Therapeutic strategies for the protection of renal oxygenation in experimental models of acute kidney injury
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GENERAL INTRODUCTION

Based on:

The impact of storage on red cell function in blood transfusion
Almac E, Ince C

The critically ill red blood cell
Almac E, Ince C.
Yearbook of Intensive Care Medicine, 2007; 799-812

Hydroxyethyl starch solutions and their effect on the microcirculation and tissue oxygenation
Yuruk K, Almac E, Ince C
Transfusion Alternatives in Transfusion Medicine, September 2007;9(3):164–172
**Background**

Critically ill patients include a wide range of patient groups sharing several frequently occurring complications, such as the development of hypovolemia and anemia. The course of developing hypovolemia and anemia, nevertheless, may differ according to the underlying condition. Effective volume therapy is the main therapeutic strategy to prevent inadequate tissue perfusion and disturbed oxygen delivery in patients undergoing hypovolemia. If hypovolemia and anemia are not corrected directly, this situation could be followed by shock, irreversible cell damage, organ failure and finally, death. In order to develop treatment strategies, the mechanisms underlying shock, resuscitation, and ischemia/reperfusion (I/R) injury should be well understood. In general, therapy of shock aims to correct the main pathology leading to shock, as well as to correct early the perfusion deficit at the cellular level and to provide adequate oxygen delivery to the cells.

**Oxygen transport to tissues**

Oxygen delivery to the tissues, in general, is simply calculated as the product of blood flow and arterial oxygen content. It is obvious that decreases in flow, arterial oxygen content (a decrease in red blood cell mass or hemoglobin oxygen saturation, or an inability to use the oxygen available in the circulation), and dissolved oxygen result in tissue hypoxia. If the decrease in oxygen-carrying capacity is more than compensatory mechanisms can handle, further decreases in oxygen delivery can lead to an increase in extraction ratio. Further decreases in oxygen delivery will result in decreases in oxygen consumption and leave the tissues hypoxic, and if not corrected this may lead to irreversible tissue damage and organ failure. If such a condition is imminent and decreases in systemic hemoglobin levels occur, the therapy of choice is the administration of blood transfusions. However, oxygen flux into the tissues and finally into the cells also depends on many other factors, such as blood flow distribution between organs and within the microcirculation, functional capillary density, red blood cell transit times, physical, rheological and functional properties of red blood cells, tissue diffusion coefficient, oxygen transport across the cell membrane, and finally mitochondrial function and oxygen requirement.

The microcirculation is a vascular system that is comprised of the smallest blood vessels (i.e., diameter < 100 mm), where oxygen delivery to the tissues is accomplished. This network of small vessels consists of arterioles, capillaries, and venules and terminal lymphatic vessels. The main purpose of the microcirculatory function is to maintain tissue oxygenation and thus organ function and, additionally,
transporting nutrients to tissue cells and to expel metabolic products. The microcirculation also plays a central role in (regional) blood pressure/flow regulation and in providing adequate immunological function and delivering therapeutic drugs to target cells. The microcirculation has an oxygen-dependent regulatory system, which is connected to the systemic circulation, but is also able to regulate and direct blood flow to the tissues depending on the metabolic need of those tissues [1]. The flow of blood in the microcirculation, even under normal conditions, is highly heterogeneous, but by its heterogeneity ensures a homogenous distribution of oxygen in the tissues [2]. Therefore, in order to regulate microcirculatory blood flow and thereby oxygen transport to the microcirculation instantly, hypoxia-detecting mechanisms are required. Under normal physiological conditions, this finely regulated system of arterioles, capillaries, and venules can supply oxygen in excess of oxygen demand, so that the tissues can continue their function under changing metabolic demands.

