultimately leads to the formation of thrombin, which plays a central role in the coagulation cascade. Thrombin facilitates the cleavage of fibrinogen to fibrin, which can then polymerize and form a fibrin network, a vital part of the haemostatic clot that restricts bleeding after vessel injury.

The enzymes in the coagulation cascade are termed coagulation factors, usually abbreviated with an “F” and assigned specific roman numerals. To distinguish between the activated factor from the zymogene, the activated factor is suffixed with an “a”. Five of the zymogens involved in the coagulation cascade are vitamin K-dependent serine proteases, FVII, FIX, FX, prothrombin and protein C [21].

Primary homeostasis
Damage to the endothelium exposes the sub endothelial matrix, e.g. collagen, which induces rapid platelet adhesion. This initiates the first step in the haemostatic response that leads to platelet plug formation. The initial “rolling” adhesion of platelets to collagen is mainly mediated by glycoprotein (GP), GPIb-XI-V. The binding of platelets to GP is promoted by von Willebrand Factor (vWF), a plasma protein that binds rapidly to exposed collagen and contains several binding sites for the GPIb-XI-V adhesion receptor. Binding to this receptor leads to rapid signal transduction and platelet activation. Following initial platelet adhesion to exposed sub endothelial matrix, platelets that have slowed down can bind directly to collagen via the GPVI receptor. This procedure plays an important role in platelet activation [22].
Secondary homeostasis

1. Two pathways of the coagulation cascade
The two pathways, named after the respective type of activation, are called the contact activation pathway (extrinsic pathway) and the tissue factor pathway (intrinsic pathway). These pathways join into a common pathway that leads to the generation of a stable blood clot [23].

2. Tissue factor pathway (extrinsic pathway)
The first protection from thrombosis is the endothelial cell layer that lines the inner lumen of the vessel and hides the underlying sub endothelium and TF. The coagulation process begins almost immediately after cell damage and exposure of TF, which is regarded as the main initiator of coagulation under normal physiological conditions. Tissue factor is expressed by platelets and leukocytes, and in the sub endothelial tissue but not on healthy EC. The extrinsic pathway is initiated when activated factor VII comes into contact with TF. Under non-pathological conditions, picomolar concentrations of FVIIa circulate in the blood and act as primer in the initiation of coagulation in the presence of exposed TF. The tenase complex TF-FVIIa cleaves Factor X (FX), the factor that links the intrinsic and extrinsic pathways, into FXa in the presence of calcium [24].

Blood Composition
White cells: white cells are responsible for the immune defense. They seek out invading organisms or materials and minimize their effect in the body.
Red cells: red cells create the bright red color. These cells are responsible for the transportation of oxygen and carbon dioxide throughout the body.
Platelets: platelets are small fragment of cell that clump together and stick to inner surface of vessels and prevent leakage.
Plasma: plasma is the extra cellular material made up of water, salts, and various proteins that, along with platelets, encourages blood to clot. Proteins in the plasma react with air and harden to prevent further bleeding [25].
OBJECTIVES
To determine the safety, effectiveness and cost-effectiveness of oxygen therapeutics in substituting true blood for transfusion.

TECHNICAL FEATURE
Depending on the type of the artificial blood, it can be produced in different ways using synthetic production, chemical isolation or recombinant biochemical technology. The ideal product has the following characteristics [26].

1. Safe to use and compatible within the human body i.e. different blood types should not matter when it is used. It should be free from all disease-causing agents.
2. Must be able to transport oxygen throughout the body. Effective oxygen delivery is dependent on the ability to load oxygen in the pulmonary capillary bed, transport the oxygen in the circulation to the tissues, unload oxygen at tissue oxygen tensions and permit the diffusion of the off-loaded oxygen into the tissue.
3. Must be shelf-stable (stored for over the year or more).
4. Does not increase arterial and pulmonary blood pressure.
5. Sufficient half-life in the circulation.
6. Does not form methemoglobin, activate complement, increase white blood cell count, reacts with plasma substitutes or platelets.
7. Absence of renal toxicity.
8. Immediate availability.
9. Easy to administer.
10. Does not overload reticuloendothelial system.
11. Does not cause oxidation and free radical formation.

The development of artificial blood can be tracked in five cycles which started in the second half of the 19th century [27].

Advantages
1. Perfluorocarbons do not react with oxygen.
2. Perfluorocarbons allow easy transportation of the oxygen to the body.
3. They allow increased solubility of oxygen in plasma.
4. Perfluorocarbons minimize the effects of factors like pH and temperature in blood circulation [28].

**Disadvantages**
1. This is often caused by phagocytosis of the perfluorocarbon emulsion by the recipient organism’s immune system.
2. Often causes flu-like symptoms.
3. Unable to remain mixed as aqueous solutions thus, they must be prepared as emulsions for use in patients.
4. PFC products cannot be used by the human body, and must be discarded this takes approximately 18-24 months.
5. Because PFC absorbs oxygen passively, patients must breathe at a linear rate to ensure oxygenation of tissue.

**MATERIALS AND METHODS**
A paraffin embedded bone marrow puncture taken in week 11 after liver transplantation, peripheral blood samples collected in weeks 16 and 18 (2 days before the patient deceased after multiorgan failure), buccal swabs (one of them slightly bloody) and eye brows of week 16 as well as paraffin sections from 21 different biopsies (prostata, trachea, heart, pelvic bone marrow, renal pelvis, colon, vertebral bone marrow, brain, both kidneys, aorta, both suprarenal glands, both lung lobes, liver, cardiac tissue, oesophagus, pancreas, stomach, and thyroid gland) taken during autopsy and a pre-transplantation blood sample of the donor were included in these investigations. DNA was extracted with the Qiamp DNA Mini Kit (Qiagen, Valencia, USA) or the Chelex method. Multiplex-STR-typing was carried out on the blood, the buccal swab and the hair samples of the recipient, the first bone marrow puncture and the donor’s sample applying the AmpFISTRIdentifiler PCR Amplification Kit (Applied Biosystems, Foster City, USA) according to the manufacturer’s instructions. Singleplex-STR-typing of the highly polymorphic SE33 locus (fluoresceinlabelled reverse primer) was performed on all samples [29]. The calculation of the percentages of the two-cell population was based on peak areas [30].
Composition of Artificial Blood

Perfluoro-octyl bromide - 28%

FO-9982 - 12%

Yolk lecithin - 2.4%

DSPE-50 H - 0.12%

Distilled water - 57.48%

CONCLUSION

We reported a case of facial PN in a 30 years old male with NF1 based on the history, physical examination, and histopathological examination. The patient was given ketotifen hydrogen fumarat 1 mg tablet twice daily which improves the pruritus significantly and also planned to have serial resection.

REFERENCES