Besides the negligible amount of oxygen dissolved in plasma, red blood cells are the only cell group responsible for the transport of oxygen to and carbon dioxide from the tissues. In order to fulfill this role, red blood cells use hemoglobin molecules which they produce during their maturation process. In addition to their role in oxygen and carbon dioxide transport between organs and lungs, new functions of red blood cells have been found which have led to the idea that red blood cells also play an important role in vascular regulation. Increasing numbers of studies have demonstrated that red blood cells induce vasodilation in the presence of hypoxia and promote oxygen transport. Two important compounds have been proposed in relation to this function: ATP and nitric oxide [3-7]. It has been proposed that nitric oxide release during hypoxia is associated with the bioavailability of S-nitrosothiol [8] and/or nitrate [9] and nitrite [5] in red blood cells, of which are able to donate nitric oxide under hypoxic condition [7]. Such hypoxia-induced, red blood cell-associated release of vasodilator substances is now regarded as an important vascular regulatory mechanism, ensuring an oxygen supply adequate for the needs of tissues.

**Anemia and hypovolemia in critical illness**

It was earlier shown that while other non-bleeding critically ill patients only exhibit a remarkable decrease in hemoglobin values in the first 3 days, hemoglobin values in septic critically ill patients kept on continuing to decrease even after 3 days [10-12]. The etiology of anemia in critically ill patients is multifactorial. Among the many causes, blood loss due to bleeding (surgical procedures and gastrointestinal
bleeding) remains the main cause. Blood loss in critically ill patients occurs often due to emergency and traumas, surgeries and gastrointestinal bleedings [12]. Hemoglobin concentrations, however, may also decrease in non-bleeding critically ill patients. Under normal physiological conditions erythropoietin production is induced by hypoxia, as occurs in decreases in red blood cell mass and anemia, which in the end corrects the tissue hypoxia. In critically ill patients, however, the erythropoietin response to anemia is blunted due to cytokines and inflammatory response [13]. Furthermore, frequent blood sampling is another contributing factor to anemia [10, 11]. Additionally, increased blood volume secondary to vasodilation may cause a decrease in hematocrit, in the presence of constant RBC mass [14]. Finally, alterations in red blood cell rheology, leading to increased destruction of red blood cells by reticulo-endothelial system, are suggested to be another factor contributing to anemia in critically ill patients [15-17]. Red blood cell membrane alterations could occur due to the production of inflammatory mediators by white blood cells, by bacteria, or by the red blood cell membrane itself.

Another important clinical complication is capillary leakage; a medical condition characterized by leaking of intravascular fluids into the extravascular space, resulting in hypovolemia and consequent hypotension, tissue edema and finally multiple organ failure due to limited microvascular perfusion. This condition is observed in patients following shock, ischemia-reperfusion, toxemias, burns, low flow states and injuries. A diminished microvascular perfusion due to reduced intravascular volume associated with an increased interstitial fluid volume plays an important role in impairing tissue oxygenation and transport of metabolites and energy substrates. Ideal volume resuscitation therapy may successfully restore intravascular volume and microcirculatory perfusion.

**Brief history of blood transfusion practice**

The unique function of blood was known by many early civilizations long before the scientific era. It was believed to have a healing ability and to be associated with life, figuring in various beliefs and myths. The first known transfusion attempt was made, according to legend, in the 15th century, when the blood of three healthy boys was transfused into the veins of the then sick pope Innocentius VIII, unfortunately without success. Two centuries later a Frenchman, Jean-Baptiste Denis, transfused the blood of a calf into a man. However, up to the beginning of the 20th century more than a half of the transfused patients died, threatening the development of transfusion medicine. This changed as a result of the findings of Karl Landsteiner who, while investigating failed blood transfusions, identified different blood types,
resulting in the ABO and rhesus blood group systems. The development of cross-
matching strongly decreased adverse transfusion reactions. A second important
development in blood transfusion practice was the introduction by Richard
Lewisohn in 1915 of sodium citrate as an anticoagulant storage solution. This
important development turned the transfusion of blood into a relatively safe and
bearable procedure for both the donor and the patient. The rapidly evolving
transfusion technology solved the problem of short storage time, which became an
issue during the Second World War due to the need for large amounts of blood. The
development of plastic containers eased the storage and transport of blood units. In
the 1950s the separation of blood components, and in the last three decades the
developments of additive solutions, rejuvenation and leukodepletion fuelled by the
increasing demand for allogeneic red blood cell transfusions, significantly improved
the quality of stored red blood cells.

**Red blood cell storage**

Continued developments in storage techniques have resulted in improved storage
times as well as red blood cell quality. In this context we refer to ‘storage’ as liquid
preservation, as this is the most common blood preservation technique currently in
use. The increasing demand for allogeneic blood transfusions has resulted in
millions of liquid-stored allogeneic red blood cell units being used annually for
transfusions worldwide. This practice is based on the theoretical expectation that
increasing the intravascular mass of red blood cells will increase oxygen delivery to
the tissues. However, accumulating evidence is showing that this expectation may
not be true, and that there is a negative relationship between the storage time and red
blood cell viability and function.

The increasing concerns about the efficacy of allogeneic blood transfusions
forces the question about the impact of storage on red blood cell function and hence
on their use for blood transfusion. First, however, the issue of how the physical and
biochemical properties of red blood cells are altered under conditions of storage
should be considered. Indeed, it has been shown that red blood cells undergo a
number of changes during liquid storage that affect their viability and their ability to
deliver oxygen to the tissues. We can classify the alterations in two major groups;
biomechanical and biochemical. These alterations are known as storage lesion. One
possible mechanism that may account for alterations in the oxygen transporting
capabilities of transfused red blood cells is their ability to generate nitric oxide under
acidic and hypoxic conditions. Nitric oxide and its products, besides many other
roles in the organisms, can be regarded as being among the major compounds
accounting for vascular regulation due to their vasodilatory action on blood vessels. Recent studies have shown that red blood cells are able to release nitric oxide in the presence of hypoxia, and that this nitrite-mediated mechanism accounts for hypoxia-induced vasodilation [8]. It could well be that this NO-mediated function of red blood cells may be affected during storage.

**Fluid therapy**

An alternative for blood transfusion is volume resuscitation using crystalloid and colloid solutions. Besides the oxygen-carrying properties of blood and its components, the condition of the microcirculation is a main determinant in achieving optimal tissue oxygenation. In this line, fluid resuscitation can be used for promoting microcirculatory function and tissue oxygenation. The main goal of fluid therapy is to reestablish an adequate circulation with sufficient arterial blood pressure and cardiac output, and ultimately to restore tissue perfusion and oxygenation [18]. Therefore, volume resuscitation therapy should focus not only on correcting systemic hemodynamics, but also on improving microcirculatory perfusion and oxygenation.

The ideal solution is one which can replace blood volume losses rapidly, normalize microcirculatory flow and function, have a sufficiently long intravascular life, be free of side effects, particularly regarding infection, coagulation and anaphylactic reactions, improve hemorrhheology, be readily metabolized and excreted, and be cost-effective. For fluid therapy to be effective, it is imperative that it reaches the microcirculation to promote tissue perfusion. The positive and negative effects of crystalloids and colloids have been discussed for a long time. The advantages of crystalloid solutions are that they are less allergic and more readily available on the market. On the other hand, colloids are more effective in resuscitation with lower volume and rarely cause peripheral edema. Several studies have shown that colloids are a more efficient regimen to ensure adequate microcirculatory flow than crystalloids [19, 20]. As such, hydroxyethyl starch (HES) solutions have been the most commonly used plasma substitutes among colloid solutions [21-23]. HES solutions have been introduced some three decades ago as an alternative to the traditional plasma expanders at that time (e.g. albumin and dextrans), and are increasingly being used for the prevention and treatment of hypovolemia in numerous clinical situations, such as surgical, trauma, burn and intensive-care patients. HES solutions are artificial colloid solutions that are modified natural polysaccharides with volume-expansion properties. Natural starches cannot be used as plasma substitutes because circulating amylase
hydrolyzes these unstable organic compounds rapidly. By substituting hydroxyethyl for hydroxyethyl groups, hydrolysis by amylase becomes delayed, thereby retarding its metabolic degradation and elimination from the circulation [24, 25].

HES solutions are characterized by their concentration, molecular weight, molar substitution ratio, degree of substitution and C2/C6 ratio. They are usually dissolved in 0.9% sodium chloride (NaCl). The molar substitution ratio expresses the molar ratio of the total number of hydroxyethyl groups to the total number of glucose molecules. Different molar substitution ratios, from 0.4 to 0.7, have been used. The degree of substitution is defined as the ratio of substituted glucose units to the total number of glucose units. The type of substitution is identified by the C2/C6 hydroxyethylation ratio, which indicates the position of the hydroxyethyl groups on the glucose molecule (C2, C3 and C6). A higher hydroxyethylation ratio leads to slower breakdown of HES [26]. Hydroxyethylation takes place at positions 2, 3, and 6 of carbon on the glucose units, but most frequently at positions C2 and C6, so that the C2/C6 ratio is generally given when referring to a particular type of HES compound [27]. The molar substitution ratio is one of the major determinant factors, besides molecular weight and C2/C6 ratio, to assess the pharmacodynamic behavior of HES. In vivo, the molecular weight of the HES compound is responsible for the colloidal activity. Therapeutic and side effects of each type of HES solution also depend on the molar substitution and the C2/C6 ratio. Higher values of these variables result in longer degradation half-life and prolonged volume-expansion effect [28] as well as increased side effects.

Stable hemodynamics and improved rheology are considered as important benefits of hemodilution with HES infusions. Even though the fluids cannot carry oxygen, increased tissue oxygenation has been found in patients, which is used as a clinical indicator of improved oxygen availability at the microcirculatory and cellular level [29]. Tissue oxygen tension can be considered as reflecting the balance between oxygen delivery by microcirculatory perfusion and oxygen consumption in the tissue. New techniques are providing more precise insight into the properties and determinants of oxygen transport to tissue. In this way, oxygen-dependent quenching of phosphorescence of the Palladium (Pd) porphyrin technique has been effective in non-invasively measuring microcirculatory oxygenation within and between organ systems following hemodilution [30-33]. The effects of different volume-replacement strategies on tissue oxygenation are not clearly known, and are the subject of ongoing research.
The critically ill kidney

As described above, anemia and hypovolemia are common complications in critically ill patient. In this respect, the kidney has been found to be highly susceptible to these conditions due to its complex morphological structure and high oxygen demand. As such, acute kidney injury (AKI) is a frequent and costly clinical complication in critically ill patients. Using the RIFLE criteria in 20,126 hospitalized patients, Uchino et al. has found that 20% of the patients as having some degrees of acute renal impairment, and 3.7% of these patients had acute renal failure (ARF) [34]. Besides hypovolemia and anemia, ischemia/reperfusion (I/R) injury occurring during surgery and shock is one of the major causes of this condition in native and transplanted kidneys [34-38]. The pathogenesis and pathophysiology AKI is highly complex [37, 38]. In addition to hypoxic hit consequent to ischemia, the reperfusion phase (e.g., as a result of clamp release, fluid resuscitation, or blood transfusion) has been associated with additional renal injury. Shock- and I/R-induced activation of inflammatory pathways has been shown to worsen ARF [39-42]. Furthermore, increased production of radical oxygen species (ROS) and reactive nitrogen species (RNS) [43-46], and a regional imbalance between vasoactive mediators leading impaired microcirculatory perfusion and to cellular damage, apoptosis and irreversible kidney failure [37, 38].

Because the efficacy of blood transfusions are still a matter of debate and red blood cell units are relatively expensive, the first step in the correction of sepsis- and hemorrhage-induced hypotension and organ hypoperfusion is aggressive volume replacement therapy using fluids [47], which aims to increase the circulating intravascular volume, blood pressure, and organ perfusion [48, 49]. However, in contrast to blood, resuscitation fluids have poor oxygen transporting capacity and rheological properties. In addition, the fluids used for volume replacement therapy have been suggested to increase inflammation and disturb homeostasis and the acid-base balance [50-53]. Over time, a variety of colloid and crystalloid solutions has been used, including isotonic saline and saline-based colloid solutions. Although saline-based solutions have been associated with disturbed acid-base balance due to non-physiological electrolyte composition and pH, these yet remain the most popular solutions for volume replacement therapy in peri-operative care [54-60]. With this in mind, it becomes more and more clear that adjuvant therapies, in addition to blood transfusion and fluid resuscitation should be used for optimal prevention and/or treatment of ARF.
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